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Nano Delivery of Flavonoids in NSCLC: Mechanistic Insights and Translational Perspectives

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Abstract:

Non-small cell lung cancer (NSCLC) has high mortality rates owing to multidrug resistance, inadequate tumor selectivity, and systemic toxicity associated with conventional chemotherapy. In contrast, flavonoids, including fisetin, quercetin, and flavokavain A, show promising anticancer activity. However, their clinical application is limited by poor solubility, instability, and insufficient intracellular accumulation. Recent studies, mainly on nanostructured lipid carriers (NLCs), have provided a strategic approach to address these challenges. This critical review examines nanocarrier-enabled flavonoid delivery systems for NSCLC, focusing on the role of lipid-based nanocarriers in enhancing pharmacokinetics, improving tumor targeting, and reversing drug resistance mechanisms. Surface-functionalized NLCs, including hyaluronic acid (HA) and protein-based ligands, facilitate receptor-mediated uptake, enhance therapeutic efficacy, and inspire current preclinical evidence. This review discusses the mechanistic advantages and translational potential of NLC-based flavonoid delivery and identifies the important challenges that must be addressed for clinical advancement.

Keywords: Nanostructured lipid carriers; Flavonoids; NSCLC; Targeted nanomedicine; Multidrug resistance; Lipid-based nanocarriers

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1. Introduction

Non-small cell lung cancer (NSCLC) has significant challenges, accounting for approximately 85% of lung cancer diagnoses, and is a leading cause of cancer-related mortality worldwide; thus, progress in targeted therapies and immunotherapy to address NSCLC remains challenging because of factors such as late-stage diagnosis, tumor heterogeneity, and persistent development of multidrug resistance (MDR) [1-2] .Traditional chemotherapeutic agents often lack the precision required to effectively target tumors, leading to dose-limiting toxicity and reduced compliance [3-4]. Flavonoids are natural polyphenolic compounds that exhibit antiproliferative, proapoptotic,

antiangiogenic, and antioxidant properties[8,9]. Fisetin and flavokavain A have demonstrated notable anticancer activity in NSCLC models. However, their therapeutic potential is limited by unfavorable physicochemical properties, such as poor aqueous solubility, rapid metabolism, and limited cellular uptake [5-6]. Nanodrug delivery offers a transformative solution, as nanostructured lipid carriers (NLCs) have emerged as an innovative second-generation lipid nanoparticle system that specifically enhances drug loading, stability, and controlled release. This review confirms that NLC-enabled flavonoid delivery can enhance anticancer efficacy against NSCLC, explores the mechanistic basis for these improved therapeutic outcomes, and highlights that NLCs present a promising opportunity in ongoing efforts to treat NSCLC [7-8]. Table 1. Challenges in the Treatment of Non-Small Cell Lung Cancer (NSCLC) and Advantages of Nanostructured Lipid Carriers.

NSCLC-Related Challenge	Limitation of Free Flavonoids	Advantage of Nanostructured Lipid Carriers (NLCs)
Poor aqueous solubility	Low solubility and poor bioavailability	Lipid matrix enhances solubilization and dissolution [9]
Metabolic instability	Rapid degradation and first-pass metabolism	Encapsulation protects flavonoids from degradation [10]
Low cellular uptake	Primarily passive diffusion	Endocytosis-mediated cellular internalization [11]
Multidrug resistance (MDR)	Efflux by P-glycoprotein (P-gp) transporters	Bypasses efflux mechanisms via intracellular uptake [12]
Non-specific distribution	Off-target exposure to healthy tissues	Passive tumor accumulation via EPR effect [13]
Systemic toxicity	Dose-limiting adverse effects	Controlled and localized drug release [14]
Poor tumor selectivity	Exposure of normal tissues	Ligand-mediated active targeting (e.g., HA–CD44) [15]
Limited clinical translation	Variable therapeutic outcomes	QbD-driven formulation reproducibility and scalability [16]

Table 1. Challenges associated with flavonoid-based therapy for non-small cell lung cancer and the mechanistic advantages offered by nanostructured lipid carriers.

2. Rationale for Nanostructured Lipid Carriers in Flavonoid Delivery

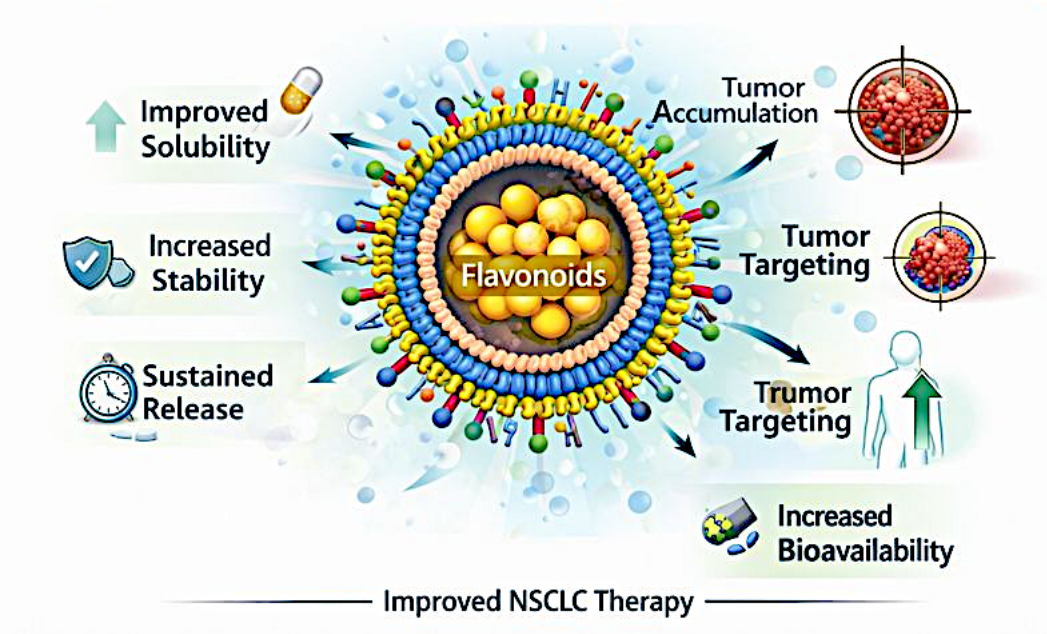

Figure 1. Rationale for Nanostructured Lipid Carriers in Flavonoid Delivery

Figure 1. Rationale of NC in flavonoid drug delivery, as its structure contains solid lipids and liquid lipids as well as modified ligands, which results in improved solubility, stability, sustained release, tumor accumulation, tumor targeting-, increases bioavailability. Nanostructured lipid carriers (NLCs) are mainly composed of a solid/liquid lipid matrix stabilized by surfactants and present several advantages over traditional solid lipid nanoparticles (SLNs), such as enhanced drug loading capacity and reduced drug expulsion during storage [17-18]. The lipid component of NLCs helps with intestinal lymphatic uptake, protects against phytochemical degradation, and facilitates sustained drug release. NLCs also provide a defensive microenvironment that enhances the solubility and systemic availability of flavonoids, which are mainly lipophilic and rapidly metabolized. Nevertheless, the nanoscale size of NLCs enhances permeability and retention (EPR) -mediated accumulation in tumor tissues. As second-generation lipid-based nano-arriers, NLCs consist of a solid lipid matrix that is partially blended with liquid lipids and stabilized by biocompatible surfactants. Compared with conventional SLNs, the dual lipid combination results in structural defects within the lipid core, thus significantly enhancing drug acc immolation compared to conventional SLNs [19-20]. Additionally, NLCs demonstrate the highest drug-loading capacity, decrease drug expulsion throughout storage, and improve physical stability. The co-occurrence of solid and liquid lipid phases facilitates greater flexibility in lipid packing, minimizes crystalline rearrangement, and ensures the sustained encapsulation of bioactive compounds. These features render NLCs particularly advantageous for the long-term delivery of lipophilic phytochemicals such as flavonoids [21].

Strategies to increase the solubilization and stability of flavonoids, which are mostly hydrophobic molecules, are needed, as they have poor solubility in water. In addition, these compounds are prone to rapid degradation and exhibit limited stability under standard physiological conditions. Encapsulating flavonoids within the lipid matrix of nanostructured lipid carriers (NLCs) provide a protective environment [22-23]. This encapsulation not only improves their solubility but also protects them from enzymatic degradation and oxidation within the gastrointestinal tract. By maintaining flavonoids in this solubilized and protected state, NLCs can significantly increase their bioavailability and prolong their circulation time, thereby increasing their therapeutic efficacy. This protection is crucial for polyphenolic compounds, which are rapidly degraded or eliminated after oral administration. Additionally, we examined how NLCs facilitate intestinal absorption and lymphatic transport [24-25]. The lipidic composition of NLCs enables their absorption through intestinal lipid transport pathways, promoting their uptake via the lymphatic system. This mechanism allows partial escape from the liver's first-pass metabolism, a common challenge for orally administered flavonoids. By enhancing lymphatic transport, an increase in bioavailability and a reduction in metabolic loss have been observed. The nanoscale size of these particles increases the surface area available for interaction with intestinal epithelial cells, thereby improving mucosal adhesion and transcellular transport, which contributes to superior oral absorption linked to traditional formulations [26-27].

Sustained Release and Pharmacokinetic Modulation: Nanostructured lipid carriers (NLCs) provide a culture method for achieving controlled and sustained release of encapsulated flavonoids by modulating drug diffusion within the lipid matrix. The kinetics of release can be finely tuned by altering the lipid composition, surfactant concentration, and processing parameters. These sustained-release profiles are crucial for maintaining therapeutic drug levels over extended periods, thereby decreasing the frequency of dosing and minimizing systemic toxicity. This strategy is particularly advantageous for chronic conditions, such as cancer and metabolic disorders, which require prolonged therapeutic exposure [28-29]. Tumor Accumulation via an Enhanced Permeability and Retention Effect: The nanoscale dimensions of NLCs, typically under 200 nm, enable their passive accumulation in tumor tissues through the enhanced permeability and retention (EPR) effect. The unique characteristics of the tumor vasculature, including increased permeability and impaired lymphatic drainage, facilitate the preferential retention of nanosized carriers at the tumor sites. In the context of flavonoid-based anticancer therapy, EPR-mediated accumulation enhances the concentration of the drug within tumor tissues while reducing the off-target exposure. This mechanism contributes to enhanced anticancer efficacy and reduced systemic adverse effects [29-30].

Adaptability for Surface Engineering and Targeted Delivery: in addition to passive targeting, NLCs offer a versatile platform for surface engineering with targeting ligands, such as hyaluronic acid, peptides, or proteins. These modifications enable receptor-mediated uptake by cancer cells, thereby enhancing intracellular drug delivery and improving therapeutic selectivity. This multifunctionality positions NLCs as highly adaptable nanocarrier systems, capable of overcoming the inherent limitations of flavonoid therapy and advancing their translational potential [31-32].

3. Surface Activation Strategies for Targeted NSCLC Therapy

The modification of nanostructured lipid carriers (NLCs) through the application of targeting ligands represents an outstanding advancement in nanomedicine. Hyaluronic acid (HA), a natural ligand of the CD44 receptor, is generally overexpressed in non-small cell lung cancer (NSCLC) and cancer stem cell populations [33-34]. NLCs that are coated with HA facilitate receptor-mediated endocytosis, significantly increasing the accumulation of drugs inside cells. Protein-based coatings, such as those using bovine serum albumin (BSA), contribute to improved nanoparticle stability, extended systemic circulation, and reduced opsonization. Compared with nonfunctionalized, NLCs dual-coated with both HA and protein layers successfully combine active targeting with stealth properties, offering enhanced tumor selectivity [35-36].

Surface engineering plays a vital role in improving nanomedicine, acting as a fundamental strategy in the development of nanocarriers. This method mostly improves the therapeutic precision, cellular absorption, and pharmacokinetic properties of nanomedicines. Through passive targeting, enabled by the enhanced permeability and retention (EPR) effect, nanosized carriers can accumulate preferentially in tumor tissues. Active targeting, facilitated by ligand-mediated interactions, extends tumor selectivity and enhances the efficiency of intracellular drug delivery. Specific ligands coated nanostructured lipid carriers (NLCs) permits receptor-specific recognition and endocytosis, effectively addressing the challenges associated with non-targeted nanocarriers [37-38].

Hyaluronic acid mediated targeting via CD44 receptors, such as hyaluronic acid (HA), a naturally occurring glycosaminoglycan, serves as a high-affinity ligand for the CD44 receptor, which is highly overexpressed in non-small cell lung cancer (NSCLC) cells and cancer stem cells. The CD44 receptor is important in tumor progression, metastasis, and drug resistance, making it an attractive molecular target for anticancer drug delivery systems [39-40]. HA-linked nanostructured lipid carriers (NLCs) utilize CD44–HA interactions to facilitate receptor-mediated endocytosis, enhancing the cellular uptake of encapsulated therapeutics. Upon binding to CD44 receptors on the cancer cell surface, HA-linked NLCs are adapted through clathrin- and caveolae-dependent pathways, resulting in increased intracellular drug accumulation compared with that of non-functionalized carriers [41]. This targeted therapy improves efficacy and decreases off-target toxicity to healthy tissues. The targeting of cancer stem cells and drug-resistant population of cancer stem cells (CSCs) significantly Contributes to tumor recurrence, metastasis, and resistance to chemotherapy [42].CD44 is a recognized marker of CSCs in NSCLC, and HA-based targeting strategies are effective in patients. By enhancing drug delivery to CD44-positive CSCs, HA-functionalized NLCs disrupt tumor regrowth and reduce the risk of relapse [43]. HA-mediated targeting has been shown to modulate intracellular signaling pathways associated with epithelial-to-mesenchymal transition (EMT) and multidrug resistance, thus strengthening the therapeutic impact of HA-coated nanocarriers [44-45].

Protein-based NLCs for enhanced stability and circulation via protein-based surface modifications, especially those incorporating bovine serum albumin (BSA), present notable

advantages in the formulation of nanoparticles. BSA, recognized for its biocompatibility and biodegradability, plays a crucial role in enhancing colloidal stability via steric hindrance, preventing the aggregation of nanoparticles [46]. The integration of BSA onto the surface of NLCs increase their stability within biological fluids and shields them from premature degradation. BSA facilitates extended systemic circulation by diminishing opsonization and subsequent uptake by the reticuloendothelial system (RES). By reducing macrophage recognition, BSA-coated NLCs exhibit prolonged blood residence time, enhancing the potential for tumor accumulation [47].

Nanostructured lipid carriers (NLCs) that are dual-functionalized with hyaluronic acid (HA) and protein-based linked represent a main approach that effectively combines active targeting with stealth characteristics. HA actively facilitates receptor-mediated targeting of CD44-expressing tumor cells, whereas bovine serum albumin (BSA) establishes a protective protein corona that prolongs the circulation time and minimizes nonspecific clearance. Compare with NLCs with either a single ligand or no functionalization, the combined effects of HA and BSA functionalization led to increased tumor selectivity, increased cellular uptake, and improved therapeutic efficacy. This dual-functionalization strategy is particularly beneficial for the delivery of bioactive compounds to non-small cell lung cancer (NSCLC)patients, where precise targeting and extended systemic exposure are crucial for effective treatment. Surface-engineered NLCs present a promising translational nanomedicine platform for NSCLC therapy [48-49]. By participating in receptor-specific targeting with improved stability and circulation properties, functionalized NLCs address significant challenges in conventional chemotherapy, such as inadequate tumor selectivity and systemic toxicity. The optimization of ligand density, surface charge, and coating composition, along with in vivo validation, will be essential for advancing HA and protein-functionalized NLCs toward clinical application [50]. Table 2. Mechanistic and Translational Impact of Nanostructured Lipid Carriers for Targeted NSCLC Therapy

NLC Functionalization Strategy	Targeting / Mechanism	Therapeutic Impact	Translational Relevance
Non-functionalized NLCs	Passive tumor accumulation via EPR effect	Limited tumor selectivity	Low [51]
HA-functionalized NLCs	CD44-mediated receptor-dependent endocytosis	Enhanced intracellular drug uptake	High [52]
HA-targeted CSC-directed NLCs	CD44 overexpression on cancer stem cells	Reduced tumor relapse and metastasis	Addresses chemoresistance [53]
BSA-coated NLCs	Reticuloendothelial system (RES) evasion (stealth effect)	Prolonged systemic circulation	Improves formulation stability [54]

Protein-coated NLCs	Surface stabilization and reduced aggregation	Enhanced systemic delivery	Scalable manufacturing [55]
Dual HA–BSA-functionalized NLCs	Combined active targeting and stealth properties	Superior tumor selectivity and efficacy	Strong clinical potential [56]
Ligand-density optimized NLCs	Controlled receptor–ligand interaction	Improved therapeutic index	QbD-compatible development [57]

Table 2. Comparison of nanostructured lipid carrier functionalization strategies, their targeting mechanisms, therapeutic outcomes, and translational relevance in non-small cell lung cancer.

4. **Is multidrug resistance in NSCLC a therapeutic challenge?**

Multidrug resistance (MDR) is determined by efflux transporters such as P-glycoprotein (P-gp) and presents a substantial obstacle in the treatment of non-small cell lung cancer (NSCLC). Flavonoids have demonstrated potential in inhibiting P-gp activity, but their clinical application is limited by inadequate intracellular concentrations [58]. Nanostructured lipid carriers (NLCs) offer a promising strategy by circumventing efflux mechanisms through endocytic uptake and improving intracellular retention. Preclinical studies have shown that flavonoid-loaded NLCs significantly reduce P-gp expression and activity, increase chemosensitivity, and induce apoptosis through mitochondrial and cell cycle–dependent pathways [59].MDR remains a primary challenge in effective NSCLC treatment, increase in associated with the overexpression of ATP-binding cassette (ABC) transporters, P-glycoprotein (P-gp), which actively eject chemotherapeutic agents from cancer cells, thus reducing intracellular drug accumulation and therapeutic efficacy [60]. Elevated P-glycoprotein (P-gp) levels are consistently observed in advanced NSCLC and are strongly correlated with poor clinical outcomes, tumor recurrence, and resistance to multiple anticancer agents. Flavonoids have attracted significant interest as potential modulators of MDR because of their ability to inhibit P-gp activity and downregulate efflux transporter expression [61]. Several flavonoids interfere with the ATPase activity of P-glycoprotein (P-gp), suppress transporter gene expression, and disrupt the membrane microdomains involved in drug efflux. These promising characteristics, of flavonoids are affected by their poor cellular uptake, rapid metabolism, and inability to achieve therapeutically effective intracellular concentrations when they are administered in the free form [62-63].

Nanostructured lipid carriers (NLCs) present a strategic approach to explain multidrug resistance (MDR) by promoting cellular uptake through endocytosis mechanisms rather than through passive diffusion. Once adopted via clathrin-mediated, caveolae-mediated, or macropinocytic pathways, NLCs effectively bypass membrane-associated efflux transporters, such as P-glycoprotein (P-gp). This approach facilitates the accumulation of flavonoids encapsulated within NLCs inside cells without immediate expulsion, which enhances drug retention and prolongs intracellular drug exposure. [64-65]

Preclinical investigations have shown that flavonoid-loaded NLCs not only circumvent efflux transporters, but also actively downregulate P-gp expression and function. Sustained intracellular

delivery of flavonoids influences signaling pathways involved in MDR regulation, including the PI3K/Akt, NF-κB, and MAPK pathways. This downregulation of P-gp at both the transcriptional and translational levels has been shown to restore chemosensitivity in resistant non-small cell lung cancer (NSCLC) cell lines [66-67].

Apoptosis increases, and cell cycle arrest is significantly prompted by the improved intracellular retention of flavonoids delivered via nanostructured lipid carriers (NLCs). These carriers play crucial roles in activating apoptotic signaling pathways that depend on mitochondrial mechanisms. Research has shown that treatment with flavonoid-loaded NLCs results in increased mitochondrial membrane depolarization, cytochrome c release, and caspase activation [68].These nanocarriers effectively induce cell cycle arrest at critical checkpoints, such as the G0/G1 or G2/M phases, significantly inhibiting tumor cell proliferation. The combined effects of efflux inhibition, mitochondrial dysfunction, and cell cycle disruption lead to a synergistic anticancer response, enhancing therapeutic outcomes [69-70].

The restoration of chemosensitivity and synergistic effects involves the initiation of nanostructured lipid carrier (NLC)-based flavonoid delivery systems, which represent a pivotal advancement in countering multidrug resistance (MDR) mechanisms, thus strengthens the efficacy of standard chemotherapeutic agents. This technique involves coadministration or co-encapsulation; flavonoids can significantly increase the sensitivity of resistant non-small cell lung cancer (NSCLC) cells to cytotoxic drugs. This approach not only permits a reduction in the required dosage but also diminishes systemic toxicity, suggesting a promising path for enhancing therapeutic outcomes in patients with drug-resistant NSCLC [71-72].

Translational Implications and Future Directions mainly show the potential of nanocarriers to modulate MDR, highlighting the potential of NLCs as easy delivery routes for intricate resistance mechanisms in NSCLC. Future investigations should prioritize the optimization of formulation parameters, the validation of efficacy in clinically relevant animal models, and the exploration of combination therapies to advance clinical translation [73].

5. Comparative advantages over conventional chemotherapy

Compared with traditional chemotherapeutic agents, such as paclitaxel, flavonoid-loaded nanostructured lipid carriers (NLCs) exhibit reduced systemic toxicity, enhanced selectivity, and improved anticancer efficacy in preclinical models. The ability to load multiple phytochemicals within a single nanocarrier facilitates synergistic therapeutic effects while minimizing adverse outcomes [74].

Thes limitations of conventional chemotherapeutic agents include the fact that conventional chemotherapeutic agents, such as paclitaxel, play a crucial role in the management of NSCLC. However, their clinical efficacy is often constrained by inadequate tumor specificity, systemic toxicity that limits dosing, and the rapid development of drug resistance. The nonspecific distribution of these agents often results in injury to healthy tissues, leading to adverse effects such as myelosuppression, neurotoxicity, and gastrointestinal disturbances. In addition,

conventional formulations often necessitate high doses to achieve therapeutic efficacy, thereby intensifying concerns about toxicity [75-76].

The mitigation of systemic toxicity through targeted nanodelivery studies revealed that Flavonoid-loaded nanostructured lipid carriers (NLCs) substantially improved upon conventional chemotherapy by minimizing systemic exposure and reducing off-target toxicity. The encapsulation of bioactive compounds within a lipid-based nanocarrier effectively prevents premature drug release and shields healthy tissues from direct exposure [77]. The biocompatible and biodegradable characteristics of lipid components contribute to an enhanced safety profile. Targeted delivery mechanisms, including passive accumulation via the enhanced permeability and retention (EPR) effect and active receptor-mediated uptake, further concentrate drug action at tumor sites [78-79]. Accordingly, flavonoid-loaded NLCs have shown reduced toxicity to normal cells while maintaining or even enhancing anticancer efficacy in preclinical studies. Enhanced Tumor Selectivity and Intracellular Accumulation: In contrast to traditional chemotherapeutic agents that rely on passive diffusion, NLC-based systems enhance tumor selectivity through their nanoscale size and surface functionalization. The tendency of NLCs to accumulate favorably in tumor tissues and undergo receptor-mediated endocytosis results in elevated intracellular drug concentrations within cancer cells. Compared with free drugs, this enhanced intracellular retention leads to prolonged therapeutic action and increased induction of apoptosis. Such selective accumulation is advantageous for heterogenicity within tumor populations and minimizing the impact on adjacent healthy tissues [80].Synergistic therapeutic effects occur through encapsulation. A main advantage of flavonoid-loaded nanostructured lipid carriers (NLCs) is their ability to coencapsulate multiple phytochemicals or integrate natural compounds with conventional chemotherapeutic agents. This coencapsulation enables the coordinated delivery of synergistic agents at optimized ratios, enhancing therapeutic efficacy while minimizing antagonistic interactions. Flavonoids can alert cancer cells to chemotherapeutic agents by modulating signaling pathways associated with cell survival, oxidative stress, and drug resistance. This synergistic interaction allows for a reduction in the dosage of cytotoxic drugs, which decreases adverse effects without compromising anticancer activity [81-82].

Modulation of drug resistance pathways: The efficacy of conventional chemotherapy is often compromised by the development of multidrug resistance (MDR), which is frequently mediated by efflux transporters such as P-glycoprotein. Flavonoid-loaded NLCs offer dual advantages by circumventing efflux mechanisms through endocytic uptake and suppressing resistance-related signaling pathways. Sustained intracellular delivery of flavonoids via NLCs contributes to the downregulation of MDR-associated proteins, the restoration of chemosensitivity, and the enhancement of the apoptotic response, thus providing a strategic advantage over traditional formulations.Enhanced anticancer efficacy in preclinical models: Preclinical studies have consistently demonstrated that compared with free flavonoids or conventional chemotherapeutic formulations, flavonoid-loaded NLCs exhibit superior anticancer efficacy [83-84].

Enhanced inhibition of tumor growth increased apoptotic indices and reduced metastatic potential have been observed both in vitro and in vivo. These findings highlight the potential of NLC-based flavonoid delivery systems to surpass traditional chemotherapy in terms of efficacy

and safety[83,84]. Clinical and translation implication involve the comparative advantages of flavonoid-loaded NLCs suggesting significant translational potential for non-small cell lung cancer (NSCLC) therapy. By addressing limitations of conventional chemotherapy, namely, toxicity, poor selectivity, and resistance, NLC-based systems offer a promising alternative or adjuntive therapeutic strategy. Continued optimization, pharmacokinetic evaluation, and clinical validation are essential to facilitate the transition from preclinical research to clinical application [85]. Table 3. Comparison of Conventional Chemotherapy and Flavonoid-Loaded Nanostructured Lipid Carriers in NSCLC

Parameter	Paclitaxel (Conventional Formulation)	Flavonoid-Loaded NLCs
Therapeutic class	Cytotoxic chemotherapeutic agent	Bioactive phytochemical-based nanotherapy [86]
Aqueous solubility	Low; requires solubilizing excipients	Improved via lipid-based encapsulation [87]
Tumor targeting	Nonspecific systemic distribution	Passive (EPR) and ligand-mediated targeting [88]
Cellular internalization	Diffusion-dependent uptake	Endocytosis-mediated uptake [89]
Intracellular retention	Limited due to efflux transporter activity	Enhanced via efflux bypass mechanisms [90]
Multidrug resistance (MDR) association	Frequently associated with P-glycoprotein (P-gp) induction	Potential modulation and suppression of MDR pathways [91]
Systemic toxicity	Dose-limiting adverse effects	Reduced off-target exposure (preclinical evidence) [92]
Pharmacokinetic behavior	Rapid clearance and variable systemic exposure	Prolonged circulation and controlled release [93]
Combination therapy suitability	Limited by cumulative toxicity	Suitable for synergistic co-delivery strategies [94]
Translational status	Clinically established but toxicity-constrained	Preclinical evidence; requires clinical validation [95]

Table 3. Comparative evaluation of conventional chemotherapy and flavonoid-loaded nanostructured lipid carriers in terms of drug properties, tumor selectivity, cellular uptake mechanisms, resistance modulation, and translational status in non-small cell lung cancer.

6. Translational challenges and future perspectives

Encouraging preclinical outcomes, several problems delay the clinical translation of NLC-based flavonoid-based treatment, including challenges in large-scale manufacturing, long-term stability, regulatory complexities, and the absence of clinical validation. Future studies should focus on the development of standardized formulation protocols, complete pharmacokinetic reporting, and in vivo and clinical Study design [96-97]. The application of quality-by-design (QbD) principles, and advanced characterization techniques, will play an essential role in facilitating the transition of NLC-based systems from laboratory research to clinical application.

Manufacturing scalability and involves the initial challenge in the clinical translation of nanostructured lipid carrier (NLC)-based flavonoid therapies, which is the scale of manufacturing processes. Techniques optimized at the laboratory scale may not effortlessly translate to large-scale production without compromising critical quality attributes, such as particle size, polydispersity, drug loading, and release kinetics [98-99]. Batch-to-batch variability remains a significant concern, when complex lipid compositions and surface functionalization strategies are applied. Solving these challenges via scalable production methods, such as high-pressure homogenization and continuous manufacturing platforms, must be optimized under industrially relevant conditions. Establishing robust process controls is essential to ensure reproducibility and regulatory compliance [100].

Long-term physical and chemical stability are critical determinants of the clinical viability of NLC formulations. Lipid crystallization, drug expulsion, aggregation, and oxidative degradation can occur during storage, potentially altering therapeutic performance. [90] Surface-functionalized systems may further complicate stability owing to ligand detachment or protein denaturation. Future studies should emphasize systematic stability testing under the International Council for Harmonization (ICH) guidelines, including the evaluation of particle size distribution, zeta potential, encapsulation efficiency, and drug release profiles over extended storage periods [101-102.]

The regulatory landscape of nanomedicine remains difficult because nanocarriers are often evaluated under both pharmaceutical and nanotechnology-specific frameworks. Regulatory agencies require comprehensive physicochemical characterization, toxicological assessment, and justification of excipient selection. For flavonoid-loaded NLCs, the natural compound composition and potential batch heterogeneity add an additional layer of complexity. Regulatory guidance for lipid-based nanocarriers is still evolving, necessitating early engagement with regulatory bodies to align development strategies with approval requirements. A thorough evaluation of immunogenicity, biodistribution, and long-term safety is essential for clinical advancement [103-104].

Pharmacokinetic and biodistribution challenges involve a restricted understanding of in vivo pharmacokinetics and biodistribution, which is a significant problem in translation.NLCs demonstrate improved bioavailability in preclinical models, and species-specific differences in metabolism and nanoparticle clearance complicate their extrapolation to human systems.

Advanced imaging techniques, quantitative biodistribution studies, and physiologically based pharmacokinetic (PBPK) modeling are needed to accurately predict human exposure. The developed approaches will enable rational dose selection and support clinical trial design [105-106].

Clinical validation and trial design provide substantial preclinical evidence that clinical data regarding flavonoid-loaded nanostructured lipid carriers (NLCs) remain limited. The absence of clearly designed clinical trials limits the evaluation of therapeutic efficacy, safety, and patient outcomes. Initial clinical studies prioritize the establishment of safety, tolerability, and pharmacokinetic profiles, involving efficacy assessments in well-defined patient cohorts. Patient stratification, biomarker-driven endpoints, and combination therapy strategies may surge trial success and expedite clinical adoption [107].

The integration of quality-by-design (QbD) principles provides a systematic outline for addressing translational challenges. QbD emphasizes the identification of critical quality attributes (CQAs), critical material attributes (CMAs), and critical process parameters (CPPs) to ensure consistent product performance. By incorporating risk assessment tools, design of experiments (DoE), and control strategies, QbD facilitates robust formulation development and scalable manufacturing. This approach aids in regulatory approval by demonstrating process understanding and quality assurance, thereby accelerating the transition from bench to bedside [108-109].

Advanced analytical techniques are crucial for ensuring the translational success of NLC-based systems. High-resolution imaging, spectroscopy, and thermal analysis provide insights into the nanoparticle structure, drug–lipid interactions, and release mechanisms. Additionally, in vitro–in vivo correlation (IVIVC) studies and predictive modeling are essential for bridging preclinical and clinical outcomes. Continued refinement of characterization methodologies will increase confidence in NLC performance and support regulatory submissions [110].

Future research should focus on consistent formulation strategies, standardizing characterization protocols, and expanding clinical validation efforts. Interdisciplinary collaboration among formulation scientists, clinicians, and regulatory experts is critical for overcoming translational barriers. Emerging trends, such as personalized nanomedicine, smart lipid carriers, and stimulus-responsive NLCs, offer promising opportunities for next-generation cancer therapies. With systematic optimization and regulatory alignment, NLC-based flavonoid delivery systems hold significant promise for clinical translation. Although flavonoid-loaded nanostructured lipid carriers demonstrate considerable preclinical potential, challenges related to scalability, stability, regulatory approval, and clinical validation must be addressed. The integration of quality-by-design principles and advanced characterization techniques will be instrumental in advancing these nanocarrier systems toward safe and effective clinical application.[111-112] Figure 2: Translation of flavonoid based targeted therapy has undergone preclinical development, manufacturing, stability, pharmacokinetics, regulatory pathway and clinical translation, as have the important parameters of QbD and future perspectives.

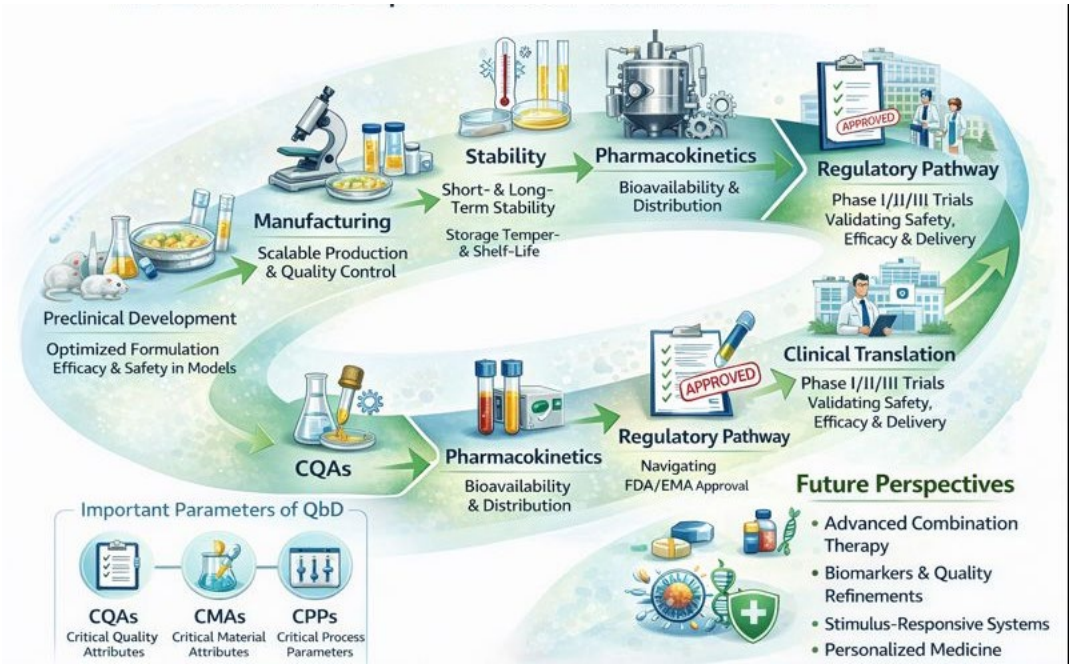

Figure 2: Translational roadmap for Flavonoid- loaded nlc in NSCLC

7. Conclusion

Nanostructured lipid carriers (NLCs) serve as sophisticated and effective platform for enhancing the therapeutic efficacy of flavonoids, mainly for non-small cell lung cancer (NSCLC). The application of NLCs for flavonoid delivery represents a promising advancement in the development of next-generation lung cancer treatments, as it enhances solubility, facilitates targeted delivery, and influences drug resistance mechanisms. Sustained interdisciplinary collaboration is imperative to transform these nanotechnological innovations into treatments that are clinically applicable.

Abbreviations:

ATP-binding cassette (ABC)

Hyaluronic acid (HA)

bovine serum albumin (BSA),

Design of experiments (DoE),

Enhanced permeability and retention (EPR),

International Council for Harmonization (ICH),

In vitro–in vivo correlation (IVIVC),

Multidrug resistance (MDR)

Nanostructured lipid carriers (NLCs)

Non-small cell lung cancer (NSCLC)

Declarations:

Ethical Approval: Not applicable. The article is a review and does not involve any studies with human participants or animals performed by the authors.

Consent to participate:

Not applicable. The article is a review and does not involve any human participants.

Consent to publish:

Not applicable. The article is a review and does not contain any individual person's data in any form.

Conflict of interest:

The authors declare no conflict of interest.

Clinical trial number:

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Data availability:

Data sharing is not applicable.

Reference:

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