ENGINEERING LIPID NANOCARRIERS FOR TARGETED DELIVERY OF RESVERATROL IN HEPATOCELLULAR CARCINOMA

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Abstract

Hepatocellular carcinoma (HCC) remains the predominant histological subtype of primary liver cancer and is characterized by high mortality, frequent late diagnosis, extensive molecular heterogeneity, and limited durable responses to systemic therapy. Resveratrol, a polyphenolic stilbene abundant in grapes, berries, and peanuts, has attracted major attention in HCC research because it modulates apoptosis, oxidative stress, inflammation, epithelial-mesenchymal transition, angiogenesis, autophagy, and oncogenic signaling networks including PI3K/Akt/mTOR, Wnt/β-catenin, NF-κB, and MAPK. However, the translational impact of free resveratrol is constrained by poor aqueous solubility, rapid metabolism, chemical instability, and very low systemic bioavailability, all of which limit intratumoral exposure and therapeutic persistence. Lipid nanocarriers including liposomes, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), nanoemulsions, micelles, and lipid-polymer hybrid nanoparticles offer a rational strategy to overcome these barriers through improved encapsulation, protection from degradation, prolonged circulation, controlled release, and tumor-selective accumulation. Emerging evidence indicates that lipid nanocarrier formulations enhance resveratrol stability, cellular uptake, and biological potency, and may enable combination treatment, ligand-directed targeting, and modulation of multidrug resistance and the tumor microenvironment in liver cancer. This review synthesizes current knowledge on HCC pathobiology, the anticancer pharmacology of resveratrol, the design principles of lipid nanocarriers, and the recent progress in resveratrol-loaded lipid systems relevant to HCC. It further discusses uptake mechanisms, intracellular trafficking, tumor microenvironment interactions, translational challenges, and future opportunities including stimuli-responsive systems, exosome-lipid hybrids, AI-assisted formulation design, and personalized nanomedicine approaches.

Keywords: *Hepatocellular carcinoma; resveratrol; lipid nanocarriers; tumor microenvironment; targeted delivery; nanomedicine.*

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1. INTRODUCTION

Hepatocellular carcinoma is one of the most consequential malignancies worldwide and accounts for the majority of primary liver cancers, with disease burden driven by chronic viral hepatitis, alcohol-associated liver disease, nonalcoholic fatty liver disease, cirrhosis, and progressive metabolic dysfunction. Despite major advances in surveillance, locoregional therapy, immunotherapy, and multikinase inhibition, many patients are still diagnosed at intermediate or advanced stages, and clinical outcomes remain compromised by recurrence, intrahepatic spread, extrahepatic metastasis, therapeutic resistance, and impaired liver (Singh et al., 2025; Singal et al., 2023). These realities have intensified the search for more selective, multitargeted, and biologically adaptable therapeutic platforms. Among naturally derived anticancer compounds, resveratrol has emerged as a particularly attractive candidate because of its broad pleiotropic activity across cancer-relevant pathways (Langdon, 2015). Experimental studies in HCC indicate that resveratrol suppresses proliferation, migration, and epithelial-mesenchymal transition, promotes apoptosis and cell-cycle arrest, regulates autophagy, attenuates inflammatory signalling, and can alter exosome secretion and oncogenic crosstalk within the tumor ecosystem (Wan & Hallajzadeh, 2025). Yet its clinical development has been impeded by pharmacokinetic liabilities, especially poor solubility, fast glucuronidation and sulfation, limited plasma persistence, and unstable tissue exposure (Stielow et al., 2023). Lipid nanocarriers provide a strong technological response to these obstacles because they can solubilize lipophilic molecules, shield cargo from premature degradation, modulate release kinetics, and enhance uptake into tumor and stromal compartments. In oncology, such systems also enable surface functionalization, co-delivery of multiple agents, and potential exploitation of tumor-associated transport pathways and vascular abnormalities. The uploaded outline appropriately positions this review at the intersection of HCC pathophysiology, resveratrol pharmacology, and lipid-based nanomedicine, with particular emphasis on recent formulation advances and translational prospects (Puri et al., 2025).

2. Global Burden and Clinical Challenges of HCC

HCC develops in a biologically complex background of chronic inflammation, fibrosis, cirrhosis, and regenerative nodules, producing marked interpatient and intratumoral heterogeneity. This heterogeneity shapes treatment response and complicates biomarker-guided decision making, especially when tumors differ in vascularity, metabolic adaptation, immune infiltration, stromal remodeling, and pathway activation (Barcena-Varela & Lujambio, 2021). Even when modern therapeutic options are available, curative resection and

transplantation are feasible for only a fraction of patients, while recurrence after local or surgical treatment remains common.

Systemic therapy for advanced HCC has improved, but the benefits are often incomplete and nonuniform. Tyrosine kinase inhibitors, immune checkpoint blockade, and combination regimens have extended survival in selected populations, yet many patients eventually develop resistance, treatment intolerance, or progressive liver dysfunction that limits continued therapy (Stühler et al., 2021). These constraints favor development of agents and delivery systems capable of improving tumor selectivity, reducing off-target toxicity, and attacking multiple malignant processes simultaneously (Manzari et al., 2021).

2.1 Limitations of Conventional Therapies

Conventional chemotherapy has historically shown limited value in HCC because hepatic tumors are intrinsically chemoresistant and often arise in cirrhotic livers with reduced tolerance for systemic toxicity. Multidrug resistance transporters, antiapoptotic signaling, altered redox biology, and hypoxic adaptation further undermine cytotoxic efficacy (Sadrinasab et al., 2025). In addition, poor vascular perfusion within some tumor regions and stromal barriers can restrict effective drug penetration. Targeted therapies and immunotherapies have transformed the field, but they also reveal major limitations. Resistance mechanisms include pathway reactivation, compensatory signaling, immune evasion, phenotypic plasticity, and immunosuppressive features of the tumor microenvironment . Consequently, adjunctive agents such as resveratrol and engineered carriers such as lipid nanoparticles are increasingly investigated as means to sensitize tumors, reshape microenvironmental responses, and improve pharmacological delivery (Rai et al., 2024).

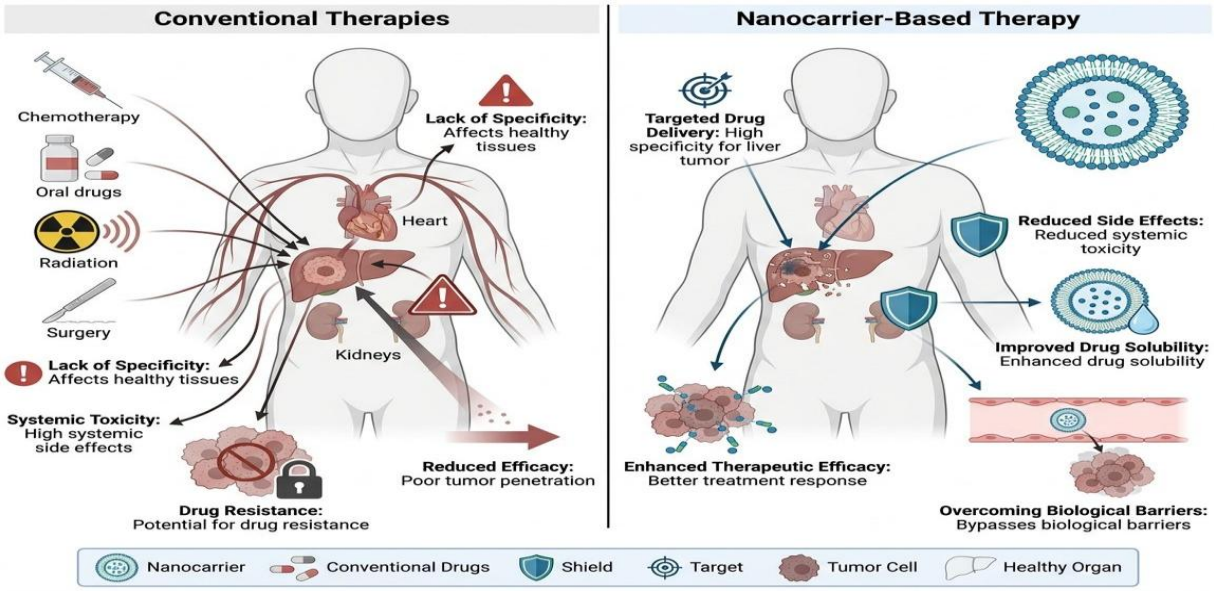

Fig 1: Schematic showing the limitations of conventional therapies.

2.2 Resveratrol as a Promising Anticancer Phytochemical

Resveratrol is a naturally occurring stilbene with well-documented antioxidant, anti-inflammatory, and antineoplastic activity across multiple disease contexts. In liver cancer models, it can regulate genes and proteins involved in survival, apoptosis, metastasis, and intercellular communication, making it appealing as a multitarget therapeutic scaffold rather than a single-pathway inhibitor (Bhuia et al., 2024). This broad mechanism profile is particularly relevant in HCC, where parallel signaling axes and tumor-promoting stromal interactions drive progression.

Preclinical work shows that resveratrol can reduce HCC cell proliferation, migration, epithelial-mesenchymal transition, and tumor growth while influencing exosome biology, autophagy, and β-catenin signaling. The ability of resveratrol to modulate oxidative stress and inflammatory signaling may also be highly relevant in HCC because liver tumorigenesis often emerges from chronic inflammatory injury and altered redox homeostasis. These properties justify continued interest in the compound even though free-drug pharmacology remains suboptimal (Le et al., 2026).

2.3 Rationale for Lipid Nanocarrier-Based Delivery

The principal rationale for loading resveratrol into lipid nanocarriers is pharmacokinetic and biopharmaceutical rescue. Encapsulation can increase apparent solubility, preserve the trans-isomer from degradation, reduce premature metabolism, improve residence time, and create sustained-release profiles that maintain therapeutically meaningful local exposure. For tumors such as HCC, lipid carriers may also improve delivery to hepatocytes, sinusoidal endothelium, macrophages, and tumor tissue through size-dependent biodistribution and membrane affinity (Kim et al., 2023; Yu et al., 2022). A second rationale is pharmacodynamic amplification. Lipid systems can increase intracellular uptake, alter endocytic trafficking, support co-delivery with chemotherapeutics or nucleic acids, and permit ligand-directed targeting against overexpressed receptors in liver tumors . This combination of formulation-enabled bioavailability and target engagement makes lipid nanocarriers especially attractive for repurposing phytochemicals with strong biological promise but weak systemic performance (Jacob et al., 2025).

3. Pathophysiology and Molecular Landscape of HCC

3.1 Etiology and Risk Factors

HCC usually arises on a background of chronic liver disease, most prominently hepatitis B virus infection, hepatitis C virus infection, alcohol-related injury, and nonalcoholic fatty liver

disease or steatohepatitis (Romão & Fonseca, 2021). These etiologies converge on chronic inflammation, hepatocyte death, compensatory regeneration, fibrogenesis, and genomic or epigenomic instability, together promoting malignant transformation. The increasing global role of metabolic dysfunction-associated liver disease has become especially important in countries where viral hepatitis control has improved (Ghazanfar et al., 2024). Cirrhosis remains a major predisposing condition, but HCC can also arise in noncirrhotic settings, particularly with HBV infection and metabolic liver disease. This etiologic diversity influences tumor biology, immune contexture, and therapy response, which helps explain why single-agent strategies often show inconsistent performance across patient populations . Effective therapeutic design therefore requires attention to both tumor-intrinsic mutations and disease-background biology (Sagnelli et al., 2020).

3.2 Tumor Microenvironment in HCC

The HCC tumor microenvironment comprises malignant hepatocytes, cancer-associated fibroblasts, endothelial cells, stellate cells, tumor-associated macrophages, lymphocytes, extracellular matrix components, cytokines, metabolites, and extracellular vesicles (Hao et al., 2021). This network supports angiogenesis, immune evasion, stromal remodeling, invasion, and resistance to systemic treatment . Exosomes are particularly relevant because they mediate transfer of proteins, nucleic acids, and lipids that can reshape adjacent tumor and stromal cells. Inflammatory and fibrotic cues in the liver create a pro-tumorigenic milieu even before overt carcinoma develops. Hypoxia, oxidative stress, acidic pH, and abnormal vasculature further influence nanoparticle transport and treatment response, making the HCC microenvironment both a barrier and an exploitable therapeutic target. Lipid nanocarriers are therefore attractive not only as passive drug reservoirs but as programmable systems capable of engaging microenvironmental features (Liu et al., 2024).

3.3 Key Signaling Pathways in HCC Progression

The PI3K/Akt/mTOR pathway is commonly activated in HCC and promotes survival, anabolic metabolism, growth, and resistance to apoptosis. Aberrant stimulation of this axis can arise from receptor tyrosine kinase signaling, loss of tumor suppressive control, or crosstalk with inflammatory and metabolic pathways (Zheng et al., 2025). Resveratrol has been reported across cancers to attenuate PI3K/Akt/mTOR signaling, supporting interest in its use as a multitarget modulator. The Wnt/β-catenin pathway is another major driver of HCC progression and is strongly linked to proliferation, stemness, immune escape, and metastatic behavior. In HCC models, resveratrol-associated effects on β-catenin nuclear translocation and pathway suppression have been observed, including through exosome-

related mechanisms . NF-κB and MAPK pathways likewise participate in inflammation, proliferation, stress adaptation, and survival, reinforcing the need for agents that can influence several signaling hubs at once rather than a single linear target (Qin et al., 2024).

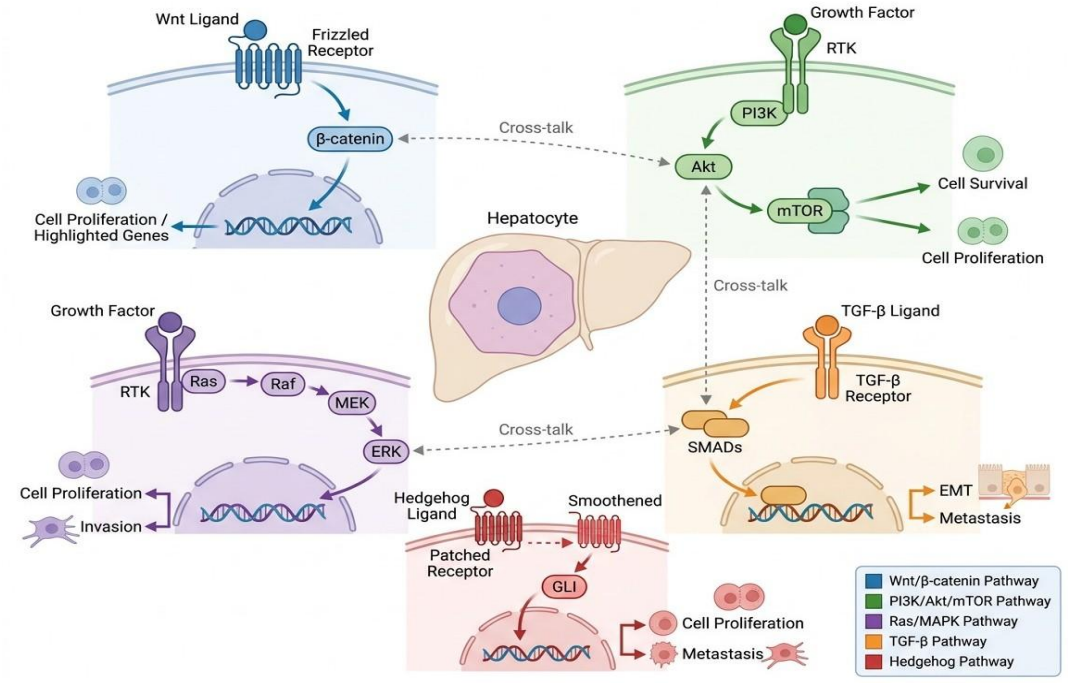

Figure 2 Key signaling pathways involved in hepatocellular carcinoma progression. Schematic illustration of a hepatocyte within liver tissue surrounded by major signaling pathways, including Wnt/β-catenin, PI3K/Akt/mTOR, Ras/MAPK, TGF-β, and Hedgehog. Distinct color-coding and directional arrows depict pathway activation, cross-talk, and their roles in regulating cell proliferation, survival, invasion, and metastasis.

3.4 Mechanisms of Drug Resistance in HCC.

Drug resistance in HCC reflects overlapping mechanisms including efflux transporter overexpression, epithelial-mesenchymal transition, cancer stem-like phenotypes, adaptive autophagy, compensatory signaling activation, impaired apoptosis, and immunosuppressive microenvironmental crosstalk. Extracellular vesicles further contribute by redistributing resistance-associated RNAs and proteins between tumor cells and stromal compartments (Zou et al., 2025). These mechanisms are dynamic and often emerge during therapy rather than existing as fixed baseline traits. Because resveratrol can influence oxidative stress, inflammation, autophagy, β-catenin signaling, and exosome biology, it is of interest as a chemosensitizing or resistance-modifying molecule. Lipid nanocarriers may strengthen this role by increasing tumor exposure and enabling co-encapsulation with standard drugs, thus potentially suppressing several resistance pathways simultaneously (Ladd et al., 2024).

4. Pharmacological Potential of Resveratrol in HCC Therapy

4.1 Chemical Structure, Sources, and Physicochemical Properties

Resveratrol is a polyphenolic stilbene typically present as trans-resveratrol in grapes, berries, peanuts, and red wine-derived products. Its aromatic structure and multiple hydroxyl groups support antioxidant reactivity but do not translate into favorable pharmaceutical behavior because the compound remains poorly water soluble and chemically labile under physiological and formulation conditions. These limitations are central to why delivery science is essential for translating its anticancer effects (Hsieh & Wu, 2010). After oral administration, resveratrol may be absorbed but undergoes rapid metabolic conversion, especially glucuronidation and sulfation, which sharply reduce the concentration of active parent compound in circulation . This mismatch between biological potency in vitro and limited exposure in vivo has been a recurring obstacle across therapeutic indications. Nanocarrier systems are thus intended not to replace its pharmacology but to make that pharmacology clinically reachable (Ahmad et al., 2022).

4.2 Anticancer Mechanisms of Resveratrol

Resveratrol induces apoptosis through regulation of mitochondrial pathways, caspase activity, proapoptotic and antiapoptotic proteins, and stress-responsive signaling networks. It also promotes cell-cycle arrest by affecting cyclins, cyclin-dependent kinases, and checkpoint regulators, thereby reducing proliferative expansion in tumor cells. In HCC specifically, reduced proliferation and migration following resveratrol treatment have been documented experimentally (Elshaer et al., 2018). The compound also exerts anti-angiogenic and anti-metastatic effects through interference with inflammatory mediators, epithelial-mesenchymal transition, extracellular matrix remodeling, and oncogenic signaling pathways. These properties are relevant to HCC because vascular invasion and metastatic dissemination are major determinants of poor outcome . Resveratrol's broad activity makes it appealing as a node-modulator in complex cancers where redundancy undermines single-target therapeutics (Hong et al., 2021).

4.3 Modulation of Oxidative Stress and Inflammation

Oxidative stress and chronic inflammation are deeply embedded in hepatocarcinogenesis, linking viral injury, lipotoxicity, fibrosis, and malignant transformation. Resveratrol can scavenge reactive oxygen species directly and alter endogenous antioxidant defense programs, while also suppressing inflammatory mediators and signaling cascades such as NF-κB (Liu et al., 2017). These actions may help blunt both tumor cell fitness and the pro-tumorigenic microenvironment. Evidence from nanocarrier studies outside oncology supports the view that encapsulated resveratrol can retain or enhance redox-modulating activity while

improving delivery efficiency. This is mechanistically important for HCC because redox imbalance contributes not only to tumorigenesis but also to therapeutic resistance and stromal adaptation (de Souza et al., 2021).

4.4 Synergistic Effects with Chemotherapeutics

Resveratrol has been widely explored as a sensitizer that may enhance response to chemotherapeutics or targeted agents by reducing survival signaling, suppressing inflammation, and modulating apoptosis or autophagy. Such synergy is particularly attractive in HCC, where conventional agents often produce partial and transient responses. Nanocarrier-based co-delivery further expands this concept by synchronizing biodistribution and release of resveratrol with partner drugs. Lipid nanocarriers are well suited for co-delivery because they can encapsulate hydrophobic compounds efficiently and be engineered for combination loading or surface targeting. For HCC, such designs may help reduce effective dose requirements, delay resistance, and improve the therapeutic index of standard agents (Castañeda et al., 2022).

4.5 Limitations of Free Resveratrol

The principal limitations of free resveratrol include poor aqueous solubility, rapid metabolism, low oral bioavailability, chemical instability, and inconsistent tissue retention. These factors mean that striking in vitro effects do not automatically translate into clinically relevant intratumoral concentrations . As a result, many promising observations remain preclinical. Formulation into lipid nanocarriers directly addresses these issues by improving entrapment, controlling release, and limiting premature loss of active drug. This formulation-centric strategy is one of the clearest examples of how nanomedicine can rescue a biologically powerful but pharmaceutically weak molecule (Summerlin et al., 2015).

5. Lipid Nanocarriers: An Overview

5.1 Classification of Lipid-Based Nanocarriers

Lipid nanocarriers encompass a broad family of systems including liposomes, solid lipid nanoparticles, nanostructured lipid carriers, nanoemulsions, micelles, and lipid-polymer hybrid nanoparticles . Although all use lipidic components to solubilize and transport hydrophobic cargo, they differ substantially in core architecture, payload distribution, surface chemistry, release behavior, and manufacturing complexity (Buse & El-Aneed, 2010). These distinctions are highly relevant for resveratrol because its stability and loading efficiency depend strongly on carrier composition.

Liposomes consist of phospholipid bilayers surrounding aqueous cores and are established platforms for drug delivery and surface functionalization . SLNs use solid lipids to create

relatively rigid matrices but may suffer limited drug loading due to crystalline packing . NLCs, by mixing solid and liquid lipids, reduce crystal perfection and generally improve loading capacity and controlled release for lipophilic compounds such as resveratrol (Subramanian, 2021).

5.2 Advantages in Cancer Therapy

Lipid nanocarriers offer several advantages in oncology, including biocompatibility, scalable fabrication, high affinity for hydrophobic drugs, reduced premature degradation, and the possibility of controlled or sustained release. Their dimensions often support prolonged circulation and tumor-associated accumulation, while surface modifications can further direct interaction with malignant or stromal cells (Lasa-Saracibar et al., 2012). These systems also provide opportunities for combination therapy and theranostic integration. For resveratrol specifically, lipid nanocarriers can preserve chemical integrity, increase apparent potency, and prolong biological action. In one nanostructured lipid carrier study, encapsulated resveratrol displayed high entrapment efficiency, stability in physiological solution, sustained release, rapid endothelial uptake, and greater potency than free resveratrol in restoring vascular responses . Although that work was not in HCC, it strongly supports the platform logic for liver cancer applications (Zhu et al., 2023).

5.3 Design Considerations

Key design considerations for resveratrol-loaded lipid nanocarriers include lipid composition, surfactant system, particle size, surface charge, encapsulation efficiency, release kinetics, and physical stability. Selection of solid and liquid lipids influences crystallinity and drug accommodation, while size and zeta potential affect colloidal behavior, biodistribution, and cellular uptake (Pimentel-Moral et al., 2018). For HCC, additional variables include liver tropism, RES uptake, protein corona formation, and compatibility with ligand-mediated targeting. Surface engineering is equally important because targeting ligands, PEGylation, charge tuning, or biomimetic coatings can modulate circulation, immunological recognition, and receptor-mediated endocytosis . In the context of HCC, relevant targets may include transferrin receptor, glypican-3-associated strategies, integrins, asialoglycoprotein receptor-related approaches, and tumor microenvironment-responsive cues (Zhang et al., 2018).

6. Resveratrol-Loaded Lipid Nanocarriers for HCC: Recent Advances

6.1 Liposomal Formulations

Liposomes are among the most intuitive carriers for resveratrol because phospholipid bilayers can efficiently incorporate hydrophobic polyphenols and support further functionalization . For HCC-oriented development, liposomes offer opportunities for passive tumor

accumulation, hepatic delivery, and co-loading with chemotherapeutic agents or nucleic acids (Jagwani et al., 2020). Their clinical familiarity is also advantageous when considering regulatory translation. However, conventional liposomes may face challenges such as drug leakage, oxidation of unsaturated lipid components, and instability during storage or circulation unless carefully optimized . Current formulation efforts therefore focus on cholesterol content, PEGylation, ligand attachment, and bilayer composition to enhance retention of resveratrol and improve liver tumor selectivity (Abishek et al., 2026).

6.2 Solid Lipid Nanoparticles

SLNs provide a more rigid lipid matrix than liposomes and can protect resveratrol from degradation while enabling nanoscale delivery . Their biocompatibility and relatively straightforward manufacturing make them appealing, especially for hydrophobic compounds (Ashfaq et al., 2023) . In oncology applications, SLNs may enhance intracellular delivery and improve sustained exposure compared with free drug. A limitation of SLNs is that highly ordered lipid crystallization can reduce loading capacity or expel drug during storage . This concern is especially relevant for resveratrol, which is why many investigators increasingly favor NLCs that deliberately introduce structural imperfections into the lipid matrix (Britto et al., 2026).

6.3 Nanostructured Lipid Carriers

NLCs are often regarded as the most promising lipid platform for resveratrol because they combine solid and liquid lipids to improve entrapment, stability, and controlled release. In a representative study, trimyristin-triolein NLCs loaded with resveratrol achieved a mean particle size of about 56 nm, a zeta potential of −25.6 mV, and entrapment efficiency above 97%, while sustaining drug release and improving potency relative to free resveratrol (Khan et al., 2024). These data strongly support the utility of NLCs for unstable hydrophobic compounds. Although this specific study focused on vascular dysfunction rather than HCC, its findings are directly informative for liver cancer nanomedicine because the same formulation advantages high loading, cellular uptake, preserved drug integrity, and sustained biological activity are precisely the features needed to improve resveratrol exposure in hepatic tumors. NLCs are therefore likely to remain central in future HCC-directed resveratrol formulation research (Beloqui et al., 2016).

6.4 Lipid-Polymer Hybrid Nanoparticles

Lipid-polymer hybrid nanoparticles combine a polymeric structural core with a lipid shell or interface, integrating the stability of polymers with the membrane compatibility of lipids . Such hybrids can offer improved mechanical robustness, tighter release control, and flexible

surface engineering compared with purely lipidic systems . For resveratrol, hybrids may be especially useful when co-delivery with another hydrophobic drug, siRNA, or imaging moiety is desired.

In HCC, the hybrid approach is conceptually attractive because it may reconcile long circulation with receptor-targeted uptake and controlled intracellular release . The challenge is to maintain scalability and biocompatibility while avoiding excessive formulation complexity that slows translation (Mukherjee et al., 2019).

6.5 Surface-Functionalized and Targeted Systems

Surface functionalization is a key next-step strategy for HCC-targeted resveratrol nanomedicine . Ligands such as transferrin, RGD peptides, aptamers, antibodies, or sugar-based motifs can improve receptor-mediated uptake by tumor cells or angiogenic endothelium . Because HCC is often molecularly heterogeneous, multivalent or adaptable targeting approaches may outperform single-ligand systems in future designs. Targeted lipid nanocarriers may also help reduce off-target distribution and improve the intratumoral concentration of resveratrol, which is especially important given the weak systemic bioavailability of the free compound. The greatest benefit may emerge when targeting is combined with controlled release and combination therapy rather than applied as a standalone engineering feature (Jiang et al., 2013).

6.6 Stimuli-Responsive Lipid Nanocarriers

Stimuli-responsive systems exploit local features such as acidic pH, elevated reactive oxygen species, enzymatic activity, or redox gradients to trigger cargo release preferentially within tumors . For HCC, such strategies are appealing because the tumor microenvironment differs from healthy liver tissue in hypoxia, metabolism, inflammatory tone, and extracellular matrix remodeling (Zhao et al., 2021). A resveratrol carrier that remains stable in circulation but discharges payload after entering the tumor could substantially improve therapeutic precision. The promise of stimuli-responsive lipid systems lies in coupling pharmacokinetic protection with conditional pharmacodynamic activation . This could be particularly valuable for resveratrol because minimizing premature leakage is essential for maintaining active compound before hepatic metabolism or systemic degradation occurs (Majumder & Minko, 2021).

6.7 Co-Delivery Systems

Co-delivery platforms seek to combine resveratrol with chemotherapeutics, kinase inhibitors, nucleic acids, or immunomodulatory cargo within a single nanocarrier . This strategy can synchronize biodistribution, improve ratio-controlled exposure, and leverage resveratrol’s

sensitizing effects against apoptosis resistance, redox adaptation, or inflammatory signaling. In HCC, where monotherapies often fail due to pathway redundancy, co-delivery is especially compelling. Lipid nanocarriers are inherently suited for this purpose because their composition can be tuned to accommodate multiple payload types or sequential release profiles . A future high-impact direction is rational co-formulation based on HCC subtype biology rather than empiric drug pairing alone (Nezhadi & Dorkoosh, 2022).

7. Mechanistic Insights into Lipid Nanocarrier-Mediated Delivery

7.1 Cellular Uptake Mechanisms

Lipid nanocarriers generally enter cells through endocytosis, including clathrin-mediated, caveolae-mediated, macropinocytic, and lipid raft-associated pathways, though the dominant route varies with size, charge, composition, and cell type . Endothelial and epithelial uptake studies with resveratrol-loaded NLCs show rapid internalization and broad cytoplasmic distribution without overt acute toxicity at active concentrations . For HCC, uptake behavior may differ between malignant hepatocytes, Kupffer cells, stromal cells, and endothelial compartments (Kazemi et al., 2022).

The role of membrane affinity is particularly important for lipid-based systems because interactions with lipid-rich microdomains can facilitate uptake even when surface charge is only modestly negative . Incorporation of liquid lipids such as triolein may further modulate membrane interaction and internalization . Such details matter because therapeutic success depends not just on accumulation in liver tissue but on effective intracellular delivery to disease-relevant compartments (Markovic et al., 2020).

7.2 Intracellular Trafficking and Drug Release

Once internalized, lipid nanocarriers traffic through endosomal and lysosomal pathways, where pH, enzymes, and membrane fusion processes influence release of resveratrol . A favorable formulation should protect the compound during circulation yet release it in a way that allows access to cytoplasmic, mitochondrial, nuclear, or signaling-relevant loci. Because resveratrol acts across multiple intracellular pathways, absolute nuclear delivery is not mandatory; sustained cytoplasmic availability may itself be therapeutically meaningful (Tung et al., 2011).

Drug release kinetics strongly shape pharmacological outcome. Sustained-release NLCs, for example, can preserve activity longer than free resveratrol, which is important when repeated high-dose administration is impractical or when tumor exposure is transient . For HCC, balancing stability with timely release remains a central engineering challenge (Gimondi et al., 2023).

7.3 Targeting the Tumor Microenvironment

Lipid nanocarriers can influence not only cancer cells but also the microenvironmental circuits that sustain HCC. By delivering resveratrol into endothelial cells, macrophages, fibroblasts, or exosome-producing compartments, these systems may reduce angiogenesis, inflammatory amplification, and prometastatic communication. This broader systems-level action may be one reason why resveratrol remains attractive despite its relatively modest potency as a free small molecule. The microenvironment-targeting concept is strengthened by evidence that resveratrol can alter exosome secretion and content in HCC cells, including effects associated with Rab27a, lncRNA cargo, autophagy, and β-catenin signaling . A nanocarrier that enhances delivery of resveratrol to exosome-regulating compartments could therefore have outsized influence on malignant crosstalk (Roma-Rodrigues et al., 2019).

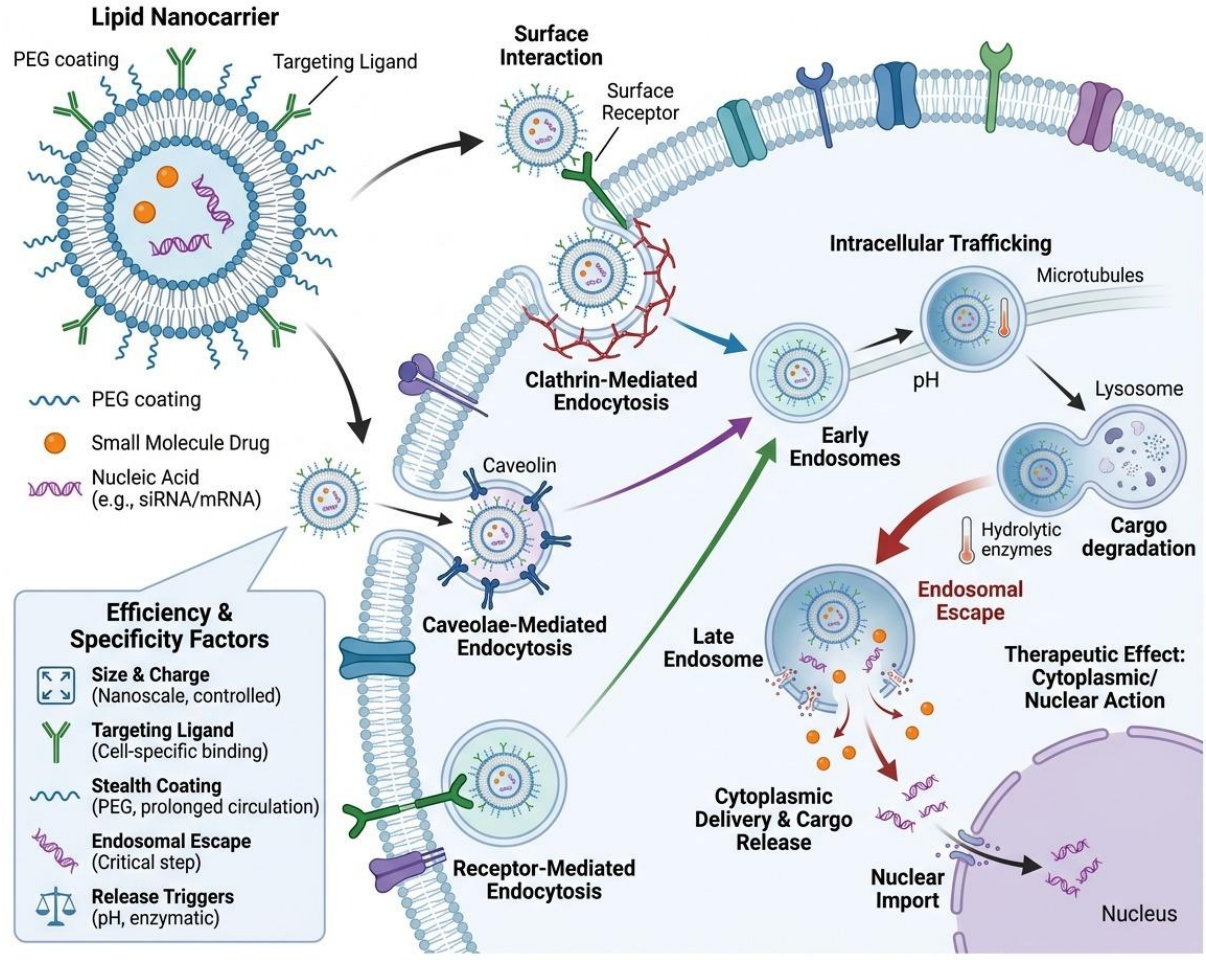

Figure 3. Mechanism of lipid nanocarrier-mediated drug and gene delivery. Schematic representation of a lipid nanocarrier encapsulating both a small molecule drug and nucleic acid, featuring surface modifications such as PEGylation and targeting ligands. The illustration highlights interaction with the cell membrane, multiple endocytic uptake pathways, intracellular trafficking, endosomal escape, and controlled release of therapeutic

payloads. Key physicochemical and functional parameters influencing delivery efficiency are indicated.

7.4 Role in Overcoming Multidrug Resistance

Multidrug resistance in HCC is driven by transporter-mediated efflux, antiapoptotic signaling, EMT, autophagy, stemness, and protective microenvironmental signaling. Lipid nanocarriers may mitigate resistance by bypassing some uptake barriers, increasing intracellular drug persistence, and enabling resveratrol-based sensitization or co-delivery. This is one of the strongest translational arguments for formulation-oriented development. Resveratrol itself has the right mechanistic profile for resistance modulation because it intersects with oxidative stress, inflammatory pathways, β-catenin activity, and autophagy. When delivered in lipid carriers, these effects may become more reliable and more compatible with clinically relevant dosing paradigms (Yang et al., 2024).

8. Emerging Strategies and Future Perspectives

8.1 Personalized Nanomedicine Approaches

Future HCC nanomedicine is likely to move toward patient-stratified design based on etiology, molecular subclass, immune landscape, fibrosis status, and prior therapy exposure . Resveratrol-loaded lipid nanocarriers may not be equally effective across all HCC phenotypes, and their rational use will probably depend on biomarkers linked to oxidative stress, β-catenin activation, inflammatory burden, or transporter expression. Personalized deployment could improve both efficacy and trial design. This perspective also argues for integrating formulation science with precision oncology datasets rather than developing carriers in isolation . The most impactful systems will likely be those matched to biologically defined subgroups rather than broadly generalized as universal liver cancer solutions (Fornaguera & García-Celma, 2017).

8.2 Integration with Immunotherapy and Gene Therapy

Immunotherapy combinations represent a major frontier because HCC treatment now relies increasingly on immune checkpoint inhibitors and antiangiogenic-immunotherapy regimens . Resveratrol’s anti-inflammatory and microenvironment-modulating actions may appear paradoxical in immuno-oncology, but carefully designed combinations could potentially reduce immune evasion, reshape suppressive stromal niches, or improve response durability. Lipid carriers are ideal platforms for such exploration because they can co-deliver nucleic acids, adjuvants, or small molecules. Gene therapy integration is equally promising . Lipid-based systems can be adapted for siRNA, miRNA, mRNA, or CRISPR-related

components, allowing resveratrol to be paired with gene-regulatory strategies that disable core HCC drivers or resistance pathways (Zafar et al., 2024).

8.3 AI-Driven Nanocarrier Design

Artificial intelligence and data-driven optimization are becoming increasingly relevant in nanomedicine for predicting formulation stability, loading, release, and biological interactions. For resveratrol-loaded systems, AI tools could accelerate selection of lipid ratios, surfactants, particle sizes, and targeting motifs based on multi-objective performance criteria such as stability, entrapment efficiency, liver tropism, and release under tumor-like conditions . This could shorten development cycles and reduce empirical screening burden. In HCC, AI-guided design could be especially valuable because successful formulations must reconcile tumor targeting with the unique clearance, metabolism, and macrophage surveillance functions of the liver. Such complexity makes purely trial-and-error formulation less efficient (Kantesaria & Panda, 2026).

8.4 Exosome-Lipid Hybrid Systems

Exosome-lipid hybrid systems have emerged as a compelling future direction because they combine the biomimetic communication properties of extracellular vesicles with the scalability and engineering flexibility of synthetic lipid nanoparticles . Given that resveratrol can modulate exosome secretion and cargo in HCC cells, hybrid systems may be especially relevant to this therapeutic space . They could potentially improve immune compatibility, cellular uptake, and tissue-selective delivery while also affecting pathological intercellular signaling.

However, major challenges remain in standardization, source selection, purification, loading reproducibility, and regulatory classification . Even so, the conceptual fit between exosome biology and HCC progression makes this an area likely to attract increasing attention (Abdel-Bar et al., 2025).

8.5 Clinical Translation Roadmap

For clinical translation, the field must move beyond proof-of-concept cytotoxicity and demonstrate reproducible manufacturing, long-term stability, biodistribution in orthotopic liver tumor models, pharmacokinetics of active parent resveratrol, safety in diseased liver, and superiority over free drug and relevant standard-of-care comparators. HCC-specific translation also requires models that capture cirrhosis, fibrosis, immune context, and vascular heterogeneity rather than relying solely on subcutaneous xenografts. Regulatory success will depend on formulation simplicity, scalable processes, robust characterization, and clinically meaningful endpoints . The most promising path may involve targeted or combination-loaded

NLCs or liposomes with strong mechanistic justification and biomarker-guided patient selection (Bozuyuk et al., 2024).

9. Conclusion

Resveratrol remains one of the most biologically versatile natural compounds investigated for HCC, with documented effects on apoptosis, proliferation, migration, oxidative stress, inflammation, autophagy, β-catenin signaling, and exosome-mediated communication. Yet free resveratrol is hindered by poor pharmaceutical performance, particularly low solubility, instability, rapid metabolism, and weak bioavailability. Lipid nanocarriers provide a highly credible solution to these barriers by increasing encapsulation efficiency, preserving active compound, improving cellular uptake, and extending biological activity. Among available systems, nanostructured lipid carriers appear especially promising because they balance loading capacity, stability, and controlled release for hydrophobic cargo such as resveratrol. The next phase of research should emphasize HCC-specific targeted formulations, combination therapies, clinically relevant disease models, and translationally rigorous pharmacokinetic and efficacy studies . If these priorities are met, lipid nanocarrier-mediated delivery of resveratrol could evolve from a compelling preclinical concept into a meaningful adjunct or component of precision therapy for hepatocellular carcinoma.

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11. Conflict of Interest

The authors declare that there are no conflicts of interest regarding the publication of this review.

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