Lipid Nanoparticles as Versatile Delivery Systems for Chemotherapeutics, Phytochemicals, siRNA, and microRNA in Hepatocellular Carcinoma: A Narrative Review

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ABSTRACT

Hepatocellular carcinoma (HCC) is one of the leading causes of cancer-related mortality worldwide. Despite advances in drug therapies, the efficacy of many anticancer drugs is limited by inadequate targeting, systemic toxicity, and the development of drug resistance. In recent years, lipid-based nanoparticles (LNPs), including liposomes, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs), have attracted attention as biocompatible and flexible delivery systems for therapeutic compounds. These nanocarriers, which can load a diverse range of compounds and nucleic acids, can improve the stability, bioavailability, and targeted delivery of therapeutic cargoes. This review summarizes the available evidence on the use of LNPs for the delivery of four major classes of anti-HCC therapeutic agents, including chemical drugs such as sorafenib and doxorubicin, plant phytochemicals such as curcumin, resveratrol, and celastrol, siRNA, and microRNA. It also examines the targeting and multiple delivery strategies for these agents and their role in enhancing treatment efficacy and overcoming drug resistance. Overall, preclinical evidence suggests that LNPs may have significant potential for the development of targeted and multimodal therapies in HCC by improving the delivery and accumulation of therapeutic agents in tumor tissue; however, challenges such as long-term safety, scalability of production, and efficiency of nucleic acid delivery still require further investigation.

Keywords: *Lipid based nanoparticles; Hepatocellular carcinoma; Phytochemicals; siRNA; microRNA; Drug delivery*

1. *INTRODUCTION*

Hepatocellular carcinoma (HCC) is the most common primary liver cancer and a leading cause of cancer-related death worldwide. Given that many patients are diagnosed at advanced stages, systemic therapy is an important part of HCC management. However, the efficacy of conventional drugs such as sorafenib is limited by drug resistance, systemic toxicity, low solubility of some compounds, and nonspecific distribution [1]. In recent years, phytochemicals and nucleic acid-based therapies have been considered as novel approaches to target different molecular pathways in HCC. Compounds such as curcumin, resveratrol, and celastrol have a diverse spectrum of antitumor activities, while siRNA and miRNA allow for the specific regulation of gene expression involved in proliferation, apoptosis, and drug resistance. However, the poor solubility and bioavailability of phytochemicals, as well as the instability, rapid degradation, and insufficient cellular uptake of siRNA and miRNA, have limited the therapeutic application of these agents [2, 3]. Lipid-Based Nanoparticles (LNPs) have been proposed as an effective strategy to overcome these limitations because of their biocompatibility, ability to load compounds with diverse physicochemical properties, and capacity for surface modification. Modern systems such as liposomes, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and LNPs can improve therapeutic efficacy by increasing the stability and bioavailability of the cargo and enabling targeted delivery. Furthermore, co-delivery of multiple chemical drugs with siRNA, miRNA, or phytochemicals enables simultaneous targeting of complementary pathways involved in tumor growth and drug resistance.[4]. Therefore, in this review, recent evidence on the use of lipid-based nanoparticles for delivering these four groups

of therapeutic agents, including targeting and delivery strategies, as well as the challenges ahead for their clinical development, is scrutinized.

2. Lipid Nanoparticles

LNPs are a class of drug delivery systems (DDSs) composed of lipids, phospholipids, cholesterol, or surfactants. They have found widespread application in drug delivery, natural compounds, and nucleic acids due to their biocompatibility, biodegradability, and ability to carry hydrophilic and hydrophobic compounds. These systems can improve the therapeutic efficacy of drugs by increasing drug solubility and bioavailability, protecting the cargo from degradation, controlling release, and enabling targeting. The most important lipid-based nanocarriers include liposomes, niosomes, solid lipid nanoparticles, and nanostructured lipid carriers [5, 6].

2.1. Liposomes

Liposomes are the best-known and oldest LNPs and consist of one or more phospholipid bilayers enclosing an aqueous core. This bilayer structure allows hydrophilic drugs to be located in the internal aqueous space and hydrophobic compounds in the lipid portion of the membrane. The most important advantages of liposomes include biocompatibility, biodegradability, reduced toxicity, and the possibility of surface modification with targeting ligands. However, their limitations include physical instability, leakage of some cargoes, and the possibility of rapid clearance by the reticuloendothelial system [7].

2.2. Niosomes

Niosomes are vesicular structures similar to liposomes, but they are primarily composed of nonionic surfactants and cholesterol rather than phospholipids. This composition has given niosomes an advantage over liposomes in terms of chemical stability and production cost in some cases. Niosomes can accommodate both hydrophilic and hydrophobic compounds and have attracted attention for delivering anticancer drugs and natural compounds by increasing drug stability and bioavailability. However, surfactant composition, particle size, membrane fluidity, and storage conditions can affect the stability and drug-loading rate of niosomes [8].

2.3. Solid Lipid Nanoparticles

Solid Lipid Nanoparticles (SLNs) consist of a lipid matrix that remains solid at room and body temperatures and are typically stabilized by a surfactant. The solid structure of these nanoparticles can protect the cargo from degradation and provide controlled, prolonged drug release. Additionally, the use of biocompatible lipids and the possibility of manufacturing by methods such as high-pressure homogenization have made SLNs attractive for development and scalability. One limitation of SLNs is the relatively regular crystalline structure of the lipid matrix, which can reduce the loading capacity of some drugs and cause gradual drug release from the matrix during storage [9, 10]

2.4. Nanostructured Lipid Carriers

Nanostructured lipid carriers (NLCs) are a newer generation of lipid nanoparticles developed to overcome some of the limitations of SLNs. In NLCs, a solid lipid is combined with a liquid lipid or oil, resulting in a more irregular lipid matrix. This structure provides more space for drug molecules and typically offers higher loading capacity and a lower likelihood of drug release during storage than SLNs. For this reason, NLCs are considered a good option for delivering hydrophobic compounds, anticancer drugs, and some phytochemicals [10].

3. Delivery of Chemotherapeutic (Chemical) Drugs

LNPs have been widely explored to improve the pharmacokinetics and tumor selectivity of established HCC chemotherapeutics. Sorafenib, an FDA-approved multi-kinase inhibitor and the mainstay of treatment for advanced HCC, has very low aqueous solubility. Encapsulation in solid lipid nanoparticles [11] and nanostructured lipid carriers [12] has been shown to increase its cytotoxicity against HepG2 cells and prolong systemic exposure relative to the free drug. Co-delivery strategies that combine sorafenib with doxorubicin in a single lipid or lipid-hybrid nanoparticle, such as N-acetylgalactosamine-modified pH-sensitive lipid nanoparticles or low-density-lipoprotein-decorated nanoparticles, have produced synergistic antitumor effects and markedly reduced systemic toxicity compared with either free drug or single-agent nano-formulations in HCC xenograft models [13]. These combination platforms reflect a wider trend: LNPs are not just passive solubilizers, but active facilitators of rational drug combinations that would otherwise be challenging to co-administer safely.

4. Delivery of Plant-Derived Phytochemicals

Phytochemicals such as curcumin, resveratrol, celastrol, and tanshinone IIA demonstrated pro-apoptotic, anti-proliferative, and anti-angiogenic activity against HCC cells, but their clinical use is limited by poor solubility, rapid metabolism, and low bioavailability. LNPs, particularly liposomes, solid lipid nanoparticles, and phytosomes, in which the phytochemical is complexed with phospholipids, substantially improve solubility and systemic exposure while enabling controlled release at the tumor site. Cationic resveratrol-loaded solid lipid nanoparticles have shown markedly higher tumor accumulation and greater antitumor efficacy than free resveratrol, attributed to favorable electrostatic interactions with the anionic cancer-cell surface [14]. Similarly, celastrol encapsulated in hyaluronic acid/cancer cell membrane-coated lipid nanoparticles achieved CD44-mediated targeting of HCC cells, inducing apoptosis while limiting off-target toxicity [15]. Co-assembly of two phytochemicals (e.g., resveratrol and curcumin) within a single liposome has also been reported to yield combined, and in some cases synergistic, antitumor activity [16]. Collectively, these findings support phytosomal and other lipid-based platforms as a practical route to translate promising but poorly bioavailable natural compounds into viable HCC therapeutics.

5. Delivery of Small Interfering RNA (siRNA)

siRNA can silence oncogenic or resistance-conferring transcripts with high specificity, but naked siRNA is rapidly degraded by serum nucleases, cleared renally, and cannot efficiently cross cell membranes. LNPs are the most clinically validated nucleic acid delivery platform, as evidenced by the approval of an LNP-formulated siRNA therapeutic for a liver disease. This success has directly informed HCC-targeted formulations. Cationic and ionizable lipid nanoparticles condense siRNA into nanoscale complexes that protect the cargo and promote endosomal escape. Ligand-decorated variants extend this specificity to tumor cells: cyclic RGD-peptide-conjugated, polyethylenimine-based lipid nanoparticles achieved integrin-mediated intracellular siRNA delivery and gene silencing in hepatocarcinoma cells [17]. More recent work has paired siRNA with machine-learning-guided ionizable lipid design: a library of fluorinated, reactive-oxygen-species-responsive lipids was optimized computationally, then functionalized with lactobionic acid for asialoglycoprotein receptor targeting, thereby enabling co-delivery of p53-restoring mRNA with Nrf2-silencing siRNA, restoring ferroptosis sensitivity and overcoming sorafenib resistance in preclinical HCC models [18]. These examples highlight both the maturity of LNP-siRNA technology and its increasing sophistication through rational, data-driven lipid engineering.

6. Delivery of microRNA (miRNA)

Beyond siRNA, LNPs have been used to restore tumor-suppressive microRNAs that are characteristically downregulated in HCC. MiR-122, a liver-specific miRNA frequently lost in HCC, was delivered using a cationic lipid nanoparticle formulation (LNP-DP1, composed of an ionizable aminolipid, phosphatidylcholine, cholesterol, and PEGylated cholesterol); this formulation restored miR-122 target-gene suppression by more than 95% in vitro and was preferentially taken up by hepatocytes and tumor cells in a murine HCC model in vivo [19]. Because many oncogenic pathways in HCC are driven simultaneously by loss of tumor-suppressor miRNAs and gain of oncogenic transcripts, several groups have pursued combined miRNA/siRNA co-delivery within a single LNP to achieve broader pathway modulation than either agent alone. As with siRNA, formulation composition (ionizable lipid structure, helper lipid, PEG density) critically determines encapsulation efficiency, endosomal escape, and hepatic selectivity, and remains an active area of formulation optimization.

7. Conclusion

Lipid nanoparticles have evolved from simple solubility enhancers into sophisticated, tunable platforms that can deliver chemotherapeutic drugs, plant-derived phytochemicals, siRNA, and microRNA to HCC by leveraging both intrinsic hepatic tropism and engineered active targeting. Preclinical evidence consistently shows improved bioavailability and tumor accumulation, and, particularly in co-delivery systems, synergistic antitumor efficacy compared with single-agent or free-drug controls. Continued advances in rational lipid design, active targeting, and multi-cargo formulation are expected to accelerate the translation of LNP-based therapeutics into clinical management of HCC.

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