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NOVEL PHYTOSOMAL DRUG DELIVERY SYSTEMS IN CANCER THERAPY: ADVANCES, MECHANISMS, AND TRANSLATIONAL POTENTIAL

Sujatha Damera[1], Mounika Kuchukuntla[2], Mani Sharma[2], Ram Mohan Manda[2], Ananda Kumar Chettupalli[3], Rajendra Kumar Jadi[2]*

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ABSTRACT
Background: Phytochemicals are medicinal plants with strong anticancer properties that alter various molecular pathways involved in tumor initiation, progression, and metastasis. Several adverse factors, however, hamper their clinical translation: low aqueous solubility, low membrane permeability, high first-pass metabolism, and rapid systemic elimination. Phytosomal drug delivery systems have emerged as a new, advanced lipid-based approach to addressing these pharmacokinetic and biopharmaceutical challenges. **Methodology:** Phytosomes are molecular complexes formed by a stoichiometric reaction between phytoconstituents and phospholipids, thereby increasing stability, improving bioavailability, and enhancing cellular uptake compared to conventional extracts and liposomal systems. Through meticulous analysis of articles from various publishers like PubMed, Science Direct, Elsevier, Bentham Science, Wiley, SAGE, Taylor and Francis publishers, and various indexing journals like Web of Sciences and Scopus databases, etc. **Result and Discussion:** This is a review of phytosomal technology in the treatment of cancers, including the principles of formulation, methods of preparation, physicochemical characterization, and the mechanisms of action of an increased anticancer effect. **Conclusion:** There is a critical discussion of preclinical and clinical evidence on phytosomal preparations of curcumin, silibinin, quercetin, catechins, and berberine. Further, present-day problems in translational research and regulation, as well as future opportunities, such as targeted and stimuli-responsive phytosomes, are also highlighted, indicating their potential as the next generation of phytomedicines in cancer therapy.

INTRODUCTION

The current landscape of cancer therapy highlights a persistent gap between advances in molecular oncology and the achievement of clinically effective treatments, particularly for metastatic disease. Although conventional chemotherapeutic

[1]*University College of Pharmaceutical Sciences, Kakatiya University, Warangal – 506 009, Telangana, India.*
[2]*School of Pharmacy, Anurag University, Hyderabad – 500 088, Telangana, India.*
[3]*Department of Pharmaceutical Technology, School of Health and Medical Sciences, Adamas Knowledge City, Adamas University, Barasat-Barrackpore Road, Barbaria, P.O Jagannathpur, District-24 Parganas (North), Kolkata – 700 126, West Bengal, India.*

For Correspondence:** **rajendrapharmacy@anurag.edu.in

agents demonstrate therapeutic efficacy, they are characterized by poor tumor selectivity, pronounced systemic toxicity, and narrow therapeutic indices. These limitations significantly restrict dose escalation, compromise long-term treatment outcomes, and hinder sustained disease control. [1]. In this regard, plant bioactive compounds (phytochemicals) have attracted significant interest due to their ability to regulate various oncogenic pathways that govern tumor initiation, progression, and metastasis.

Several clinically significant anticancer agents are of botanical origin; nonetheless, direct clinical use of the most promising phytochemicals, including curcumin, quercetin, and silibinin, remains minimal. This is mainly due to their low aqueous solubility, low membrane permeability, high first-pass metabolism, and rapid systemic excretion, leading to low bioavailability & low intracellular drug levels [2]. To overcome these pharmacokinetic & biopharmaceu- tical difficulties, investigations into lipid-based nanocarrier systems have been conducted, with phytosomes emerging as a unique and logical formulation approach. Phytosomes are lipid-soluble molecular complexes resulting from a stoichiometric interaction between phytoconstituents and phospholipids, usually phosphatidyl-choline, that allow superior membrane permeation and stability compared to traditional extracts or liposomal formulations [3]. Instead of giving a general report on the phytosomal technology, the current review concentrates on the critical analysis of the translational relevance of phytosomal drug delivery systems in cancer treatment and their potential to circumvent clinical obstacles, their comparison to other nanocarriers, and the limitations that hinder their development to routine use in the oncology sphere [4].

OBJECTIVE

The current review is not intended to present a detailed overview of phytosomal drug delivery systems, as there are already several in-depth reviews in the literature. Rather, the presented article is a critical discussion of the translational applicability of phytosomal preparations in cancer treatment. Its main concerns involve evaluating how phytosomes can overcome major clinical impediments associated with anticancer phytochemicals, such as low bioavailability, metabolic instability & low cellular uptake. Also, this review will compare phytosomes & other lipid-based nanocarriers in clinical & regulatory terms, critically examine preclinical & clinical evidence to define aspects of success and limitations, & note gaps & future directions in the literature, including targeted, stimuli-responsive, and clinically translatable phytosomal systems.

Limitations of Conventional Phytochemicals in Cancer Therapy

As signaling pathways are dysregulated in cancer, phytochemicals have potent anticancer effects, including inhibition of NF-κB, PI3K/Akt/mTOR, and Wnt/β-catenin. Although they exhibit strong in vitro antibacterial activity, their clinical efficacy has been limited by a major discrepancy between laboratory results and clinical outcomes. This translational failure has been mainly explained by the fact that several pharmacokinetic and biopharmaceutical constraints are linked with the traditional phytochemical delivery:

Solubility and Dissolution Rate

Compounds are poorly soluble in aqueous solution at physiological pH, leading to poor dissolution in gastrointestinal fluids and severely limited absorption, with a significant portion of the dose administered remaining intact [5].

Permeability Barriers

Even in the solubilized state, there are further barriers to absorption. Polyphenols with high molecular weight, including epigallocatechin-3-gallate (EGCG) or P-glycoprotein and multi-drug resistance-associated proteins, are actively excreted by transporters and result in decreased net bioavailability [6].

Metabolic Instability

There is massive first-pass metabolism, which highly impairs systemic exposure. Enterocytes and hepatocytes rapidly conjugate substantial numbers of phytochemicals to produce metabolites with reduced biological activity and short systemic half-lives [7]. As a result, in vivo plasma conc. that can produce the same anticancer effects as *in vitro* are seldom efficacious [8].

Chemical Degradation

Under gastrointestinal conditions, further financial limitations arise from the chemical's instability, which restricts its therapeutic use. Some phytochemicals are likely to oxidize or disintegrate via hydrolysis before absorption, thereby reducing their activity [9]. All these constraints are why potent anticancer phytochemicals are usually unable to show positive clinical activity despite strong preclinical performance. These barriers need to be addressed by delivery systems that can increase

solubility, safeguard against degradation and metabolism, and enhance membrane transport- thus becoming the basis of enhanced lipid-based formulations with true translational potential.

Rationale

The concept of phytosomal drug delivery systems is anchored in the biomimetic nature of phospholipids, particularly phosphatidylcholine (PC), a significant structural constituent of biological membranes. This biomimicry provides the scientific basis of the application of phytosomes to enhance the clinical translation of anticancer phytochemicals that otherwise do not perform well in the clinic:

Amphiphilic Transformation

Phytosomes are formed by stoichiometrically complexing polar phytoconstituents with the polar head group of phospholipids to form lipid-compatible molecular complexes that can be easily partitioned into biological membranes. This change enables the passive diffusion across the gastrointestinal epithelium, hence enhancing oral absorption more than free phytochemicals or traditional extracts do.

Molecular Stability

There is also improved molecular stability due to a hydrogen bond between the phytochemical and the phospholipid head group. This interaction safeguards the active constituent against untimely hydrolysis & oxidative breakdown in the gastrointestinal tract, a liability generally found in physical mixtures or straightforward lipid preparations. Consequently, phytosomes are used to maintain the pharmacological activity of drugs during transit across biological barriers, thereby better preserving the drug's biological activity [10].

Targeting Potential

Intrinsic targeting potential is also demonstrated by phytosomes, since rapidly growing cancer cells are found to require more lipids to generate membranes. Phytosomes can also be targeted to tumor cells, with the advantage that phytochemicals are delivered more efficiently to the cell by the phospholipid-rich surface of the phytosome, and that efflux effectors may also be avoided [11].

Hepatoprotection

In addition, the phosphatidylcholine carrier itself has the potential to possess hepatoprotective properties, especially in the oncology setting, whereby patients are often subjected to hepatotoxic chemotherapeutic regimens [12]. Even with these mechanistic benefits, phytosomal formulations cannot be guaranteed to be clinically successful solely based on their enhanced physicochemical properties. Formulation reproducibility, scalability, cost, and regulatory acceptability are powerful determinants of translational results. Thus, the phytosomes offer a logical approach to overcoming the main pharmacokinetic obstacles in phytochemicals. Still, their therapeutic efficacy in cancer treatment needs to be critically evaluated in the context of translation and disease, rather than on theoretical advantages. Even though carriers based on phosphatidylcholine in phytosomal formulations are usually regarded as biocompatible and possibly have hepatoprotective effects, the relatively high level of phospholipid present in such systems can also affect systemic lipid metabolism. A theoretical issue is the so-called lipid sink effect, in which an excess of circulating phospholipids can react with lipophilic endogenous lipid transport pathways or bind to plasma lipophilic molecules.

These interactions may modify the distribution of co-administered lipophilic drugs or affect liver lipid-metabolizing enzymes. High-dose exogenous phospholipids might have a hypothetical effect on lipoprotein transport systems or hepatic lipid processing in oncology patients, whose metabolic pathways are often altered by disease progression or chemotherapy. Although existing clinical research has not revealed any serious metabolic toxicity associated with the use of phytosomal formulations, this area remains underexplored. The proposed future research must thus assess the long-term metabolic outcomes of the phospholipid-rich nanocarriers, especially in patients undergoing combination therapy with other lipid-based drugs or formulations.

Literature Search

The search strategy consisted of a structured, systematic literature search to cover all scientific knowledge available on phytosomal drug delivery systems for cancer therapy. Key scientific databases, including PubMed, ScienceDirect, Scopus Science Web, Wiley Online Library, Taylor and Francis, and Bentham Science, were systematically searched to identify relevant articles. The following combinations of keywords and Boolean operators were used to perform the literature search: phytosomes, phytosomal drug delivery system, phytochemical nanocarrier, phospholipid complex, lipid-based drug delivery, and phytosomes in cancer therapy. The search strategy was

refined using Boolean operators such as AND and OR. Articles published between 2000 and 2025 were searched. Manual screening of the reference lists of relevant review articles and research papers was also conducted to identify additional relevant studies. Peer-reviewed research articles and review papers that targeted phytosomal formulations and their method of preparation, physicochemical characterization, pharmacokinetic enhancement, and anticancer products were included as inclusion criteria. Articles published in non-English languages were excluded. The exclusion criteria were conference abstracts lacking full text, duplicate articles, articles unrelated to phytosomal drug delivery, and articles that provided insufficient information on the experimental design and mechanisms. The PRISMA-style of the literature screening process has been used to guarantee transparency in the study identification and selection. In the first instance, 320 articles have been referenced using the database. After eliminating duplicate records, 260 articles remained for title and abstract screening. After screening, 145 articles were taken to full-text assessment. In the end, 59 studies were included in this review using the predetermined inclusion and exclusion criteria.

CONCEPT AND EVOLUTION

Definition and structural characteristics

Phytosomes are lipid-compatible molecular complexes formed by a stoichiometric reaction between standardized phytoconstituents and phospholipids, usually phosphatidylcholine, and are usually assembled in aprotic solvent systems. In contrast to liposomes, where the drug is literally incarcerated in an aqueous core or lipid bilayer, phytosomes are discrete chemical structures in which the phytochemical is molecularly bound to the phospholipid head group. Phytosomes are stable due to the presence of non-covalent interactions, mainly hydrogen bonding between the polar functional groups of phytoconstituent (e.g., hydroxyl or carboxyl groups) and the polar head of the phospholipid. This molecular interaction between phytoconstituents and phospholipids is commonly confirmed using spectroscopic techniques such as Fourier transform infrared spectroscopy (FTIR) and proton nuclear magnetic resonance (^{1}H NMR), which demonstrate the formation of hydrogen bonding and molecular complexation rather than a simple physical mixture. The schematic mechanism of phytosome formation is illustrated in Figure 1[13].

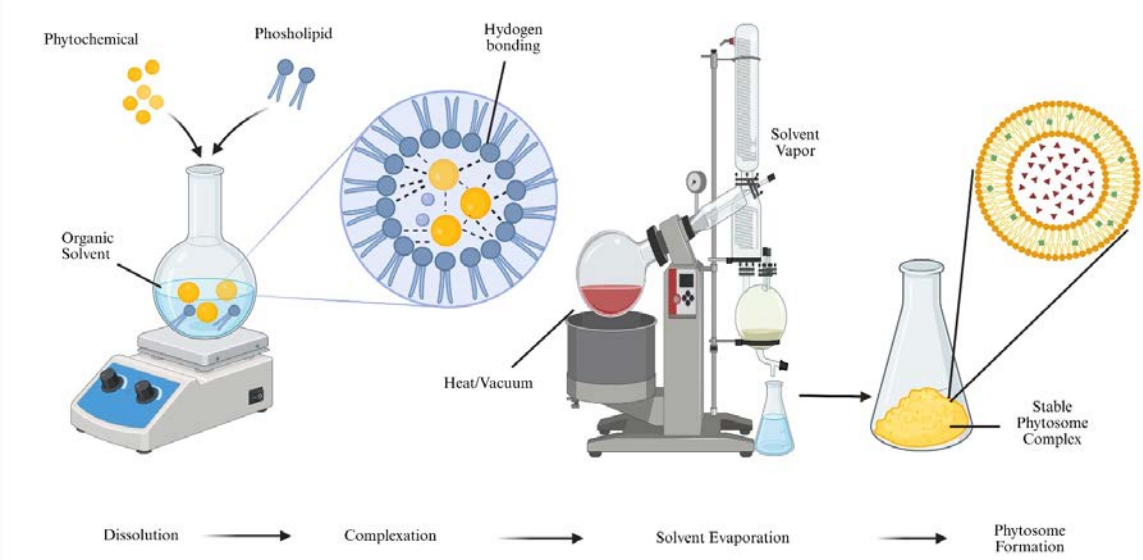

Figure 1: **Schematic representation of phytosome formation showing the molecular interaction between phytoconstituents and phosphatidylcholine through hydrogen bonding, resulting in the formation of a lipid-compatible phytosomal complex**

This type of complexation yields specific stoichiometric ratios, typically 1:1 or 1:2 (drug: lipid), which provide drug-to-lipid ratios and improve formulation stability compared to standard vesicular systems [3]. The stoichiometric ratio of phytochemical to phospholipid in phytosomal complex is not random, but is highly determined by the chemical structure and functional groups of the phytoconstituent. Phytochemicals with only one dominant polar functional group, e.g., one hydroxyl or carboxyl group with the ability to form hydrogen bonds with the phosphatidylcholine head group, can typically form stable complexes in a 1:1 molar ratio. Conversely, polyphenolic compounds containing more than one hydroxyl group, like curcumin, quercetin, catechins, etc., can react with more than one phospholipid molecule, leading to a 1:2 drug-lipid

stoichiometric ratio. The degree of interaction with the phospholipid head group depends on the number and spatial orientation of hydrogen-bonding sites, the polarity of the molecule, and the steric structure of the phytochemical. Polar molecules, or molecules with more than two phenolic groups, usually require additional phospholipid molecules to stabilize the complex and enhance lipid compatibility. Hence, the stoichiometric ratio is optimized in experimental formulation development to achieve the highest possible complex stability, entrapment efficiency, and bioavailability.

Comparison of Phytosomes with Other Vesicular Systems

To better appreciate the evolution of phytosomes, it is essential to compare them with other developed lipid-based delivery systems, such as liposomes, niosomes, and pharmacosomes, as summarised in Table 1.

Table 1: Comparative analysis of phytosomes and other vesicular systems [5, 13-18]

Feature	Phytosomes (Herbosomes)	Liposomes	Niosomes	Pharmacosomes
Interaction nature	Chemical bonding (hydrogen bonds) between the drug and the lipid headgroup	Physical entrapment of the drug in the aqueous core or lipid bilayer	Physical entrapment using non-ionic surfactants & cholesterol	Covalent bonding between the drug & lipid
Stoichiometry	Defined stoichiometric ratio (typically 1:1 or 1:2)	Variable; drug loading depends on volume and solubility, often requiring a high lipid ratio	Variable; surfactant-dependent	Defined stoichiometry (1:1)
Stability	High chemical interaction prevents drug leakage and segregation	Lower; prone to drug leakage, fusion, and aggregation during storage	Moderate; depends on surfactant chemistry	High due to the covalent bond
Bioavailability	Superior; complex is absorbed as a unit, enhancing membrane permeation	Good for parenteral; oral bioavailability is often limited by degradation in the gut	Good; surfactants can enhance permeation but may raise toxicity concerns	Good
Drug loading	High efficiency; no "waste" of lipid volume	Can be low for hydrophilic drugs; requires large amounts of excipients.	Moderate to High	High
Primary use	Oral and topical delivery of poorly soluble herbal extracts.	Parenteral (IV) delivery of chemotherapeutics (e.g., Doxil)	Topical and ocular delivery: a cheaper alternative to liposomes	Targeted delivery

This analogy underscores that liposomes are optimal for the intravenous delivery of toxic drugs (e.g., reducing the cardiotoxicity of doxorubicin), and phytosomes are specifically designed to address the oral bioavailability dilemma of phytochemicals.

Advantages and Limitations

Structurally, phytosomes are amphiphilic and can self-assemble into micelles or vesicle aggregates in water [19]. In contrast to liposomes, phytosomes encapsulate the drug with various lipid molecules in a central aqueous compartment, leading to uniform distribution at the molecular level and increased membrane affinity, thereby reducing drug leakage [20]. This structural property is the basis of the enhanced oral bioavailability observed in several phytosomal formulations, and systemic exposure to compounds such as silibinin and curcumin has been reported to be increased. Although these are the benefits, phytosomal technology cannot be used across the board. Complexation of phytoconstituents with appropriate polar functional groups is mostly limited, so it cannot be used with compounds of a strongly non-polar character or with fully ionized compounds. Also, phytosomal complexes can be pH-sensitive and therefore require protective formulation strategies, such as buffering or enteric coating [3]. The cost of manufacturing pharmaceutical-grade phospholipids and solvent purification is also a challenge to large-scale production. These shortcomings underscore the importance of critically evaluating phytosomes in light of their overall physicochemical performance, particularly with respect to scalability, cost-effectiveness, and clinical translatability [21].

COMPOSITION AND FORMULATION DESIGN

Phytoconstituents used in cancer therapy

Phytosomal technology has been applied to anticancer phytochemicals that have shown outstanding in vitro efficacy but have not yielded repeatable clinical effects due to poor pharmacokinetics. Accordingly, pharmacological novelty is a secondary factor in selecting phytoconstituents for incorporation

into a phytosomal formulation, and more so because of the need to address poor solubility, low membrane permeability, rapid metabolism, and insufficient exposure at systemic sites.

Curcumin, one of the most widely studied compounds, has demonstrated extensive anticancer effects, though it has very poor bioavailability. Its phytosomal preparation has demonstrated significantly improved systemic absorption and enhanced therapeutic effect in clinical practice, especially in pancreatic and colorectal cancers. Likewise, silibinin has been formulated as silibinin phytosome, which has facilitated the administration of higher doses of silibinin, leading to a biological effect: reduction in prostate-specific antigen (PSA) in patients with prostate cancer [22, 23]. Phytosomal delivery has also been advantageous for other polyphenols, such as quercetin & green tea catechins (EGCG), which have shown increased oral absorption & cellular uptake, making them useful as part of a combination regimen with standard chemotherapeutic agents [24]. Phytosomes of berberine have shown better intracellular accumulation & anticancer effects than free berberine salts, especially in models of liver cancer [8]. Also, phytosomal preparations of Ginkgo biloba extracts have been investigated for anti-angiogenic & tumour growth inhibitory effects, but there is still no significant clinical evidence [25]. Altogether, these illustrations indicate that phytosomes are a formulation-based approach to salvage clinically inefficient phytochemicals rather than to create novel anticancer agents, thereby emphasizing their translational significance.

Phospholipid selection and complex formation

The phospholipid best suited for phytosomal formulations is phosphatidylcholine, which is biocompatible, membrane-mimicking, and compatible with polar phytoconstituents. It is a zwitterionic head group that allows stable hydrogen bonding, and the hydrophobic tails increase membrane permeation and uptake [19]. Translational On a translational standpoint, high-purity pharmaceutical-grade phospholipids must be used to provide formulation stability and ensure reproducibility from batch to batch, but this imposes substantial production costs and limits commercial viability at large scale [26]. There is frequently a preference towards using natural phospholipids because of their cost and availability, or synthetic phospholipids because they are more chemically stable and can be composed to a higher degree, but at a much higher cost. The trade-off between these materials is thus a compromise between the formulation performance and cost practicality [27].

Preparation Techniques

Solvent-based complexation methods are typically used to prepare phytosomes, enabling close interactions between the phytochemical and the phospholipid. The traditional methods of solvent evaporation and antisolvent precipitation are applicable on a large scale in the laboratory and are efficient for forming complexes. Nevertheless, their dependence on organic solvents, multiprocess processing, and solvent extraction raises concerns about scaling, environmental friendliness, and legal requirements [28]. New manufacturing methods, such as supercritical fluid technology, provide alternatives to minimize solvent use and enable greener production with enhanced regulation of particle measurement and morphology. Although these benefits exist, they are hampered by high operational costs and technical complexity, which prevent their widespread use in industry today. In turn, the decision on the type of preparation should be based not only on the efficiency of the formulations but also on the scalability and regulatory viability [29].

Comparison of Supercritical Fluid Technology and Conventional Solvent Evaporation

Recently, an alternative phytosomal preparation method using supercritical fluid technology has become a viable green technology. Unlike traditional solvent evaporation techniques, which use organic solvents, e.g., ethanol or chloroform, supercritical carbon dioxide (SC-CO2) enables complex formation under solvent-free or low-solvent conditions. The method decreases the toxicity of the residual solvent and enhances the greenness of the production process. Formulation-wise, the research has indicated that normal solvent evaporation techniques generally yield entrapment efficiencies of about 70-85 percent, depending on the drug-lipid ratio and process conditions. By comparison, similar or slightly better entrapment efficiencies can be achieved, usually cited at around 8095, in supercritical fluid methods due to better molecular dispersion and better control over particle formation. In addition to potentially increased entrapment efficiency, supercritical fluid processing also offers the opportunity to control the size distribution and morphology of the particles much more effectively. Nevertheless, the effectiveness of this approach is not widely adopted in practice due to the cost of its operation, the need for special equipment, and its complexity. Thus, despite solvent evaporation being the most common method in laboratory-level and early translational research, supercritical fluid technology is becoming a promising, sustainable manufacturing strategy for phytosomal systems.

Optimization Strategies and Design of Experiments

Quality by Design (QbD) principles have replaced folk formulation development processes in phytosomal formulation development to enhance reproducibility and translational reliability. To mitigate essential process parameters, such as drug-to-phospholipid molar ratio, reaction temperature, and complexation time, Design of Experiments (DoE) techniques, such as Box-Behnken and Central Composite Designs, are typically used to optimize these conditions. Among these factors, the proportion of drugs to lipids warrants special attention because errors can result in either incomplete complexation or an excessively high lipid content [30]. The common goals of optimized phytosomal systems are to achieve specified critical quality parameters, such as a fine particle size distribution, a low polydispersity index, high entrapment efficiency, and sufficient surface charge. Although this formulation's robustness can be enhanced, the direct relationship between it and long-term clinical outcome has not been fully developed, underscoring the need for more translationally oriented formulation strategies [31].

Physicochemical Characterisation

Physicochemical characterization will be necessary to verify phytosome formation, formulation stability, and in vivo performance. Phytosomes, in contrast to traditional vesicular systems, are based on a specified molecular complexation; hence, characterization of the system concentrates on particle properties, as well as indicators of drug-phospholipid interaction and formulation reproducibility.

Particle size, polydispersity index, and zeta potential

Some physicochemical parameters are critical quality attributes (CQAs) in the formulation of phytosomal nanocarriers for cancer treatment, as they directly affect in vivo behavior, biodistribution, and therapeutic efficacy. Some of the most important CQAs are particle size, polydispersity index (PDI), and zeta potential. In the case of cancer-targeted nanocarriers, the particle size, usually between 80 and 200 nm, is considered optimal to exploit the enhanced permeability and retention (EPR) effect within tumor tissues. This nanoparticle size range accumulates in the tumor vasculature and undergoes minimal renal clearance. The polydispersity index must be low (below 0.3) to provide a uniform particle distribution and reproducible biological behavior [20]. Another essential parameter, not only for colloidal stability but also for systemic circulation and cellular interactions, is the zeta potential. Nanocarriers that have moderately negative or positive surface charges (about ±20 30 mV) are more electrostatically stable and have lower aggregation. Also, interactions with the plasma proteins and the reticuloendothelial system (RES) are strongly influenced by the surface charge. Nanoparticles with high charge levels can be rapidly opsonized and eliminated by macrophages. In contrast, middle-range charged and near-neutral particles can be characterized by much longer systemic circulation and longer half-lives in vivo. This oncotic circulation increases the likelihood of tumor accumulation via passive targeting mechanisms such as the EPR effect. Thus, zeta potential maximization is crucial for the stability of formulations and for the regulation of pharmacokinetics, biodistribution, and tumor targeting in phytosomal drug delivery systems [30].

Morphological Characterisation

The vesicular or micellar organization of phytosomes and particle size data obtained by dynamic light scattering are confirmed by additional morphological analyses using transmission or scanning electron microscopy. Phytosomes usually have smooth surfaces and are discrete, spherical structures. Nevertheless, morphology does not determine successful complexation and must be interpreted in conjunction with molecular characterization methods [26].

Entrapment efficiency and drug loading

The phytosomal system has a high level of EE because the drug is not entrained in the phospholipid but is molecularly bound to it. Well-established stoichiometric ratios enable effective drug loading at low levels of excipient overload [3]. Although high entrapment efficiency is highly desirable for formulation, it does not always translate into therapeutic efficacy, highlighting the need to match physicochemical information with biological performance [30].

Solid-state and molecular interaction studies

True phytosome formation has to be confirmed by evidence of drug-phospholipid interaction at the molecular level. Differential scanning calorimetry is typically used to identify alterations in thermal behavior, including loss or shifts in the drug's melting endotherm, changes in crystallinity, and changes in molecular dispersion within the lipid matrix. Complex formation is further evidenced by Fourier transform infrared spectroscopy and nuclear magnetic resonance spectroscopy, which detect modifications in characteristic functional group vibrations or proton environments arising from hydrogen

bonding. Lastly, these methods are all that is needed to make phytosomes more than a mere physical combination, and they are necessary to maintain formulation integrity.

Stability studies

The stability studies assess the ability of phytosomes to maintain particle size, drug content, and the complex intact under storage conditions. Hydrogen bonding can be altered by other factors, including temperature, humidity, and pH, leading to complex dissociation. Although short-term stability has been reported to be positive in most studies, there is limited information on long-term stability under clinically relevant conditions, which is a major challenge for translation [32]. All in all, physicochemical characterization is a critical piece of evidence of phytotransformation and the quality of a formulation [33]. Most reported studies, however, focus on physicochemical optimization without any direct relationship to in vivo pharmacokinetics or clinical outcomes. In future studies, the characterization parameters should be associated with therapeutic delivery performance to improve the clinical translatability of phytosomal drug delivery systems [34]. The stability of phytosomal complexes in different physiological environments is an important consideration for effective drug delivery. Phytosome formation relies primarily on hydrogen bonding interactions between the polar functional groups of phytochemicals and the phosphate or carbonyl groups of phosphatidylcholine. Although hydrogen bonds are relatively weaker than covalent interactions, the overall stability of the complex is enhanced by the amphiphilic phospholipid environment, which shields the phytochemical within the lipid-compatible structure. In the slightly acidic tumor microenvironment (pH ~6.5–6.8), partial weakening of hydrogen bonding interactions may occur due to protonation of functional groups. However, available experimental evidence suggests that phytosomal complexes generally remain structurally associated during systemic circulation and initial tumor accumulation. Rather than complete dissociation, the mildly acidic conditions may facilitate controlled release of the phytochemical from the phospholipid complex, thereby enhancing intracellular availability at the target site.

Nevertheless, the pH-dependent stability of phytosomal complexes remains an area that requires further investigation. Advanced analytical techniques such as differential scanning calorimetry, FTIR spectroscopy, and in vitro release studies under simulated physiological and tumor pH conditions are necessary to confirm the stability and release behavior of phytosomal formulations.

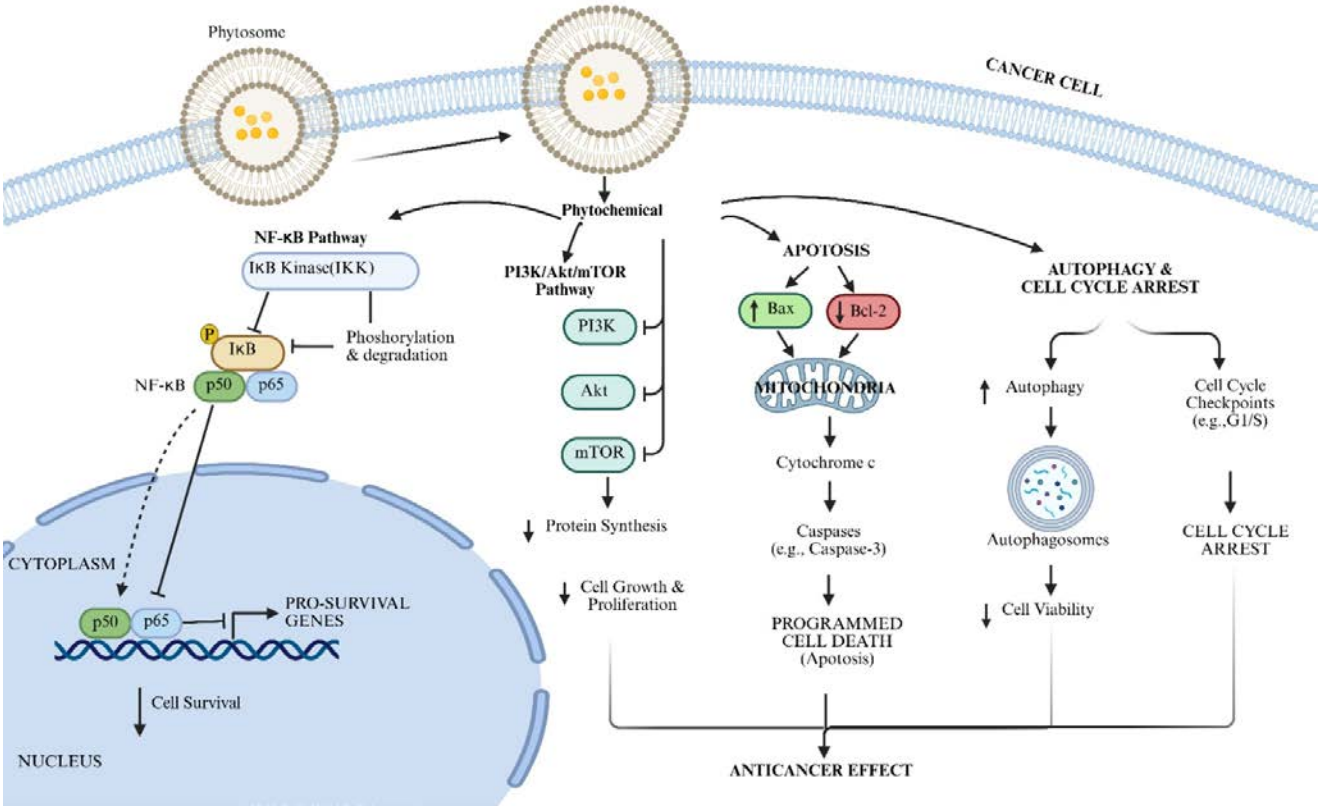

Figure 2: Intracellular anticancer mechanisms of phytosome-delivered phytochemicals

Mechanisms of Enhanced Anticancer Activity

The enhanced anticancer effect of phytosomal preparations is mainly due to improved pharmacokinetics and cellular delivery, rather than to the discovery of new pharmacological effects. Phytosomes can be used to deliver biologically relevant concentrations of phytochemicals to tumor sites by changing the disposition and cellular levels of the bioactive compounds, further enhancing the intrinsic anticancer properties of the parent compounds.

Improved Solubility and Bioavailability

Phytosomal complexation converts poorly water-soluble phytochemicals into a lipid-soluble form that can interact effectively with biological membranes. This amphiphilic property helps it partition into the membranes of the gastrointestinal epithelium, thereby increasing absorption and prolonging systemic exposure [35].

Various phytosomal preparations have been documented to have increased area under the concentration-time curve (AUC) and a long circulation time, allowing long plasma concentrations that are otherwise difficult to attain with conventional extracts. This is an important pharmacokinetic improvement required to translate in vitro anticancer activity into in vivo activity.

Cellular Uptake and Intracellular Trafficking

Phytosomes have a phospholipid-enriched surface that is very similar to that of cellular membranes and therefore internalize well via passive diffusion and endocytic routes [36]. This membrane affinity enables intracellular delivery of phytochemicals and can partially overcome efflux processes such as drug extrusion via P-glycoprotein [37]. Many intracellular concentrations. of drugs is therefore achieved, and cytotoxicity in cancer cells is increased compared with free phytochemicals [38].

Modulation of Apoptosis, Autophagy, and Cell Cycle

Upon intracellular internalization, phytochemicals delivered to the cell via phytosomes exhibit enhanced effects, owing to increased availability in the intracellular environment (Figure 2). Some of these effects include induction of apoptosis by regulating pro- and anti-apoptotic proteins, inhibition of survival signaling pathways, including PI3K/Akt/mTOR, and inhibition of transcription factors involved in tumor proliferation, inflammation, and metastasis, such as NF-κB. Notably, the mechanisms do not belong solely to phytosomes but are also enhanced by improved delivery and prolonged intracellular retention of the active compounds [39].

Pharmacokinetics and Bio-Distribution

Phytosomal encapsulation has the potential to modify drug distribution patterns by ensuring that phytochemicals remain intact and allowing selective concentration in tumor tissues. The nanoscale phytosomal systems could also employ passive targeting, e.g., the improved permeability of tumor vasculature, thereby enhancing local drug exposure. Nevertheless, the extent to which these distribution benefits translate into significant clinical benefit is variable and not adequately proven in large-scale clinical trials [40].

Translational Perspective

Phytosomal formulations have repeatedly shown superior anticancer effects in preclinical models; however, a significant portion of the effect is attributable to a more efficient delivery system rather than to a new biological action. Most mechanistic evidence is based on in vitro and animal research, and there are few direct correlations between mechanistic improvements and patient outcomes. Hence, the mechanistic benefits should be viewed with caution and confirmed through rigorous pharmacokinetic-pharmacodynamic and clinical studies.

In-Vitro and In-Vivo Evaluation of Phytosomal Anti-Cancer Systems

The preclinical testing of phytosomal preparations provides critical information on their potential therapeutic effects; the validity of this rests on their capacity to predict clinical effects. It has been shown in both *in vitro* and *in vivo* experiments that phytosome-based systems exhibit increased anti-cancer activity compared to free phytochemicals, principally due to improved delivery rather than changes in pharmacological activity.

***In vitro* cytotoxicity and cellular uptake studies**

As reported *in vitro* by cancer cell lines, the phytosomal formulations have been found to have lower half-maximal inhibitory concentration (IC_{50}) than the respective free phytochemicals. To a large extent, this increased cytotoxicity is due to an increased cellular uptake and prolonged retention in the cell. Fluorescence-based uptake analysis and quantitative assays show that phytosome-bound phytochemicals are more readily taken up by cancer cells, supporting phospholipid-mediated membrane interactions in intracellular delivery [41]. Despite these benefits, in vitro models do not capture key factors

(systemic metabolism, tumor microenvironmental complexity, and immune interactions, etc.). Accordingly, improved cytotoxicity is better evidence of improved delivery, but it cannot predict in vivo or clinical activity [42].

***In vivo* anti-tumor efficacy and safety assessment**

Animal research has also shown that phytosomal formulations are better than traditional extracts in inhibiting tumor growth and in their pharmacokinetic profiles. Phytosomal delivery of curcumin, silibinin, and quercetin has been shown to produce better tumor volume reduction and longer systemic exposure in xenograft and chemically induced tumor models than free drugs [43]. Notably, lower systemic toxicity and greater tolerability are reported in many studies, as evidenced by maintained body weight and the absence of organ dysfunction. Such observations suggest that phytosomes may increase the therapeutic index of phytochemicals. Nevertheless, cross-study comparability and translational predictability are hampered by variability in animal models, dose schedules, and endpoints [44].

Bridging the Gap between In-Vitro IC50 Values and In-Vivo Therapeutic Efficacy

Although in vitro cytotoxicity-based assays are useful for measuring the anticancer effects of phytosomal preparations, half-maximal inhibitory concentrations (IC50) values commonly do not translate into therapeutic effects in vivo. The discrepancy arises from the inability of conventional two-dimensional (2D) cell culture systems to recapitulate the complexity of the tumor microenvironment, including vascularization, extracellular matrix interactions, metabolic gradients, and immune system interactions. Several experimental approaches have been offered to enhance the translational utility of preclinical research. To begin with, three-dimensional (3D) tumor spheroid models and organoid systems are used, which offer a more physiologically relevant architecture that better represents tumor penetration and drug diffusion. Such models can more accurately represent nanoparticle delivery and intracellular delivery efficiency. Second, pharmacokinetic-pharmacodynamic (PKPD) modeling would be beneficial for correlating in vitro cytotoxicity data with systemic drug and tumor concentrations in vivo. These techniques can enable scientists to anticipate therapeutic windows and can optimize the dosage of phytosomal preparations. Third, more sophisticated in vivo imaging and biodistribution techniques, such as fluorescence or radiolabelled nanoparticle imaging, can provide important information on tumor localization, systemic clearance, and off-target localization. Such data will be crucial in supporting the claim that improved cellular uptake in the in vitro test can translate into better tumor treatment. Lastly, experimental models that account for tumor microenvironment-relevant parameters, such as hypoxia, pH gradients, and immune interactions, have the potential to increase the predictive power of preclinical testing. Collectively, the measures could help close the gap between in vitro potency and in vitro anticancer efficacy of phytosomal drug delivery systems.

Comparative Performance with Conventional Extracts

Phytosomes are always shown to be better bioavailable and antitumor effective in preclinical systems than non-formulated phytochemicals or control lipid systems. Phytosomal formulations have been shown to exhibit synergistic effects when combined with conventional chemotherapeutic agents, thereby reducing the dose of cytotoxic drugs. Although these observations are positive, they rely heavily on short-term efficacy endpoints rather than survival outcomes [45].

Translational Limitations of Preclinical Evidence

Most phytosomal anticancer systems are still limited to laboratory and preclinical research, despite good performance in preclinical trials. The existing data are limited in translational value due to a lack of standardization in experimental design, the absence of pharmacokinetics-pharmacodynamics correlations, and the use of surrogate endpoints. Moreover, very little research directly addresses long-term safety, reproducibility, or scalability, which are key to clinical progress.

Targeted and Advanced Phytosomal Approaches

Although traditional phytosomes primarily rely on increased bioavailability and passive delivery, most recent research has focused on developing advanced phytosomal systems with enhanced targeting and controlled drug release. The strategies are designed to enhance tumor selectivity, minimize off-target effects, and enhance therapeutic efficacy, but their clinical application is in its infancy.

Ligand-functionalized and tumor-targeted phytosomes

Active targeting protocols refer to the surface modification of phytosomes using receptor-overexpressing surface ligands on cancer cells. Ligands such as folic acid, hyaluronic acid & peptides have been investigated to induce receptor-mediated endocytosis and increase the intracellular delivery of

phytochemicals. As an example, hyaluronic acid-conjugated phytosomes have been shown to increase uptake in tumor cells overexpressing CD44. In contrast, folate-modified systems have been shown to increase affinity for tumor cells expressing folate receptors [46]. Although the ligand-functionalized phytosomes show good *in vitro* and *in vivo* performance, the ligand-functionalized phytosomes are associated with the problems of translational performance, including the complexity of formulation, surface conjugation stability, and the ability to obtain a batch-to-batch performance reproducibly. In addition, heterogeneity in receptor expression across tumors may limit the usefulness of active targeting in clinical practice [47]. Several ligand-functionalized phytosomal systems have been explored to enhance tumor-specific targeting through receptor-mediated uptake. These ligands are typically selected for their affinity for receptors overexpressed on cancer cells. By conjugating targeting ligands to the surface of phytosomal carriers, it is possible to enhance cellular uptake via receptor-mediated endocytosis and increase the accumulation of phytochemicals in tumor tissues (Table 2).

Table 2: Examples of ligand-functionalized phytosomal or lipid-based nanocarriers for targeted cancer therapy

Ligand	Target receptor	Cancer types commonly targeted	Functional advantage
Folic acid	Folate receptor (FR-α)	Ovarian, breast, and lung cancer	Receptor-mediated endocytosis and improved tumor uptake
Hyaluronic acid	CD44 receptor	Breast, pancreatic, colorectal cancer	Enhanced targeting of CD44-overexpressing tumor cells
RGD peptides	Integrin receptors (αvβ3)	Glioma, melanoma	Targeting of angiogenic tumor vasculature
Transferrin	Transferrin receptor (TfR)	Brain tumors, leukemia	Improved cellular uptake in rapidly proliferating cells
Antibody fragments	Tumor-specific antigens	Various cancers	High specificity targeting

Stimuli-responsive and smart phytosomal systems

Phytosomes can be stimuli-responsive, releasing their therapeutic cargo in response to tumor-associated stimuli, such as acidic pH, redox conditions, or external stimuli, such as heat or magnetic fields. The objective of these systems is to increase local drug release and reduce systemic exposure. pH-sensitive phytosomes, such as those, can take advantage of the acidic microenvironment in the tumor to increase selective release of the drug. Despite their ability to achieve high control over drug delivery, such smart systems have only limited practical applications due to the complexity of formulations, their inability to scale, and the lack of solid clinical validation. The predictability and safety of stimulus-induced release in humans have not been properly investigated [48, 49].

Combination therapy and co-delivery strategies

The phytosomal platforms have also been investigated for co-delivering phytochemicals with traditional chemotherapeutic agents. This strategy aims to leverage the chemo-sensitizing capabilities of phytochemicals, which may not only increase anticancer activity but also reduce dose-proportional toxicity of cytotoxic agents. Preclinical results indicate synergistic effects with some combinations, but the optimal drug ratios, timing, and protracted safety have not been systematically studied [50]. It is important to clarify that phytosomal formulations generally do not introduce entirely new pharmacological mechanisms compared with the parent phytochemicals. Instead, their primary role is to enhance drug delivery by improving solubility, membrane permeability, and intracellular accumulation. As a result, the observed improvement in anticancer activity is mainly attributable to increased bioavailability and more efficient delivery of the active compound to tumor cells.

The synergistic effects observed in some combination therapy studies should therefore be interpreted cautiously. In most cases, such synergy does not arise from a novel pharmacological mechanism introduced by the phytosomal carrier itself. Rather, improved cellular uptake and prolonged intracellular retention of phytochemicals may enhance their interaction with existing molecular targets or increase the effectiveness of co-administered chemotherapeutic agents. Consequently, phytosomes function primarily as delivery enhancers that amplify the intrinsic pharmacodynamic properties of phytochemicals rather than creating fundamentally new therapeutic mechanisms.

Translational and Clinical Perspectives

To translate phytosomal drug delivery systems developed in laboratory research into clinical oncology, it is important to consider manufacturing feasibility, regulatory aspects, and the

quality of clinical evidence. Despite their demonstrated reliability in enhancing the pharmacokinetics of anticancer phytochemicals, the transition of phytosomes into clinical practice remains uneven and limited.

Scale-up, Manufacturing, and Regulatory Considerations

Large-scale production is one of the key translational limitations to the phytosomal formulations. Solvent-based complexation methods are used to form the majority of phytosomes and are suitable for laboratory use, but they pose challenges for industrial-scale production. At large production volumes, controlling critical quality attributes such as drug lipid stoichiometry, particle size distribution, and residual solvent content becomes more complex. Furthermore, the need to use pharmaceutical-grade phospholipids greatly increases production costs, rendering them commercially unviable and unavailable [29].

There is a lack of regulatory classification of phytosomal products, and the process varies by geographic region. In most instances, phytosomes are marketed as nutraceuticals or dietary supplements rather than as therapeutic drugs, which limits their clinical claims, despite their proven pharmacokinetic benefits. To transform phytosomal preparations into regulated anticancer therapeutics, toxicological review, standardized botanical extracts, and carefully designed clinical trials would be necessary. The absence of harmonized regulatory regimes for phytosomal systems continues to hinder their clinical development.

Comparative Production Cost Considerations

From a translational perspective, manufacturing cost is an important factor influencing the clinical feasibility of lipid-based nanocarriers. Compared with liposomal drug delivery systems, phytosomal formulations generally involve simpler preparation processes and fewer structural components. Liposome production often requires multiple lipid constituents, such as phosphatidylcholine, cholesterol, and stabilizing agents, as well as complex processing techniques, including thin-film hydration, extrusion, or high-pressure homogenization.

These processes frequently require specialized equipment and strict process control, contributing to higher manufacturing costs. In contrast, phytosomes typically involve a stoichiometric complexation between a phytochemical and a single phospholipid component, commonly phosphatidylcholine, using relatively simple solvent-based complexation methods. As a result, phytosomal systems may have lower formulation complexity and potentially reduced production costs at laboratory and pilot scales. However, the requirement for pharmaceutical-grade phospholipids and solvent purification still contributes significantly to overall manufacturing expenses. Therefore, while phytosomes may offer a more cost-efficient alternative than some liposomal systems, their economic feasibility depends on scale-up strategies, raw material sourcing, and manufacturing optimization.

Clinical Evidence and Current Development Status

Several phytosomal preparations have already undergone early-stage clinical trials, primarily as an adjunct to standard chemotherapy. These papers have documented enhanced bioavailability, tolerable safety profiles, and regulation of surrogate biomarkers, including inflammatory indicators or tumor proliferation indices. Nevertheless, the majority of available clinical data are Phase I or Phase II trials involving small patient groups and brief follow-up periods (Table 3). Notably, there is an apparent lack of strong Phase III trials with survival-based endpoints that would allow conclusive inferences about clinical effectiveness.

Table 3: Clinical trials of phytosomal formulations in oncology [23, 40, 51-53]

Formulation (Trade Name)	Phytochemical	Indication	Phase	Key outcomes
Meriva®	Curcumin	Pancreatic Cancer	Phase II	Combination with Gemcitabine showed a disease control rate of 61.3%, well tolerated.
Siliphos®	Silibinin	Prostate Cancer	Phase II	High-dose silibinin phytosome (up to 13 g/day) showed stabilization of PSA levels and delayed disease progression in some patients, with manageable toxicity [59]
Greenselect® Phytosome	EGCG (Green Tea)	Breast Cancer	Pilot (Phase I/II)	Increased BA; EGCG detected in breast tissue; significant reduction in Ki-67 proliferation index.
Berberine Phytosome	Berberine	PCOS / Metabolic	Clinical	Improved insulin resistance and lipid profiles, relevant for metabolic regulation in cancer.

Challenges in Clinical Translation

The gap between good performance in preclinical studies and poor performance in clinical adoption underscores the need for more translational-relevant research strategies. Standardized formulation guidelines, pharmacodynamics-pharmacokinetic relationship, and clinical endpoints should be the areas of clinical development in the future. Phytosomes can also have their most natural application as an adjuvant or combination therapy, in which increased delivery of phytochemicals can either improve therapeutic outcomes or reduce toxicity from conventional anticancer agents [9].

Safety, Toxicological, and Regulatory Aspects

Safety, toxicological profile, and regulatory classification of the phytosomal drug delivery system are important and should be evaluated in depth to facilitate clinical translation. As much as the idea of phytosomes seems to be a safer alternative to traditional synthetic nanocarriers, owing to their biocompatible constituents, such postulations need to be supported by systematic preclinical and clinical evidence.

Metabolic Fate of Phospholipid Carriers

Although phosphatidylcholine is widely regarded as a biocompatible and physiologically relevant lipid, understanding the metabolic fate of the phospholipid carrier in phytosomal formulations is important for long-term safety evaluation. After systemic administration, phosphatidylcholine-containing nanocarriers are typically metabolized through endogenous lipid metabolic pathways. Enzymes such as phospholipases can hydrolyze phosphatidylcholine into lysophosphatidylcholine and free fatty acids, which subsequently enter normal lipid metabolic cycles, including membrane biosynthesis and lipoprotein transport. Despite this inherent biocompatibility, prolonged exposure to phospholipid-rich formulations during chronic cancer therapy may, in principle, alter lipid distribution or accumulation in organs involved in lipid metabolism, particularly the liver and spleen. Such accumulation could potentially influence lipid homeostasis or interact with hepatic lipid-processing pathways. Current preclinical studies generally report good tolerability and minimal systemic toxicity for phosphatidylcholine-based nanocarriers; however, long-term biodistribution and metabolic fate studies remain limited. Therefore, comprehensive pharmacokinetic and tissue distribution analyses are necessary to evaluate whether repeated administration of phospholipid-based carriers could lead to tissue accumulation or metabolic perturbations, particularly in patients undergoing prolonged anticancer therapy.

Safety and Toxicological Considerations

Phytosomal preparations consist mostly of naturally occurring phytochemicals as well as phospholipids, including phosphatidylcholine, which is naturally present in biological membranes. The available acute and sub-chronic toxicity profiles for a wide range of phytosomal preparations have mostly yielded positive safety profiles, with high tolerability and no organ toxicity most often observed at therapeutic doses. In other animal trials, phytosomes have been shown to reduce systemic toxicity compared to free phytochemicals, likely due to increased bioavailability and reduced dose [44].

Nonetheless, phytosomes cannot be evaluated for safety based on the established safety of their constituents. Biodistribution, tissue accumulation, and metabolic fate of phytochemicals can be changed in molecular complexation and nanoscale organization. The long-term toxicity, immunogenicity, and any drug-drug interactions are not well-researched, especially in the case of chronic cancer treatment regimens. In addition, considerable variation in botanical extracts between batches of homogenates raises concerns about the reproducibility of toxicological results, highlighting the importance of standardized raw materials and effective safety assessment procedures [54].

Regulatory Challenges

The regulatory classification of phytosomal products remains unclear and varies across jurisdictions. In most localities, phytosomes are sold as nutraceuticals or dietary supplements without making therapeutic claims, even when pharmacokinetic benefits have been demonstrated. Under the conditions that phytosomal formulations are used as anticancer therapeutics, they undergo rigorous regulatory requirements, such as extensive toxicological tests, quality control of botanical sources, and have to prove clinical activity [55]. One of the most significant regulatory issues is that phytosomes have dual character as both formulation-enhanced botanical products and nanocarriers. There tends to be a lack of specific regulations to guide such hybrid technologies, leading to confusion about the approval process. Furthermore, there are no harmonized international standards for characterization, stability testing, and clinical evaluation, which makes it more difficult to obtain acceptance from regulatory authorities.

Regulatory Roadmap for Clinical Translation of Phytosomal Therapeutics

Although most phytosomal products are currently sold as nutraceuticals or dietary supplements, they must be properly brought through the approved pharmaceutical regulatory procedures to be converted into approved therapeutic drugs. The United States has several possible approval pathways that can be used in various scenarios, depending on the phytochemical's properties and the level of clinical information available.

The FDA 505(b)(2) regulatory way is one of the possible ways, and the applicant is free to depend on printed literature or prior approved drug information partially, but present new information on improvements in formulations, safety, and clinical effectiveness. The pathway will be of particular interest to phytosomal preparations of established phytochemicals such as curcumin or silibinin, for which existing pharmacological and safety data are already available. Another alternative is phytosomal preparations under the FDA Botanical Drug Development pathway, which provides regulatory guidance for complex plant mixtures intended for therapeutic use. This route includes strict standardization of botanical raw materials, repeatable manufacturing regimes, and appropriately designed clinical trials that prove effectiveness. In the European regulatory system, analogous products might be reviewed as herbal medicinal products by the European Medicines Agency (EMA) or under the hybrid application route, in which partially established active substances can be reformulated using novel delivery technologies. Thus, effective regulatory translation of phytosomal anticancer formulations will most likely rely on robust quality regulation of botanical extracts, normalization of phospholipid complexation mechanisms, in-depth toxicological testing, and efficient clinical trials that demonstrate the therapeutic benefit of phytosomal formulations relative to standard formulations.

Clinical Safety Evidence

There have been no significant clinical studies comparing phytosomal formulations with a placebo. Yet, the majority of those tested have shown good safety and tolerability, especially when administered as supplements alongside conventional chemotherapy. Reported side effects are normally mild and gastrointestinal. However, available clinical safety data are mostly from small-scale Phase I or Phase II trials with short-term follow-up. There is a limited body of long-term safety data, particularly among oncology patients receiving combination therapies.

Translational and Regulatory Outlook

To enter a broader regulatory framework and gain acceptance in clinical practice, future phytosomal drug delivery system development should place greater emphasis on standardized formulation procedures, extensive toxicological characterization, and quality-by-design principles. There should be a clear distinction between nutraceutical and pharmaceutical positioning to eliminate ambiguity in regulation. Significantly, efficacy assessment must be combined with safety assessment to ensure that the increased bioavailability is not translated into unexpected toxicity.

Future Directions and Emerging Trends

The changes in the research priorities will require altering the research focus toward clinical translatability & regulatory readiness to make further phytosomal drug delivery developments in cancer therapy. Although phytosomes have proven to provide consistent changes in bioavailability and preclinical efficacy, their long-term effects will be identified by their ability to meet clinical, manufacturing, and regulatory demands [56]. Emerging studies are also investigating nano-sized phytosomal systems to enhance tumor accumulation and intracellular delivery. Passive targeting by optimizing particle size and surface can be enhanced; size reduction is likely to greatly enhance clinical benefit, although it remains unlikely to be sufficient on its own.

Future research needs to quantify specific pharmacokinetic-to-pharmacodynamic relationships to rationalize nanoscale optimization in clinical practice [57]. Improvements in tumor specificity. Surface-functionalized phytosomes containing ligands that facilitate receptor-mediated uptake are also a promising avenue for enhancing tumor specificity. However, the clinical translation of targeted phytosomes remains limited due to tumor heterogeneity, the greater complexity of the formulations, and the difficulty in producing large quantities. Simple and repeatable targeting plans with proven clinical benefit compared to non-targeted systems will be required. There are potential applications of stimuli-responsive phytosomal systems that deliver drugs in response to tumor-specific stimuli, such as pH or redox gradients. Although the experimental results are encouraging, the effectiveness of such

systems is poorly tested with respect to clinical predictability and safety. The next step should focus on robustness, safety, and reproducible designs rather than on elaborate stimulus-responsive designs [58].

CONCLUSION

Our findings conclude that phytosomal drug delivery systems provide a scientifically robust and formulation-driven approach to overcome key biopharmaceutical and pharmacokinetic limitations of anticancer phytochemicals, including poor aqueous solubility, limited membrane permeability, rapid metabolism, and low systemic availability. Phospholipid complexation of bioactives such as curcumin, silibinin, quercetin, catechins, and berberine consistently enhances bioavailability, cellular uptake, and therapeutic performance, primarily through improved delivery efficiency rather than modification of intrinsic pharmacological activity, thereby improving the therapeutic index with minimal systemic toxicity in preclinical settings. However, despite promising experimental evidence, clinical translation remains constrained by limited large-scale clinical trials, variability in botanical extract standardization, insufficient long-term safety data, manufacturing scale-up challenges, and regulatory ambiguity. Our review highlights the need for standardized formulation strategies, quality-by-design implementation, robust PK–PD correlations, and well-designed clinical studies to facilitate successful bench-to-bedside translation. With continued technological refinement and regulatory alignment, phytosomes hold strong potential to evolve as clinically viable platforms for transforming anticancer phytochemicals into evidence-based therapeutic interventions.

From a regulatory perspective, the successful clinical translation of phytosomal drug delivery systems will increasingly depend on the practical implementation of Quality by Design (QbD) principles. QbD enables systematic identification and control of critical quality attributes (CQAs), critical material attributes (CMAs), and critical process parameters (CPPs) during formulation development. For phytosomal systems, key CQAs may include particle size distribution, zeta potential, drug–lipid stoichiometry, and entrapment efficiency, while CMAs involve phospholipid purity and phytochemical characteristics. By applying statistical design of experiments (DoE), formulation variables such as drug-to-lipid ratio, reaction temperature, and solvent conditions can be optimized to ensure consistent product quality and batch-to-batch reproducibility. Such structured development strategies align closely with regulatory expectations from agencies such as the FDA and EMA, which increasingly emphasize risk-based pharmaceutical development and robust manufacturing controls. Therefore, integrating QbD principles into phytosomal formulation design may significantly facilitate regulatory approval and support the transition of phytosomal technologies from experimental systems to clinically approved therapeutic products.

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NIL

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTION

Sujatha Damera wrote the original draft. Mounika Kuchukuntla helped with the data analysis. Mani Sharma worked with figures, data interpretation, and bibliography. Ram Mohan Manda helped collect data. Ananda Kumar Chettupalli created a graphical abstract and a critical revision of the article. Rajendra Kumar Jadi communicated and guided in the journey from the draft preparation to publication. All authors reviewed and consented to the final approval of the article.

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