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Unlocking the Potential of Phyto Nanotherapeutics in Hepatocellular Carcinoma Treatment: A Review

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Abstract: Hepatocellular carcinoma is the fifth leading cancer in related diseases most commonly in men and women. The curative treatments of liver cancer are short-listed, associated with toxicities and therapeutically. Emerging nanotechnologies exhibited the possibility to treat or target liver cancer. Over the years, to phytosome solid lipid nanoparticles, gold, silver, liposomes, and phospholipid nanoparticles have been produced for liver cancer therapy, and some evidence of their effectiveness has been established. Ideas are limited to the laboratory scale, and in order to develop active targeting of nanomedicine for the clinical aspects, they must be extended to a larger scale. Thus, the current review focuses on previously and presently published research on the creation of phytosomal nanocarriers for the treatment of hepatocellular carcinoma. In hepatocellular carcinoma (HCC), phytosomal nanotherapeutics improve the targeted delivery and bioavailability of phytochemicals to tumor cells, thereby reducing systemic toxicity and increasing therapeutic efficacy. In order to address the intricate molecular processes implicated in HCC, this strategy is essential.

Keywords: hepatocellular carcinoma, liver cancer, phytosome, nanocarrier, clinical trials

Introduction

Hepatocellular Carcinoma (HCC) constitutes a global burden, ranking as the third common disease of cancer-related to dies after colorectal and respiratory cancers. It was also the sixth diagnosed cancer, with an estimated 865,269 new cases and 757,948 deaths (GLOBOCAN 2022) from liver cancer occurring in the year 2022.[1,2] The projection indicates the number of new HCC cases per year will be rise by 55% from 2020 to 2040, potentially reaching 1.4 million diagnoses by 2040. Additionally, it is estimated that 1.4 million people will be could die from hepatic cancer in 2040, which would be a 56.4% increase from 2020.[3] Liver cancer and its incidence depend upon multiple factors such as demographic displacements, lifestyle changes, and environmental segments. Increasing incidences of obesity and metabolic disorders across the globe are laying a foundation for the prevalence of liver cancer in the future. Moreover, the regular use of some drugs typically used to treat hepatitis B and C is another cause seen rising chances for HCC.[4] HCC has limited treatment options and often is not discovered until a late stage, which can have a big impact on patient outcomes. Meanwhile, liver transplantation is a viable option for the treatment of HCC and as a finally, this treatment has become standardness for many patients with liver cancer. The use for liver transplant increased life expectancy and cured this disease.[5] The United States Food and Drug Administration (USFDA) has launched Sorafenib also known as Nexavar® (Bayer Pharmaceuticals), as a first-line chemotherapeutic agent for the treatment of hepatic between 2000 and 2007. Despite the other treatment options that have been relatively ineffective and associated with severe side effects, including chemotherapy or radiation therapy alone or in combination with surgical resection.[6] The management of HCC becomes intricate due to various reasons including the intricacies related to the disease itself and limitations present in conventional approaches. Furthermore, HCC had shown to be diagnosed late because of the clinical silence during the early period in many cases and frequently presented at an advanced stage which resulted from delay in treatment Moreover, the

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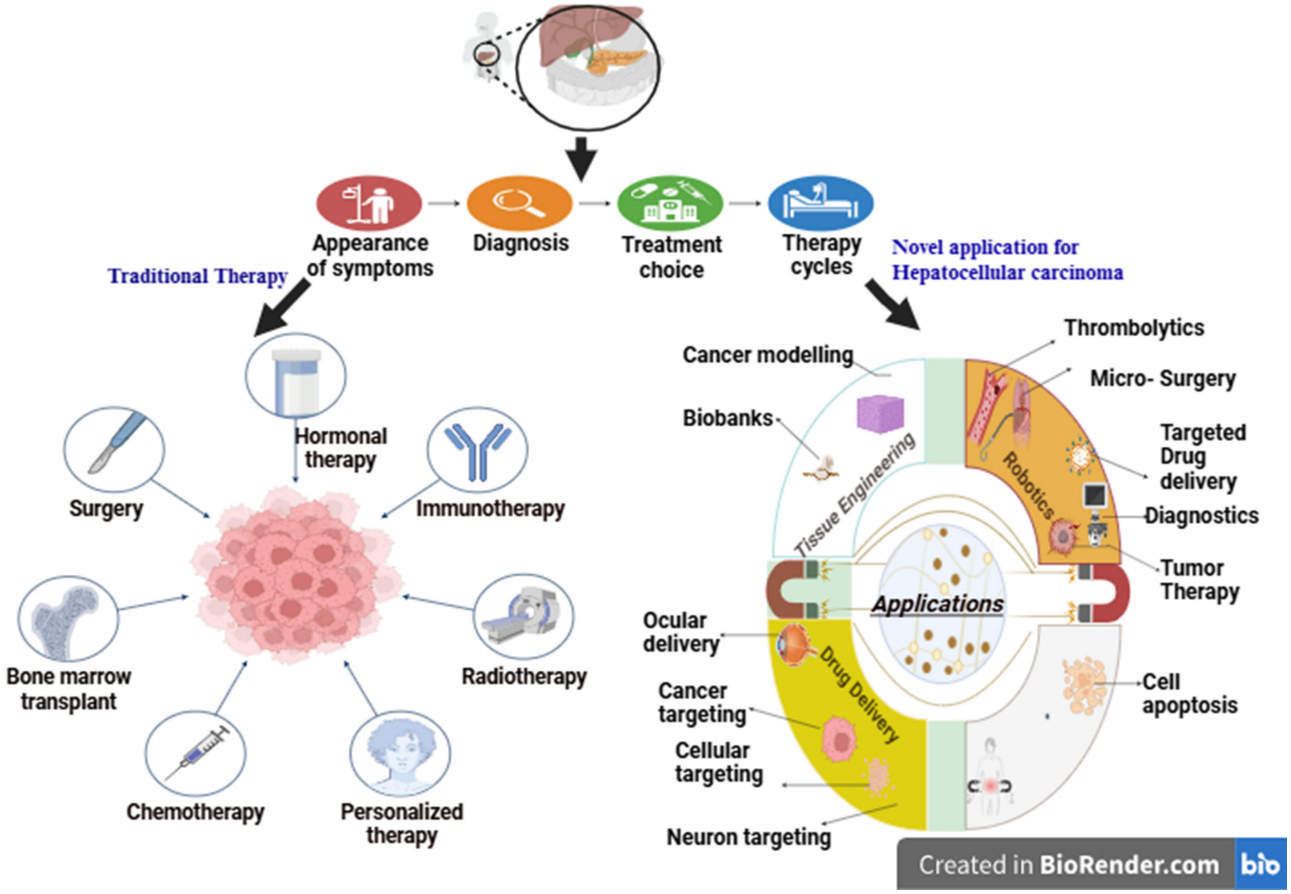
Graphical Abstract



outcome of the treatment may be affected by that its terminal diagnosis decreases therapeutic possibilities. HCC tumors are equally challenging and complicated as they exhibit heterogeneity.[7,8] The intrinsic variety of HCC tumors makes it difficult to create a single therapeutic strategy that works for every subtype. Since no two tumors are exactly comparable due to this heterogeneity, developing a therapeutic strategy that works for all tumors is challenging.[9] For HCC, a many numbers of patients are treated with traditional treatment modalities including surgeries, and hepatic transplantation, such as transarterial chemo-embolization (TACE). However, these techniques are restricted to the dimensions and location of the liver tumor and to more systemic liver function.[10] There are limitations to these treatments which point out the need for improved and more targeted therapies with better outcomes for patients. Thus, the toughest challenges in liver cancer treatments arise due to late diagnosis, tumor heterogeneity, and the emergence of resistance toward conventional therapy.[11] Exploring solutions to these difficulties demands novel investigative strategies to design a more personalized, effective, and adaptable treatment for the heterogeneous nature of liver cancer.[12]

Nanocarriers are important role in the treatment of HCC, the most common type of liver cancer. These nanoscale delivery systems increase the effect of therapeutic agents by improving stability, and bioavailability.[13] Tailored distribution is accomplished through surface changes that allow the nanocarriers to identify and bind to tumor-specific receptors.[14] Moreover, the specific microenvironment of tumors, such as their acidic pH or high enzyme levels, can be tailored by nanocarrier designers to ensure the precise and regulated release of the medication at the tumor location. This exact delivery minimizes systemic toxicity while optimizing the therapeutic effect. Additionally, because nanocarriers can encapsulate various medications, combination therapy which is frequently used to treat HCC can be used to

overcome drug resistance. Thus, advances in nanotechnology have the potential to significantly improve patient outcomes for hepatocellular carcinoma patients by providing more effective and less harmful treatment alternatives.[15] Phytosomal nanotherapeutics have emerged as available treatment option for hepatocellular carcinoma (HCC), even though they can boost the bioavailability and therapeutic efficiency of natural substances. Encasing phytochemicals in phospholipid vesicles, phytosomes are advanced drug delivery vehicles that improve the stability, solubility, and absorption of phytochemicals. For the treatment of hepatocellular carcinoma (HCC), where drug resistance, toxicity, and tumor heterogeneity usually present difficulties for traditional therapy, phytosomal formulations provide a number of advantages.

These nanotherapeutics can reduce systemic side effects while increasing the concentration of the active ingredient in the tumor microenvironment by specifically targeting liver cells.

Although phytosomal nanotherapeutics can increase the bioavailability and therapeutic efficiency of natural substances, they have emerged as a promising treatment option for hepatocellular carcinoma (HCC). Phytosomes are sophisticated drug delivery vehicles that enhance the stability, solubility, and absorption of phytochemicals by encasing them in phospholipid vesicles. Phytosomal formulations provide various benefits for the treatment of hepatocellular carcinoma (HCC), where drug resistance, toxicity, and tumor heterogeneity frequently pose challenges for conventional therapy.These nanotherapeutics can reduce systemic side effects while increasing the concentration of the active ingredient in the tumor microenvironment by specifically targeting liver cells. The phytosomes' phospholipid bilayer imitates the cellular membrane, which improves the medicinal medicines' ability to penetrate and be absorbed by cells.[15,16]

Moreover, curcumin, resveratrol, and silybin natural substances utilized in phytosomal formulations have anti-inflammatory, antioxidant, and anti-cancer qualities that can stop the formation of tumors, trigger apoptosis, and stop them from spreading.[17]

By modifying important signaling pathways involved in tumor progression and survival, phytosomal nanotherapeutics can overcome drug resistance mechanisms in HCC, as shown by recent research. Furthermore, when paired with traditional chemotherapeutics, these formulations have demonstrated synergistic effects that may lower the necessary dosage and related toxicity.[18] Therefore, phytosomal nanotherapeutics give hope for better results for patients with this difficult cancer by presenting a novel and promising. The number of research on HCC has expanded dramatically over the years, which is a reflection of both societal demand and scientific interest in better understanding the disease's genesis process and treatment. Nanotechnology facilitates the creation and modification of unique multifunctional nanomaterials for cancer therapy, diagnosis, or both at the same time in the modern technological era. Since HCC is the second most prevalent cause of cancer related death worldwide and a high percentage of deaths are caused by delayed diagnosis, the use of nanomedicine based systems with theranostic applications in the treatment of HCC has become increasingly popular.[19] Advances in nanomedicine have made it possible to identify unchecked proliferating tumor cells in vivo with greater sensitivity and specificity thanks to nano-based contrast agents. It has been demonstrated that one of the cutting-edge approaches to support the development of fresh therapeutic or preventative measures is nanomedicine.[20] As demonstrated above, the scientific community uses a variety of nanomaterials in cancer detection and treatment, particularly for HCC. There has been a greater consideration for NPs in targeted and controlled HCC therapy, as seen by the volume of papers over the last 20 years. We outlined the nanoparticles developed for HCC early diagnosis and treatment in this review; however, The USFDA-approved nanomedicine for HCC is currently available.

It is also noteworthy that the Japanese FDA has approved neocarzinostatin-loaded nanostructures and styrene-maleic acid co-polymers.[21,22]

Hepatocellular Carcinoma: An Overview

To fully understand the concept and evolution of HCC, it is imperative to investigate the fundamental molecular and cellular mechanisms that propel its growth. A variety of potential causes can combine to cause the initiation and later stages of HCC development. Among these possible contributing factors, some are well established including long-standing chronic inflammation/cirrhosis in the liver, viral hepatitis infections (such as infection with hepatitis B/C),[22,23] genetic changes or mutations, along with other environmental agents such as alcohol use and exposure to aflatoxin. In HCC, chronic inflammation of the liver like that due to viral hepatitis infection, or even the one resulting from NASH

(low-alcoholic hepatitis)-results in a favorable situation for malignancy advancement.[23] In addition to creating an environment conducive to neoplasm development, inflammation triggers an intricate chain of events favoring cellular overgrowth and subsequent stress from DNA damage combined with high potential susceptibility to genetic modifications that convert normal liver cells into cancerous ones.[24] Cirrhosis is a late-stage scarring of the liver caused by non-alcoholic steatohepatitis, viral hepatitis, or prolonged alcohol consumption (NASH), raises one's chances of developing liver cancer.

> The fibrotic and regenerative processes in cirrhosis create a hepatocarcinogenic environment per se because hepatic cells are more vulnerable to malignant transformation.

Infections with viruses such as hepatitis B and C cause most cases of liver cancer.[24,25] These viruses can insert their genetic combinations into the genome in infected cells, which can disturb several cellular processes and activate specific oncogenic pathways that lead to cancer. Liver cancer evolution also involves genetic mutations, either inherited or acquired in normal liver cells. Dysfunction of major genes for control of cell division, DNA repair processes, and signaling cascades may result in the unrestricted process of tumor growth.[25] Environmental factors such as chronic alcohol addiction and exposure to toxicity, also promote liver cancer formation through DNA damage and upregulation in tumor growth. By deciphering this complex dance, and the molecular highways and byways taken towards liver cancer development, researchers as well as those in clinical practice may be able to develop targeted treatments for therapy, early detection screenings, or even personal specific approaches to fight this devastating illness.[26]

Current Treatment Modalities for HCC and Their Limitations

As of right now, ablation medicines, systemic therapy, liver transplantation, and surgical resection are the available therapeutic options for HCC. Treatments other than surgical excision and liver transplantation can be considered palliative only. These procedures have the potential to be curative.[27] Meanwhile, systemic therapy can be given by a hepatologist or oncologist for advanced unresectable cases. The use of Atezolizumab plus bevacizumab and Durvalumab plus Tremelimumab is recommended for the among-line treatment of progressed HCC patients with CTP-A liver disease. Advance care planning is a critical component of palliative-intent therapy for all patients.[28] The toughest part about treating liver cancer is that there are very few curative measures. The estimated percentage of people who receive surgery or transplant for it is an extremely minute fraction. There are potential treatment constraints related to tumor size, liver function, and patient performance status. Ultimately, an interdisciplinary approach across multiple specialties is essential in developing causal.[29]

In Figure 1. Shows each of these varied modalities, surgical treatment, chemotherapy, aimed (molecule-blocking) treatments as well as radiation therapy all have a tremendous role in the management and care associated with HCC. Surgical procedures: The most commonly utilized surgical procedure is hepatectomy, an operation in which the diseased portion of a liver infiltrated with cancer is surgically removed. This surgery can be used more frequently against early-stage or small-sized cases of HCC.[30] Also, for some patients who present with liver-limited cancer and are amenable to transplantation, a curative option would be liver transplantation. Able to destroy the cancer cells within your liver using ablation therapy techniques such as radiofrequency ablation, and microwave ablation. Chemotherapy, composed of systemic chemotherapy and transarterial chemoembolization (TACE), is delivered systemically to every cancer cell in the patient's body or injected straight into the tumor by the hepatic artery.[31] Pembrolizumab targets certain molecules that help cancer cells grow, and/or make the immune system more effective at destroying cancer cells. High-energy X-rays are used in treatments like external beam radiation and stereotactic body radiation therapy (SBRT) to precisely target the tumor. While neighboring normal tissue is targeted for minimal damage, cancer cells will be eliminated as a result. Furthermore, the aforementioned strategies are frequently applied in concert to produce better outcomes and guarantee a high standard of living for those suffering from HCC.[32]

Need for Innovative Therapeutic Strategies

The limited efficacy of the existing therapies and an urgent requirement for robust, targeted results in innovative therapeutic action in HCC. The treatment landscape of HCC is a bleak, anti-cancer drugs and treatments are associated

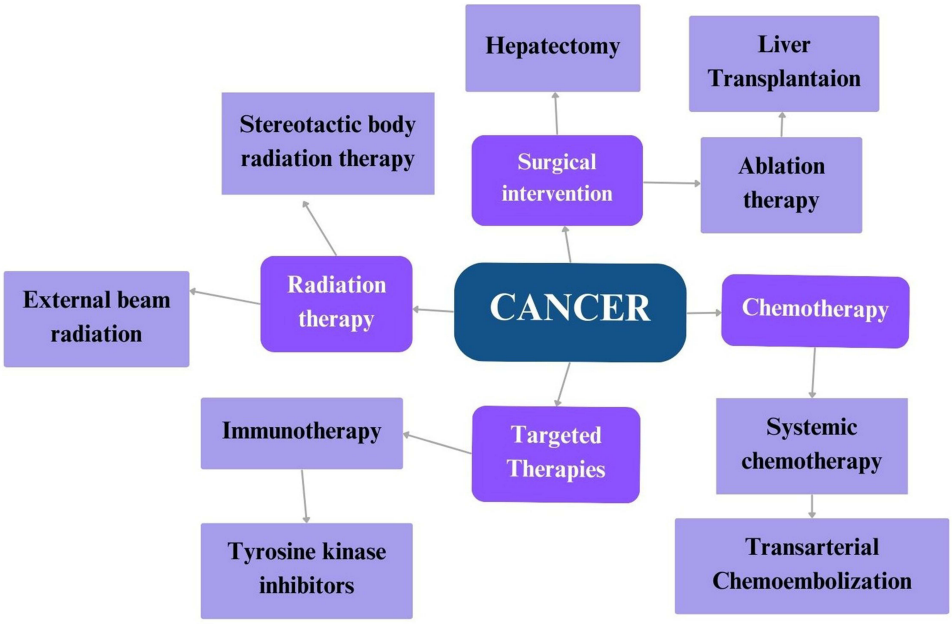


Figure 1 Recent advances in Cancer.

with very high mortality as the 5-year survival rate was only 10%.[33] The late-stage detection of the disease, tumor heterogeneity, and resistance to traditional therapies are among the main issues encountered while trying to cure HCC. The emergence of new therapeutic approaches is necessary to enhance HCC diagnosis and therapy. In this scenario, nanotechnology has shown to be extremely beneficial in research. This implies that the nanoparticles can be systemically functionalized to target specific receptors on HCC cells, which in turn offers great promise for increased effect and decreased systemic toxicity.[34] Furthermore, nanotechnology also provides the framework for creating targeted therapies aimed at selected genetic mutations/hallmarks or any molecular pathway responsible for causing HCC. The HCC also involves extensive research in the area of immunotherapy. Immunotherapy is promising in many cancers that have been tested such as liver HCC. Immunotherapy is currently a promising approach that may be used for a long time to treat HCC by stimulating the body's immune system to fight against liver cancer cells.[35]

Application of Nanotechnology for Hepatocellular Carcinoma Therapy

Nanotechnology has fundamentally changed the hepatocellular carcinoma (HCC) treatment paradigm, which provides novel approaches that both lower side effects and increase treatment success. The creation of nanocarriers, manufactured particles intended to transport medications directly to cancer cells is the main way that nanotechnology is applied in HCC therapy. These nanocarriers, which have different features that make them appropriate for different therapeutic purposes, include liposomes, dendrimers, and polymeric nanoparticles.[36] The capacity of nanocarriers to enhance the pharmacokinetics and pharmacodynamics of anticancer medications is one of their main benefits. Drug problems like poor solubility, instability, and rapid degradation are greatly reduced when medications are encapsulated within nanocarriers. Additionally, because of its encapsulation, the therapeutic drugs can be released gradually and under control, maintaining a constant medication concentration at the tumor site throughout an extended period.[37] Targeted delivery is a significant benefit of nanotechnology in HCC treatment. Nanocarriers can be functionalized with ligands or antibodies that bind specifically to receptors overexpressed on HCC cells, such as EGFR or glypican-3 (GPC3). This focused strategy minimizes the influence on healthy liver tissue and other organs, hence decreasing systemic toxicity and side effects often associated with conventional chemotherapy.[38]

Additionally, nanocarriers can be engineered to react to specific aspects of the tumor microenvironment, such as the high amounts of enzymes or acidic pH present in malignant tissues. This responsiveness makes sure that medications are released mostly around the tumor, improving the local therapeutic effect and protecting healthy cells in the process.[39]

Nanotechnology not only makes medication administration possible, but it also makes multimodal therapy possible by enabling the co-delivery of several therapeutic agents. Combination therapy is made possible by this, and it can help with the problem of medication resistance that is frequently seen in HCC treatment. For instance, gene therapy medicines and chemotherapeutic medications can be delivered by nanocarriers concurrently, creating a synergistic effect that increases treatment efficacy overall.[40]

Moreover, theranostics the application of nanoparticles in imaging and diagnostics—offers a double advantage. Through accurate medication delivery, real-time monitoring of therapy response, and tumor visualization, these nanoparticles can help tailor and optimize treatment plans for individual patients.[41]

Phytosomes: Concept and Characteristics

Phytosomes are sophisticated nanocarriers designed to improve the effectiveness and bioavailability of phytochemicals, or medicinal molecules obtained from plants. These cutting-edge delivery methods are specifically made to get over the drawbacks of many phytochemicals' quick metabolism and low absorption.[42] By attaching phytochemicals to phospholipids, such as phosphatidylcholine, a process known as phytosome formation is achieved. This creates a complex that resembles the natural cell membrane and enhances the solubility and absorption of the bioactive substances.

Phytosomes are distinguished structurally by their special formation, in which the hydrophilic phytochemical and the hydrophobic phospholipid create a combination.[43] As a result, the structure becomes more compatible with biological membranes, greatly improving the active ingredient's distribution. One of the main structural components of phytosomes is the spherical vesicle. For the transport of drugs, phytosomal nanocarriers have many beneficial features. They have better permeability and solubility, which are essential to improving the poorly soluble oral bioavailability of phytochemicals. Phytosomes are also a good fit for medicinal applications because of their great biocompatibility and minimal toxicity.[44]

The complexation of a phytochemical with a phospholipid molecule is the mechanism by which phytosomes are formed. Solvent evaporation techniques, in which the phytochemical and phospholipid are the phytosome complex produced by dissolving it in an appropriate solvent and letting it evaporate are typically used to aid in this process.[45] Because the resultant complex is more lipophilic than the original phytochemical, it can pass through biological membranes more easily. The complexation of a phytochemical with a phospholipid molecule is the mechanism by which phytosomes are formed. Solvent evaporation techniques, in which the phytochemical and phospholipid are dissolved in a solvent and evaporated to create that phytosome complex, are typically used to aid in this process.[46] Because the resultant complex is more lipophilic than the original phytochemical, it can pass through biological membranes more easily. When it comes to drug distribution, phytosomes are superior to conventional formulations in several ways. First off, a larger percentage of the prescribed dose will reach systemic circulation thanks to their increased bioavailability, which improves therapeutic results. Because of their structural resemblance to cell membranes, phytosomes can integrate and transport across biological barriers more effectively. By minimizing adverse effects and lowering the required dosage, this targeted administration offers a safer and more effective medicinal use.[47] Moreover, phytosomes have sustained release qualities that lower the frequency of administration and maintain therapeutic drug levels for prolonged periods. This is especially helpful for long-term treatments needed for chronic diseases. Furthermore, phytosomes can be engineered to include several active substances, opening the door to combination treatments for complicated illnesses with diverse pathologies. In phytoconstituents flavonoids are interesting compounds consisting of phenolic structures and are found in various fruits, vegetables, stems, roots, flowers, wine, and tea. Flavonoids exhibit a variety of biological properties, such as anti-inflammatory, antibacterial, anti-cancer, and antioxidant properties. The solubility of flavonoids may be a significant factor in their medicinal efficacy.[48] The low solubility in water and minimal intestinal retention which reduces the degree of absorption, humans hardly suffer from acute toxicity caused by the consumption of flavonoids except in rare cases of allergy cases.[49]

To deliver higher absorption and bioavailability, a patented method known as Phytosome uses phospholipids to facilitate the preparation of standardized extracts. Phytosomes are sophisticated herbal remedies that are formed by attaching specific ingredients from herbal extract on top of phosphatidylcholine which enables the new product to be

assimilated effectively and as a result, produce more therapeutic effects as compared to any other ordinary form of medicine.[50]

Phytosomes are lipid-compatible micelle-like molecular aggregates. Researchers have focused on this delivery system due to its controlled release, maximized therapeutic efficacy, minimized side effects, ease of manufacture, stability of the medication, protection of the stomach from luminal enzymes, and drug transport across biological barriers. Nanoparticles contain flavonoids and phospholipids.[51,52] Phospholipid is a type of compound lipid that serves as a significant component of the biomembrane as well as a precursor to platelet activation factor arachidonic acid and secondary messengers involved in signal transduction. Phospholipids as a components of the biomembrane have a high level of biocompatibility and hence make ideal drug delivery carriers for drug transport across the biological barrier.[53] Additionally, the polar and hydrogen bonding physicochemical properties of phospholipids interact with the respective bioactive/flavonoids for the formation of a complex.[54] It has been noted that the soluble complex of phospholipid enhances water solubility, permeability, stability, and targeting ability which in turn enhances oral bioavailability.[55]

Phytosomal Nanocarriers for Liver Cancer Therapy

Thus, it is necessary to ascertain the effect of resveratrol and thymoquinone individually and in combination on HepG2. Estimates were made for morphological alterations, cell death, caspase-3 activity, glutathione, and malondialdehyde levels. Thymoquinone and Resveratrol were shown to have IC50 values HepG2 anti-tumor action. The vitality of the cell did not decrease. Thymoquinone and resveratrol therapy increased caspase-3 enzyme activity and decreased malondialdehyde levels in comparison to the control group.[56] The accumulating evidence has shown that EGCG, the author said about altering these findings described in the literature in terms of the possible involvement of epigallocatechin-3-gallate in the HCC treatment.[56,57]

Active Targeting Based Phytosomal Nanocarriers

Active targeting of liver cancer for phytosomes involves the use of targeting ligands or proteins that precisely bind to receptors overexpressed on liver cancer cells, allowing for tailored delivery of the beneficial substances. It has been demonstrated that using this strategy will minimize off-target effects while increasing therapeutic efficacy and drug delivery.[58] The transferrin protein, which binds to the overexpressed transferrin receptor (TFR) on liver cancer cells, is one of the most widely employed targeted ligands in liver cancer therapy. It has been demonstrated that transferrin-conjugated phytosomes attach to TfR selectively and deliver their cargo to liver cancer cells, increasing the effectiveness of treatment.[59] Yasmiwar et al work, for instance, showed the potential of this strategy for liver cancer therapy by showing that transferrin-conjugated quercetin phytosomes dramatically decreased erythema, redness, itching, and inflammation in a mouse model of liver cancer. The folate protein, which binds to the overexpressed folate receptor (FR) on liver cancer cells, is another targeted ligand utilized in liver cancer therapy. It has been demonstrated that folate-conjugated phytosomes bind to FR selectively and deliver their cargo to liver cancer cells, increasing the therapeutic efficacy.[60]

In particular, a study by Moradi Marjaneh et al showed the potential of this strategy for liver cancer therapy by showing that folate-conjugated curcumin phytosomes significantly lowered tumor development and metastasis in a mouse model of liver cancer.[61] Other targeting ligands, including as lactoferrin (LF) and galactosylated-chitosan, have also been employed in liver cancer therapy in addition to transferrin and folate. Galactosylated chitosan targets ASGP and GA receptors, whereas LF exhibits intrinsic targeting effect for liver cancer cells by attaching to LDL-related protein receptors. These targeting ligands have been found to boost tumor-targeting capabilities, limit contact with human tissue, and decrease opsonization and fast clearance of nanoparticles, leading to enhanced therapeutic efficacy and safety.[62] To sum up, the process of actively targeting liver cancer with phytosomes entails the utilization of proteins or ligands that bind to receptors that are overexpressed on liver cancer cells. This allows for the targeted delivery of bioactive chemicals. It has been demonstrated that using this strategy will minimize off-target effects while increasing therapeutic efficacy and drug delivery.[63] Among the targeting ligands used in liver cancer therapy are transferrin, folate, lactoferrin, and galactosylated chitosan. Studies have shown that these ligands improve tumor-targeting capacity, decrease interaction with bodily tissues, and decrease opsonization and rapid clearance of nanoparticles, all of which improve therapeutic efficacy and safety.[64]

Galactosylated Ligands

Because hepatocytes exhibit high levels of asialoglycoprotein receptors (ASGPR), an is essential for successful liver targeting. Due to these receptors' strong affinity for galactose residues, medications and treatments can be delivered to the liver with selectivity. The purpose of this work is to investigate the role that galactosylated ligands play in liver targeting, as well as the mechanisms and clinical uses of these compounds. Galactosylated ligands utilize the high expression of ASGPR on hepatocytes. Particular receptors called ASGPRs are mostly present on the surface of liver cells.[65] The galactose residues found on galactosylated ligands bind these receptors with a strong affinity. Galactosylated ligands attach to ASGPRs upon delivery, promoting receptor-mediated endocytosis. Through this process, the ligand-receptor complex is internalized by hepatocytes, enabling the targeted delivery of medications to the liver. The liver is essential for several physiological processes, including metabolism and detoxification.[66] Therapeutics can be delivered to the liver with precision to maximize effectiveness and reduce side effects. Galactosylated ligands have proven to be clinically relevant in the treatment of liver illnesses, including metabolic disorders, liver cancer, and hepatitis. They make it possible to deliver medicine, nucleic acids, and imaging agents to hepatocytes selectively, which enhances therapeutic results and lowers systemic toxicity.[67]

Lactobionic Acid Ligand

Lactobionic acid (LBA) is an unique ligand known for its exceptional ability to target the liver, making it a crucial component in drug delivery systems aiming for hepatic targeting. This one-page document aims to highlight the significance of LBA in liver targeting, elucidating its mechanism of action and providing references for further exploration.[68] LBA possesses a dual functionality owing to its structure, which combines the sugar moiety (lactose) with a carboxylic acid group. This unique structure allows LBA to interact specifically with hepatic receptors, particularly the asialoglycoprotein receptors (ASGPRs) abundantly expressed on the surface of hepatocytes.[69] The LBA-conjugated drugs or nanoparticles selectively bind to ASGPRs, facilitating their internalization via receptor-mediated endocytosis into hepatocytes. This technique reduces systemic exposure and off-target effects by efficiently delivering medicinal drugs directly to the liver. LBA's liver-targeting potential is extremely important from a therapeutic standpoint in a variety of disease contexts. For example, LBA-based formulations have demonstrated encouraging outcomes in the treatment of liver illnesses, including cirrhosis, hepatitis, and liver tumors, in the field of hepatology.[70] Additionally, by extending the duration of flow and decreasing clearance rates, LBA conjugation improves the pharmacokinetic information of medications, maximizing therapeutic efficacy and minimizing side effects. Furthermore, hepatospecific antagonists such as LBA have been investigated for use in diagnostic imaging techniques to improve the visualization of the liver shape and function.[71]

Glycyrrhetinic Acid (GA) Ligands

The natural triterpenoid compound is derived from licorice root it's a GA (Glycyrrhiza glabra). Its pharmacological properties, particularly its liver-targeting abilities, are important field of drug delivery technology. The GA is characterized by its pentacyclic structure and carboxylic acid moiety. This unique structure enables its interactions with hepatocytes, making it an ideal ligand for liver targeting.[72] GA exerts its liver-targeting effects primarily through the recognition and binding to the hepatocyte membrane receptors, such as the glycyrrhetinic acid receptor (GAR). The liver-targeted properties of the GA have been extensively utilized including nanoparticles, liposomes, and micelles. These GA-conjugated delivery systems offer enhanced drug accumulation in the liver, leading to improved therapeutic outcomes and reduced systemic side effects.[73] GA-based drug delivery systems hold great promise for the treatment of various liver diseases, including viral hepatitis, liver fibrosis, and hepatocellular carcinoma. Moreover, GA conjugation enhances the efficacy of existing drugs while minimizing their dose-dependent toxicities. GA ligand serves as a versatile tool for achieving liver targeting in drug delivery applications. Its unique properties offer new opportunities for the development of effective therapies for liver-related disorders, ultimately improving patient outcomes.[74]

Bile Acid Receptor Targeting Ligands

Ligands have been given considerable focus for their application in liver targeting because of the liver's function in bile acid metabolism and regulation.[75] FXR is a receptor expressed mainly in the intestine involved in the synthesis,

transportation, and metabolism of bile salts. Some examples of ligands include obeticholic acid (OCA) that have proved effective in conditions including primary biliary cholangitis (PBC) and non-alcoholic steatohepatitis (NASH) through balancing of bile acids. OCA is semi semi-synthetic bile acid derivative that is a selective agonist of FXR and requires genes that are associated with the synthesis of bile acid, transport, and inflammation.[76] The G protein-coupled receptor (GPCR) expressed to the liver, intestine, and other tissues mediates bile acid signaling to regulate metabolic pathways. Ligands like INT-767, a dual TGR5 and FXR agonist, exhibit potential in metabolic disorders including diabetes, obesity, and liver diseases. Activation of TGR5 promotes bile acid-dependent energy expenditure, glucose homeostasis, and anti-inflammatory effects in life.[77] Liver targeting with bile acid receptor ligands is crucial for addressing various liver diseases, including cholestatic liver diseases, NASH, and liver fibrosis. Targeted delivery to the liver enhances therapeutic efficacy while minimizing off-target effects, improving patient outcomes. Bile acid receptor ligands offer a promising approach for precision medicine in liver disorders by modulating bile acid signaling pathways.[78]

Stimuli-Responsive Phytosomal Nanocarriers

Targeted drug delivery systems have emerged as huge approaches in the treatment of liver cancer, offering enhanced efficacy, and improved patient outcomes. The targeted galactose–modified pH-sensitive noises for controlled delivery of tanshinone II to treat HCC.[79] Results showed that noisome formulations improved the targeted drug delivery to HCC cells because of galactose ligand moiety affinity for the ASPG receptor overexpressed on HCC cells. The targeted delivery of niosomes improved the dissolution performance of a drug in the acidic medium of hepatic carcinoma cells. The drug dissolution enhanced the inhibitory and apoptosis effect on HCC cells and confirmed the prepared formulation's anticancer effect.[80] The targeted formulations also improved the prolonged circulation time within the blood circulation by enhancing the AUC of the drug. Findings suggest that vesicle formulation supporting galactose moiety could enhance the targetability and anticancer effect of tanshinone II on HCC.

Targeted delivery systems specifically deliver therapeutic agents to liver tissues.[81] This specificity minimizes off-target effects and maximum activity of drugs at the location of the tumor. Jianzhong et al concluded that targeted two engineered lipid nanocarriers using two aptamers A54-PEG-SLN/OXA, and A15-PEG-SLN/SAL sequential therapy for liver cancer cells. Developed nanocarrier with aptamer A54-PEG-SLN/OXA improved the targetability with enhanced anticancer effect on BEL-7402 hCC cell lines. Another aptamer-based nanocarrier A15- PEG-SLN/SAL enhanced the targetability and and inhibited tumour growth. Results suggest that aptamer-conjugated nanocarrier is specifically targets cancer cells and enhances the effect on HCC cells.[82]

Following intracellular uptake, the micelles showed the disulfide bond cleavage via a higher GSH level thus enhancing the cytotoxicity and apoptotic effects. The micelles displayed prolonged blood circulation time enhanced bioavailability and drug accumulation within liver cancer cell lines.[83] The micelles inhibited tumor growth and enhanced survival time in a mice-bearing xenograft model. This Study shows that micelles' dual functionality could enhance the targetability, cytotoxicity, and bioavailability of tanshinone IIA. The aptamer (L5) conjugated nanoparticle-loaded paclitaxel and studied its effect on HCC targeting neoplastic hepatocytes. The L5 functionalized paclitaxel nanoparticles interacted with two cell surface receptor biomarkers.[84] The developed nanoparticles internalized within the target site via clathrin-mediation endocytosis following interaction.[59] Upon internalization, the nanoparticles produced an anticancer effect via MAPK activation increased ROS lipid peroxidation, and induced apoptosis of the nucleus. Results suggest that the site-specific delivery of prepared nanocarrier could provide a promising approach for HCC treatment. The (EGCG) functionalized chitin polymer matrix was synthesized.[85] The ionic crosslinked CE-loaded honokiol (HK) NPs possessed size, zeta potential, and morphology. To further assess the CE-HK NPs, and that results were compared with free HK. CE-HK NPs can significantly suppress the HepG2 cells for proliferation in G2/M phase and cause the reduction in mitochondrial membrane potential. Non-spherically symmetrical Gd-based CE-HK NPs hindered the tumor growth.[86] The apigenin-loaded nanoparticles and studied their delayed effect on the development of HCC. This work showed that apigenin nanoparticles produced considerable availability in the blood and liver following administration.[87] Following administration, the apigenin-loaded nanoparticles sustained the apigenin release in HCC cell lines and chemical-induced carcinogenesis in animals. The study concludes that apigenin has an anticancer potential and, thus, could be utilized in combination with other MDR inhibitors to provide a better anticancer effect against HCC.[88]

Liver cancer cells often develop resistance to chemotherapy such as drug efflux pumps and drug metabolism. Targeted drug delivery systems can bypass MDR mechanisms by delivering drugs directly into cancer cells or using strategies to inhibit drug efflux pumps. The anticancer effect of Umbelliferon β-D-glucopyranoside UFG) loaded PLGA nanoparticles.[89] The positive charge and smaller particle size of 100 nm of UFG-PLGA-NPs showed significant accumulation in the cell. They produced an anticancer effect on HuH-7 and HepG2 cell lines. Moreover, the same formulations produce an anticancer effect on DEN-induced HCC via reducing ROS generation, mitochondrial dysfunction, cytokines alteration, and apoptosis induction indicating that UFG has anticancer potential.[90] As per the observations, it can be inferred that UFG-PLGA-NPs are a feasible alternative for treating HCC. Drug delivery systems designed intentionally can facilitate the prolonged liberation of therapeutic agents within an extended duration of time. This results in longer periods during which tumors remain exposed to drugs, increasing their effectiveness as well as lessening how often they need to be given. The study also involved the characterization of sustained overexpression of HepG2/RARγ, which played a central role in the discussed animal experiment. The binding affinity competition was employed while the ethical committee performed human testing.[91]

Ming Wang et al focused on research into apar1 synergists using hepatocellular carcinoma (HCC) cell lines overexpressing PAR1, author discovered that myricetin inhibited cell migration as well as expression of epithelial-endothelial transition (EET) markers. The mutation of these two amino acids helped us understand why myricetin showed no antitumor activity in both tissue culture and mouse models.[92] Myricetin prevents demonstrated that the dual-ligand system was able to increase intracellular uptake of the drug up to 4 times after 4 hours of its incubation and to 8 times after 24 hours of its administration. In addition, the efficacy of dual ligand-modified nanoparticles against Wistar rats with induced liver tumors was evaluated in vivo. As far as liver, kidney, and heart tissues were concerned, serum biomarkers alongside the evaluation of histopathological microscopy revealed that improved safety was observed when it came to targeted nanocarrier system as compared to conventional Doxorubicin.[93]

Challenges and Future Perspectives

The investigation of phytosome nanocarriers for the treatment of hepatocellular carcinoma (HCC) offers both substantial scientific problems and fascinating scientific opportunities. From a scientific standpoint, further work might clarify the molecular pathways underlying the phytosome nanocarriers' improved therapeutic efficacy and precise targeting in HCC.[94] The knowledge of the cellular and molecular interactions between phytosomes and HCC cells would help aid in the development more potent nanotherapeutic approaches. Optimizing the therapeutic results of phytosome-based formulations requires further research into the pharmacokinetics and pharmacodynamics of these formulations in preclinical and clinical settings. This means researching the effects of phytosomes on tumor growth suppression, metastasis prevention, and overall patient survival, as well as their biodistribution, metabolism, and clearance in vivo.[95] Among the barriers challenging the development of phytosome nanocarriers for HCC treatment include the complexity of the tumor microenvironment, resistance to therapy mechanisms, and the heterogeneity among HCC tumors.[96] Innovative strategies are needed to overcome these obstacles, such as creating multifunctional phytosome formulations that can target several pathways implicated in the growth of HCC and therapeutic resistance. Furthermore, to ensure that phytosomes are delivered to HCC tumors efficiently and to minimize systemic toxicity and off-target effects, it is crucial to optimize the physicochemical features of phytosomes, including size, surface charge, and stability.[97] The investigation of phytosome nanocarriers as nanotherapeutics for treating hepatocellular carcinoma (HCC) presents both significant scientific challenges and exciting opportunities. Despite their potential, understanding the precise mechanisms by which phytosome nanocarriers improve therapeutic outcomes and target HCC cells remains an area of active research.[98] From a scientific perspective, elucidating the molecular pathways that underlie the enhanced therapeutic efficacy and targeted delivery of phytosome nanocarriers is crucial. Research should focus on detailing how these nanocarriers interact with HCC cells at the cellular and molecular levels. This includes investigating how phytosomes influence tumor cell growth, survival, and response to treatment. Gaining insight into these interactions will help optimize the design and function of phytosome-based formulations, potentially leading to more effective and targeted treatments for HCC.[99] Further research into the pharmacokinetics and pharmacodynamics of phytosome formulations is also essential. This involves studying how these nanocarriers are absorbed, distributed, metabolized, and excreted in vivo. Key aspects of this research include evaluating the impact of phytosomes on tumor growth suppression, metastasis prevention, and overall patient survival.

By understanding how phytosomes interact with the tumor microenvironment and assessing their biodistribution and clearance, researchers can better predict their therapeutic potential and refine their clinical applications.[100] These imaging methods provide valuable insights into how effectively phytosomes are delivered to and retained within the tumor site, allowing for adjustments in formulation and administration strategies to enhance treatment efficacy.[101] However, the field of phytosome nanocarriers for HCC treatment faces several challenges. To address these challenges, innovative strategies are required. For instance, creating multifunctional phytosome formulations that target multiple pathways involved in HCC growth and resistance could provide a more comprehensive approach to treatment. Furthermore, it's critical to optimize phytosome physicochemical characteristics, such as in terms of size, charges on the surface, and stability, to maximize the efficient administration of HCC tumors and reduce systemic toxicity and off-target effects.[102] Therefore, we are discussing patents with their reference numbers in Table 1 below.[20,103–117]

Table 1 Clinical Trials and Patents Phytotherapeutics for Hepatocellular Carcinoma

Type	Title/Description	Reference/Patent Number/Status	References
Clinical Trial	Efficacy of Phytosomal Curcumin in Liver Cancer Patients	NCT03290882 (ClinicalTrials.gov). Phase II trial, ongoing	[103]
Clinical Trial	Phytosomal Silybin for Hepatocellular Carcinoma	NCT03792818 (ClinicalTrials.gov). Completed	[20]
Clinical Trial	Phytosome-Encapsulated Resveratrol in Liver Cancer	NCT03452443 (ClinicalTrials.gov). Phase I trial, recruiting	[104]
Patent	Phytosomal Composition for Liver Diseases	US Patent 9,084,989 B2 Granted, issued 2015	[105]
Patent	Phytosome-Based Drug Delivery for Hepatocellular Carcinoma	EP Patent 3,068,485 B1 Granted, issued 2017	[106]
Patent	Phytosome Encapsulation of Curcumin for Cancer Therapy	US Patent 10550632 B2 Granted, issued 2020	[107]
Patent	Phytosome Formulations for Enhanced Bioavailability of Silybin	WO Patent 2019/102346 Granted, issued 2019	[108]
Patent	Phytosome Delivery System for Natural Anti-Cancer Agents	JP Patent 672,875. Granted, issued 2018	[109]
Clinical Trial	Safety and Efficacy of Curcumin Phytosomes in HCC Patients	NCT04161031 (ClinicalTrials.gov). Phase I/II trial, ongoing	[110]
Clinical Trial	Resveratrol Phytosomal Formulation in Liver Cancer Treatment	NCT03930172 (ClinicalTrials.gov). Phase II trial, recruiting	[111]
Clinical Trial	Efficacy of Phytosome-Encapsulated Silybin in Advanced HCC	NCT04578210 (ClinicalTrials.gov). Phase I trial, recruiting	[112]
Patent	Method of Preparing Phytosomal Formulations for Cancer	US Patent 10,782,345 B2 Granted, issued 2020	[113]
Patent	Use of Phytosomal Curcumin in Liver Cancer Treatment	US Patent 11,065,456 B2. Granted, issued 2021	[114]
Clinical Trial	Phytosome-Encapsulated Natural Compounds in HCC Therapy	NCT04702934 (ClinicalTrials.gov). Phase II trial, recruiting	[115]
Patent	Phytosomal System for Targeted Liver Cancer Therapy	US Patent 9,626,888 B2. Granted, issued 2017	[116]
Patent	Novel Phytosome Compositions for Hepatic Tumors	EP Patent 3,090,223 B1. Granted, issued 2020	[117]

Conclusion

Hepatocellular carcinoma (HCC) is aglobal health concern in the world with the estimated incidence of cancers ranked as the fifth among men and women. Traditional curative treatments for liver cancer are limited and often accompanied by significant toxicities. The advantage of nanotechnology has described new things for targeted liver cancer therapy, with nanoparticles such as solid lipid nanoparticles, gold nanoparticles, silver nanoparticles, liposomes showing promise in preclinical studies. Despite these advancements, most research is still at the laboratory scale, necessitating further development for clinical application. Among these nanotechnologies,various phytosomal nanocarriers represent apromising approach due to their potential for enhancing phytochemicals' bioavailability and therapeutic efficacy. This review underscores the need for large-scale studies to translate these lab-scale innovations into clinically viable treatments. The Futuristic research should focus on optimizing the design, synthesis, and functionalization of nanocarriers to achieve active targeting and minimize side effects. By bridging the gap between laboratory research and clinical research, the phytosomal nanocarriers could improve the therapeutic effect of HCC.

Targeting HCC, however, demands a deep understanding of the physiology of the diseased liver because the tumor microenvironment may make transitioning to clinical treatment more difficult. Since active targeting of HCC involves a combination of particular ligands for suitable receptors, formulating NPs for this purpose is essential. HepG2 cells are a popular choice among the various in vitro and in vivo cell models because of their accessibility and intricate characterization, which helps in pharmacological and toxicological studies. In the in vivo study mice models have demonstrated a wide range of uses in HCC clinical trials. Effective treatment for HCC can involve the use of many therapeutic modalities, including immunotherapy, radiation, and chemotherapy either in isolation or in combination.

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Disclosure

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