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Review Article

Phytosomes: A Promising Nanocarrier for Enhanced Delivery of Herbal Compounds in Cancer Therapy

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ABSTRACT

Cancer is a life-threatening disease that remains a global health problem, with millions of people diagnosed yearly. Despite significant progress in cancer treatment, conventional chemotherapy still faces several limitations, including poor solubility, low bioavailability, lack of selectivity, and severe side effects. Therefore, alternative therapeutic strategies are necessary to improve cancer therapy. This review aimed to provide an updated overview of phytosome complexes and their potential application in cancer therapy, including their formulation techniques, transportation mechanism through phytosome, and recent investigations on their efficacy in treating different types of cancers. In recent years, nanotechnology has emerged as a promising approach to cancer therapy, as it enables the delivery of therapeutic agents to the tumor site with higher selectivity and efficiency. Phytosomes are a nanotechnology-based drug delivery system conjugating plant extracts or phytoconstituents with phospholipids. This conjugation results in the formation of a complex with improved solubility, stability, and bioavailability. Phytosomes have been shown to enhance the pharmacokinetic profile of phytoactive compounds, allowing for better targeting and sustained release. Phytosomes of curcumin, resveratrol, and quercetin have demonstrated anticancer properties in various *in vitro* and *in vivo* models. Moreover, phytosomes have been used to deliver chemotherapeutic agents, such as paclitaxel, docetaxel, and camptothecin, with improved efficacy and reduced toxicity. Phytosome complexes offer a promising platform for cancer therapy due to their ability to enhance the bioavailability and efficacy of phytoactive compounds. Incorporating phytosomes in cancer therapy could lead to the development of more effective and less toxic treatments for different types of cancers. Further studies are needed to elucidate the mechanism of action of phytosomes and to optimize their formulation for clinical use.

1. Introduction

Cancer is a complex disease that results from the uncontrolled growth and proliferation of cells[1]. It is a leading cause of death worldwide, and its incidence is expected to rise in the coming years. Despite significant progress in cancer treatment, chemotherapy remains limited due to poor solubility, low bioavailability, and systemic toxicity[2]. Therefore, there is a need to develop novel drug delivery systems that can overcome these limitations and improve cancer therapy. Nanotechnology-based drug delivery systems have emerged as promising platforms for improving cancer therapy[3]. These systems utilize various nanostructures, such as liposomes, micelles, dendrimers, and nanoparticles, to deliver anticancer agents to the site of action[4,5]. Among them, lipid-based

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nanocarriers have received significant attention due to their biocompatibility, low toxicity, and ease of preparation[6]. These nanocarriers include liposomes, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and phytosomes[7].

Phytosomes are lipid-based nanocarriers that conjugate plant extracts or phytoconstituents with phospholipids[8]. This conjugation results in the formation of a complex with improved solubility, stability, and bioavailability[9]. Several studies have reported the potential of phytosomes in cancer therapy[10]. For instance, phytosomes of curcumin, resveratrol, and quercetin have shown anticancer properties in various *in vitro* and *in vivo* models [11]. Moreover, phytosomes have been used to deliver chemotherapeutic agents, such as Paclitaxel, Docetaxel, and Camptothecin, with improved efficacy and reduced toxicity[12,13]. Phytosomes can be prepared using various techniques, including solvent evaporation, thin-film hydration, and coacervation[14]. Solvent evaporation involves dissolving the phytoconstituent and phospholipid in a common solvent and evaporating the solvent to form a thin film[15]. Thin-film hydration hydrates the thin film with an aqueous phase to form liposomes. Coacervation involves mixing the phytoconstituent and phospholipid in a non-aqueous solvent and then adding water to create phytosomes[16]. These techniques can be modified to achieve different properties, such as size, drug loading capacity, and stability[17]. Phytosomes are characterized by their stability, size, and drug-loading capacity. The stability of phytosomes is due to the formation of chemical links between phospholipid molecules and phytoactive agents. The size of phytosomes ranges from 50-200 nm, which allows them to bypass the reticuloendothelial system and accumulate at the tumor site through the enhanced permeability and retention effect[18]. The drug-loading capacity of phytosomes depends on the solubility of the phytoconstituent and the type of phospholipid used.

2. Advantages of phytosomes

Phytosomes are a promising delivery system for phytoactive compounds, as they offer several advantages over other delivery systems. One of the main advantages is their simple production method compared to other nano delivery systems, such as NLC and SLN. This ease of production makes phytosomes a cost-effective option for drug delivery[19].

Another major advantage of phytosomes is their ability to improve the oral absorption of polar phytoactive compounds, leading to better bioavailability and greater therapeutic effects[20]. This is due to the ability of the phospholipid molecules in the phytosome to form chemical links with the phytoactive compounds, increasing their stability and solubility in aqueous solutions.

In addition, phytosomes have been found to significantly increase drug/nutraceutical entrapment, allowing for a more targeted and efficient delivery of the active compound to the site of action [21]. The enhanced cellular uptake of phytoactive constituents further reduces the required dose, minimizing potential side effects and toxicity.

Furthermore, the use of phosphatidylcholine in phytosomes provides hepatoprotective and synergistic effects when combined with other hepatoprotective constituents[22-24]. This dual effect can be beneficial in the treatment of liver diseases.

Phytosomal formulations have also shown potential in enhancing percutaneous absorption of phytoconstituents, making them a viable option for topical applications in treating skin conditions[25].

Finally, phospholipids in phytosomes offer a dual nutritional benefit, as they not only enhance the delivery of phytoactive compounds but also provide essential nutrients for cellular membrane function and overall health[26].

In summary, the advantages of phytosomes make them an attractive option for delivering phytoactive compounds, offering enhanced cellular uptake, improved bioavailability, and reduced required doses, among other benefits. Further research and development in this area can potentially revolutionize cancer therapy and other areas of medicine.

3. Phytosome in cancer therapy

Nanophytosomes have emerged as a promising drug delivery system for improving the bioavailability and efficacy of plant-derived anticancer compounds. These lipid-based nanocarriers offer several advantages over traditional delivery systems, such as improved cellular uptake, increased bioavailability, and reduced toxicity. Recent studies have explored the potential of nanophytosomes in cancer therapy, demonstrating their efficacy in delivering phytoconstituents to cancer cells with minimal cytotoxic effects on normal cells.

3.1. Silibinin phytosome

Silibinin is a natural flavonolignan compound extracted from milk thistle (Silybum marianum) and used as a traditional medicine for liver diseases[27]. In recent years, *Silibinin* has gained considerable attention due to its potent anticancer activities against various cancer cells, including hepatocellular carcinoma, prostate cancer, breast cancer, and lung cancer[28-30].

Several mechanisms have been proposed to explain the anticancer effects of *Silibinin*. One of the major mechanisms is the inhibition of cancer cell proliferation through the induction of cell cycle arrest and apoptosis. *Silibinin* has also been shown to inhibit angiogenesis, invasion, and metastasis of cancer cells by targeting various signaling pathways, such as NF-κB, Wnt/β-catenin, PI3K/Akt, and MAPK[31].

However, one of the major challenges in using *Silibinin* as a therapeutic agent is its poor bioavailability, which limits its clinical efficacy. To overcome this limitation, various drug delivery systems, including nanoparticles, liposomes, and phytosomes, have been developed to

improve the solubility, stability, and targeting of *Silibinin*[32,33].

Phytosomes are a novel drug delivery system that involves complexing a drug with phospholipids to form a lipid bilayer structure. This structure improves the bioavailability of the drug by increasing its absorption and reducing its metabolism and elimination. Ochi et al. 2016 demonstrated the potential of phytosomes in improving the therapeutic effects of *Silibinin* by co-encapsulating it with glycyrrhizic acid, another anticancer compound, in nanophytosomes[34]. The results showed that the co-encapsulated nanophytosomes were more potent than individual *Silibinin* and glycyrrhizic acid in inhibiting the proliferation of hepatocellular carcinoma cell lines.

Similarly, Lazzeroni et al. 2016 investigated using Silybin nanophytosomes (SNPs) as a delivery system for treating early breast cancer patients [35]. The results showed that the SNPs significantly increased the plasma levels of Silybin and its accumulation in the tumor tissue, which led to a significant reduction in tumor size and improved clinical outcomes. This study demonstrated the potential of nanophytosomes in overcoming poor bioavailability of Silybin and improving its therapeutic efficacy.

In conclusion, *Silibinin* has shown promising anticancer activities against various cancer cells, but its poor bioavailability remains a major challenge in its clinical application. Nanophytosomes, as a novel drug delivery system, have shown great potential in improving the bioavailability and therapeutic efficacy of *Silibinin* by improving its absorption, stability, and targeting. Further studies are needed to optimize the formulation and dosage of nanophytosomes and to evaluate their safety and efficacy in clinical trials.

3.2. Sinigrin phytosome

Cancer is a major public health concern worldwide, and skin cancer is one of the most prevalent types of cancer [36]. Using wound healing agents with concomitant cytotoxic effects against cancer cells is an attractive approach to treating skin cancers. *Sinigrin*, a natural compound found in the Brassicaceae family, has been shown to have antitumor activities. In an innovative study, Mazumder et al. investigated the wound-healing effects of *Sinigrin* on normal human keratinocyte cells (HaCaT) and the anticancer effects of its phytosomal formulation on A-375 melanoma cells [37]. The study revealed that *Sinigrin*-loaded phytosomes had significant superiority over free *Sinigrin* in cytotoxicity against A-375 cell lines. Moreover, minimal cytotoxic effects were observed on normal cells (HaCaT). The *in vitro* wound healing investigation on HaCaT cells showed 50% more wound closure at various concentrations and times. These results suggest that *Sinigrin*-loaded phytosomes may be a promising candidate for cancer therapy and cancerous wound treatment [38].

Phytosomes are a novel delivery system that has been shown to improve the bioavailability of natural compounds, including anticancer agents. Phytosomes are lipid-based nanoparticles containing a natural compound, such as *Sinigrin*, encapsulated within a phospholipid bilayer[39]. This encapsulation increases the solubility and stability of the compound, thereby enhancing its bioavailability.

Using *Sinigrin*-loaded phytosomes as a therapeutic agent is a novel approach to treating skin cancers. *Sinigrin* has been shown to have antitumor effects by inducing apoptosis and inhibiting cell proliferation. The phytosomal formulation of *Sinigrin* may allow for more efficient delivery of the compound to cancer cells while minimizing its effects on normal cells[40].

In conclusion, using *Sinigrin*-loaded phytosomes as a delivery system for treating skin cancers has great potential. Combining wound healing and the anticancer effects of *Sinigrin*-loaded phytosomes may lead to more effective treatments with a fewer side effects. Further studies are warranted to fully explore the potential of *Sinigrin*-loaded phytosomes as a novel cancer therapy.

3.3. Mitomycin phytosome

In addition to its potent antitumor activities, Mitomycin C (MMC) has also shown promising results in treating a wide range of cancers[41-43]. However, the rapid absorption of MMC into systemic circulation has been a major obstacle in its clinical application. This leads to a decrease in the plasma concentration of the drug in the relevant sites, resulting in a decrease in therapeutic efficacy.

Researchers have developed various drug delivery systems for MMC to overcome this limitation. One such innovative approach was developed by Hou et al., who developed a delivery system of MMC-soybean loaded phytosomes PC (MMC-SPC) complex with a mean particle size of 210nm[44]. The phytosome complex comprises a phospholipid bilayer shell that encapsulates the MMC and protects it from rapid absorption into systemic circulation.

In vitro release studies showed that the MMC release from the phytosome complex was sustained after its first burst release, indicating that the phytosomes effectively protected MMC from rapid absorption into systemic circulation[45]. Using phytosomes also increases the lipophilicity of MMC, further enhancing its ability to penetrate cancer cells.

In vivo studies on H22 solid tumor-bearing model mice showed that the tumor inhibition rate of the phytosomes loaded with MMC was six times more than that of MMC injection[44]. This indicates that the phytosome complex significantly improved the therapeutic efficacy of MMC.

The development of MMC-loaded phytosomes as a drug delivery system represents a novel approach to cancer therapy. The use of phytosomes provides a means to protect MMC from rapid absorption into systemic circulation and to enhance its therapeutic efficacy against cancer cells. Further studies in this area may lead to the development of more effective and targeted cancer therapies.

3.4. Curcumin phytosome

Curcuma longa, commonly known as turmeric, is an

ancient traditional herb used for its medicinal properties for centuries[46]. It contains natural hydrophobic polyphenols and chemical compounds called curcuminoids, which have been shown to have comprehensive pharmacological activities, including beneficial effects on treating different types of cancers[47]. However, curcumin therapeutic is often hindered by its poor solubility and bioavailability in oral administration. This has led to the design of several formulation methods and other approaches to combat those obstacles and facilitate its clinical application[48].

One such approach is using delivery systems to enhance the solubility and bioavailability of curcumin. In a comparative study conducted by Purpura et al. 2018, the plasma levels of curcuminoids with different delivery systems, including curcumin-gamma-cyclodextrin (CW8), curcumin phytosome (CSL), and standard plain curcumin (STDC), were investigated via oral administration[49]. The plasma measurement for demethoxycurcumin showed a similar plasma level for CSL and CW8 delivery systems, significantly more than STDC. For bisdemethoxycurcumin, the CSL plasma level was significantly more than CW8. However, for curcumin, the plasma level reported the supremacy of CW8 to CSL. Although in this study, curcumin plasma level for CW8 was reported to be more than for CSL, both delivery systems showed significantly more plasma levels than plain curcumin.

In addition to delivery systems, other approaches to enhance the therapeutic efficacy of curcumin have also been explored. For instance, curcumin-based nanoparticles have been developed to increase the bioavailability and targetability of curcumin in cancer cells. In a recent study by Rashidzadeh et al. 2019, curcumin-loaded nanostructured lipid carriers (NLCs) were developed and evaluated for their potential in breast cancer therapy[50]. The results showed that the curcumin-NLCs exhibited higher cellular uptake and cytotoxicity in breast cancer cells, compared to free curcumin. Moreover, the curcumin-NLCs showed improved tumor accumulation and therapeutic efficacy in a mouse model of breast cancer.

Furthermore, curcumin has been combined with other natural compounds to enhance its therapeutic efficacy. In a study by Khanna et al., a combination of curcumin and piperine, a natural alkaloid found in black pepper, was evaluated for its therapeutic potential in treating multiple myeloma[51]. The results showed that the curcumin-piperine combination exhibited a significant inhibitory effect on multiple myeloma cells compared to curcumin alone.

In conclusion, curcumin is a promising natural chemical agent with beneficial effects on treating different types of cancers. However, its poor solubility and bioavailability in oral administration often limit its therapeutic efficacy. Therefore, various approaches, including delivery systems, nanoparticles, and combination therapy, have been explored to overcome these limitations and enhance the therapeutic efficacy of curcumin. These novel approaches hold great promise for the future development of curcumin-based cancer therapies (Figure 1).

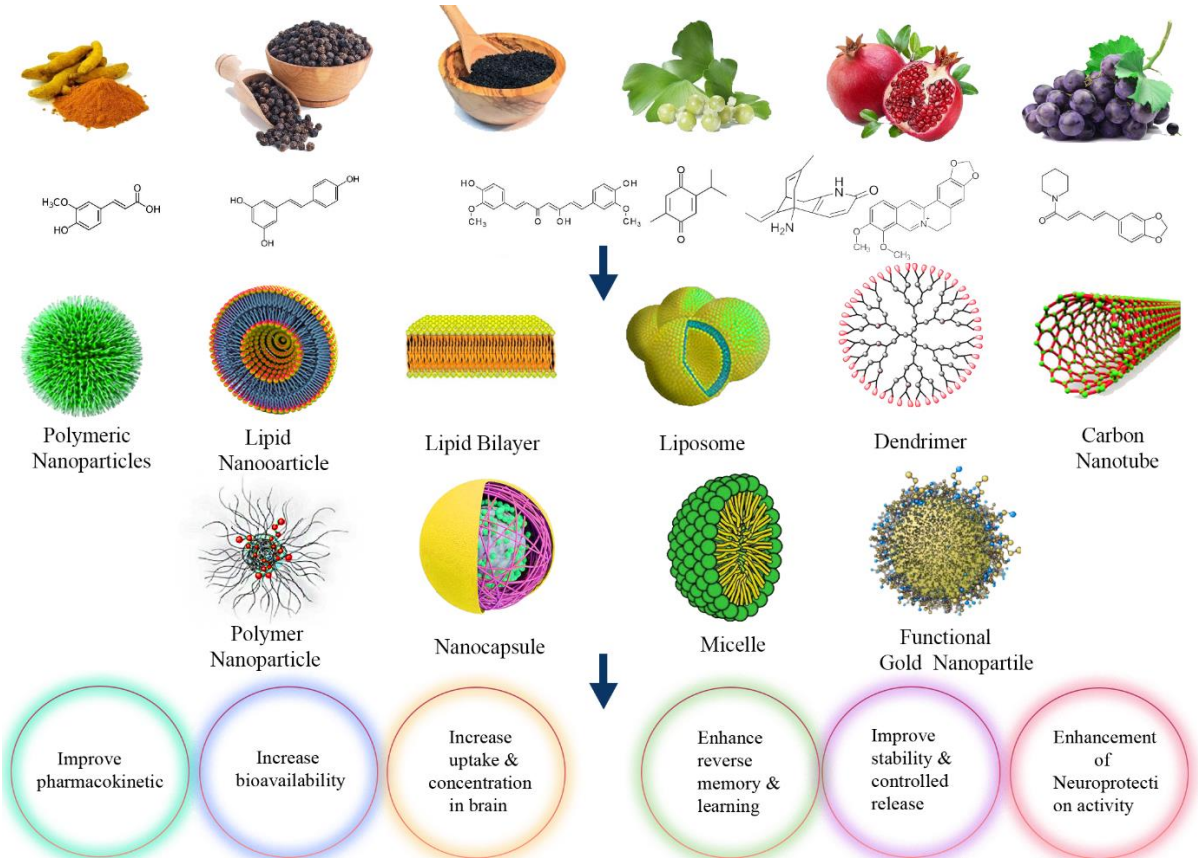

Figure 1. Current status of phytosomes

4. Challenges and future

While the potential of phytosome technology for cancer therapy is promising, there have been limited investigations on using phytosomes as a carrier for anticancer agents. Despite this, a few products have emerged on the market, such as Meriva® (curcumin phytosomes) and Siliphos® (Silybin phytosomes)[52]. One major challenge facing the industrial production of phytosomes is the pH sensitivity of their structures, which can impact their physicochemical stability[53]. This challenge must be addressed for the industrial-scale production of these nanocarriers to be feasible in the future.

One interesting aspect of phytosomes is that they can be produced using food-grade procedures, which can remove the potential side effects associated with non-food-grade production methods. This is important for ensuring that the phytosomes are safe for cancer therapy. Flavonoids and other herbal medicines have recently gained much attention in cancer therapy, but their poor oral bioavailability has limited their clinical applications[54]. Lipid-based nanoparticles, such as phytosomes, offer many advantages over other drug carriers due to their biocompatibility, biodegradability, low cost, and abundant availability of raw materials[55].

Phytosomes can be used as effective carriers for drug delivery because their cores consist of phospholipids and cholesterol, similar to biomembranes[56]. These lipids are readily accepted by the human body without causing antigenic or pyrogenic responses, making them a promising option for cancer therapy. Phytosomes are also biologically neutral and induce low immunogenic reactions[57].

However, some challenges are still associated with using phytosomes for drug delivery. One concern is their ability to merge with bilayer phospholipid biological membranes, which could result in non-specific drug delivery to healthy tissues[58]. To address this issue, new approaches for active targetings, such as antibody- or peptide-targeted delivery, must be developed and applied to increase the anticancer efficiency of phytosomes while reducing their toxicity to normal tissues[59].

Despite the challenges associated with the formulation of nanophytosomes, this concept and technology hold great promise for cancer therapy. Recent developments in industrial-scale production of vesicular systems, including extruding methods, offer optimistic horizons for the commercial fabrication of these systems. While the high cost of raw materials, such as pegylated soy phosphatidylcholine may pose a challenge, the formulating herbal and synthetic anticancer agents into nanophytosomes has already been shown to increase oral bioavailability and reduce tumor growth[60]. Future studies assessing the efficacy and toxicity of nanophytosomes in large animal models and Phase I/II clinical trials will be necessary to explore their potential for cancer therapy fully.

5. Conclusion

The efficacy of botanical preparations is mainly attributed to their health-promoting compounds, including flavonoids and other phenolic compounds. Hence, it is essential to employ appropriate delivery mechanisms to deliver sufficient quantities of active ingredients to the body. Phytosomes represent a novel drug delivery system that enhances the bioavailability of phytoconstituents and other natural plant-based compounds through the gastrointestinal tract. The advantages of phytosomes over other conventional nano-delivery carriers are undeniable. Formulating phytosomes is facile and can be easily scaled up for commercial production. Additionally, the preparation, characterization, and analytical techniques for this delivery system are well-established. Phytosomes demonstrate excellent potential as a nano-formulation technique for nutraceuticals, and they could serve as a promising candidate for delivering hydrophilic plant compounds for cancer therapy.

Declarations

Competing interests

The authors have declared no conflicts of interest.

Authors' contributions

The study was conceptualized by Muhammad Saeed, with all authors participating in the development of the methodology. Formal analysis and investigation of the research were carried out by all authors, and the writing process, including the preparation of the original draft and subsequent review and editing, was a collaborative effort. Muhammad Saeed provided supervision for the project, and all authors thoroughly reviewed and approved the final version of the manuscript before submitting it for publication in the present journal.

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Ethical considerations

The authors declare that this manuscript is original and has not been submitted elsewhere for possible publication. The authors also declare that the data used/presented in this manuscript has not been fabricated.

Availability of data and materials

The authors will provide data from the present study in case of request.

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