Phytochem Rev
https://doi.org/10.1007/s11101-024-09947-7

Phytosomes: a critical tool for delivery of herbal drugs for cancer

Phytosomes: Advancing Herbal Medicine Delivery

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Received: 3 April 2023 / Accepted: 23 February 2024

Abstract Phytosomes represent specialized vesicular structures akin to liposomes, encapsulating active phytoconstituents within a lipid core. Many phytoconstituents, such as glycosides and flavonoids, exhibit hydrophilic properties and encounter challenges traversing lipid-based cellular membranes. Nevertheless, the lipid core of phytosomes enhances their permeability across these barriers, thereby augmenting the bioavailability and efficacy of enclosed plant components. Cancer remains a prominent global cause of mortality, posing significant challenges for existing treatments, which often entail serious side effects associated with conventional approaches like surgery, radiation therapy, and chemotherapy. In exploring alternative strategies, the utilization of herbal active compounds in cancer treatment shows considerable promise in synergizing with conventional methods. While natural plant-derived active components demonstrate robust in vitro pharmacological activity, their in vivo absorption is often limited. Addressing this constraint, phytosomes emerge as a burgeoning nanotechnology offering a solution by enhancing the adaptability of bioactive phytoconstituents within lipid-rich barriers. This study delves into a meta-analysis of the physicochemical attributes of phytosomes, elucidating their structural intricacies. Furthermore, the review discusses the advantages and disadvantages of phytosomes as carriers for herbal drugs, shedding light on patented phytosome technologies and associated clinical trials. Additionally, it examines several prominent phytosome-based herbal constituents showcasing notable anticancer properties. Lastly, the review addresses the challenges and potential future directions regarding the use of phytosomes in cancer therapy.

Keywords Phytosomes · Herbal medicines · Phospholipid · Nanocarrier · Drug delivery · Liposomes

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Published online: 04 April 2024

Introduction

Cancer arises from the abnormal and uncontrolled activity of transcriptional factors, often driven by genetic mutations. Statistics highlight cancer as a leading cause of death in developed countries. According to a World Health Organization (WHO) report from 2008, there were 13 million new cancer diagnoses and almost 8 million cancer-related deaths globally. Furthermore, projections suggest that by the year 2050, there could be an estimated 27 million new

cases of cancer and an annual death toll of 17.5 million from the disease (Ramasamy and Agarwal 2008). In recent times, significant strides have been made in developing new anti-cancer drugs, especially innovative drug delivery systems. These advancements aim to improve the effectiveness and availability of medications, ensuring targeted drug delivery to cancerous cells while minimizing harm to healthy cells.

Nanotechnology represents a pioneering approach in targeted drug delivery for cancer treatment and is poised to revolutionize future medical advancements. Various nanostructures, including nanoparticles, liposomes, dendrimers, and micelles, serve as controlled release systems in the battle against cancer (Mateti et al. 2021). Leveraging their distinct attributes such as nano-scale dimensions (200 nm), enhanced drug pharmacokinetics and pharmacodynamics, and superior in vitro stability with primary drug accumulation at tumor sites, lipid-based nanocarriers like liposomes, phytosomes, Solid Lipid Nanoparticles (SLNs), and Nanostructured Lipid Carriers (NLCs) demonstrate enhanced biodistribution and prolonged retention effects. In the pursuit of targeted delivery of anticancer agents using nanocarriers, the development of well-designed delivery systems is paramount. Herbal remedies have long been integral to healthcare practices in developing countries, owing to their natural antibacterial properties. Ongoing research investigates the properties and potential applications of tropical plant extracts to develop nano-based treatments for ailments such as cancer (Palmier 2017). Natural substances, typically in extract form, undergo rigorous investigation for their bioactive potential. Extracts demonstrating promising bioactivity undergo further processing to isolate and identify active components. Plants, in particular, have been extensively examined as natural reservoirs for anti-cancer properties (Yap et al. 2021). Although natural plant-derived active compounds exhibit potent in vitro pharmacological effects, their in vivo absorption often remains moderate (Lu et al. 2019; Alhakamy et al. 2020a, 2020b; Cott 1995; Awasthi et al. 2011). The challenge of low water solubility and consequently restricted in vivo absorption underscores the necessity for innovative medication delivery techniques. Nanotechnology-driven delivery systems are emerging as solutions to enhance the bioavailability of compounds with low solubility (Gandhai et al. 2012; Bombardelli et al. 1989; Dang 2000; Rasaee et al. 2014).

The term "phytosome," derived from the combination of "phyto" and "some," encompasses both plants and cellular structures. It is also known as "herbosome" in certain literature. Phytosomes, akin to liposomes, aim to enhance bioavailability and absorption, overcoming drawbacks of traditional plant extracts. This innovative vesicular drug delivery technology incorporates plant extracts or hydrophilic phytochemicals into phospholipids to form micelles in the presence of water (Karpuz et al. 2020). Plant extracts rich in polyphenols intensify this relationship even more. Polyphenolic compounds are encapsulated by the micellar arrangement, which is the result of the bonding of polar functional groups of lipophilic chemicals with the charged phosphate head of phospholipids through hydrogen bonds and polar interactions. Phytosomes are different from liposomes in that they incorporate the bioactive substance into the micelle and link chemically with the polar heads of phospholipids as shown in Fig. 1. Phytosomes transport both water—and lipid-soluble substances via liposomes, in contrast to liposomes, which can only hold molecules that are soluble in water. Phytosomes are used as a vesicular drug delivery mechanism in cancer treatment, especially in tumor therapy. Phytosomes that have a molecular weight more than 40 kDa and a nanometric size range of 100–1200 nm actively target tumor cells, improving penetration and retention, in contrast to conventional vesicular drug delivery systems that passively target drug carriers. This dual approach combines passive targeting to increase drug bioavailability with active targeting to specifically deliver drugs to the site of action, offering an effective strategy for delivering bioactive compounds (Azeez et al. 2018).

Role of herbal medicines in cancer therapy

For a significant duration, herbal remedies have stood as the cornerstone of healthcare in developing nations. Plants, owing to their inherent antibacterial properties (Manach et al. 2004; Mascarella 1993; Bombardelli et al. 1994), have been prominently featured in therapeutic practices. Consequently, there has been a surge in research interest focused on exploring extracts from terrestrial plants to develop next-generation nanomaterial-based therapies for conditions such

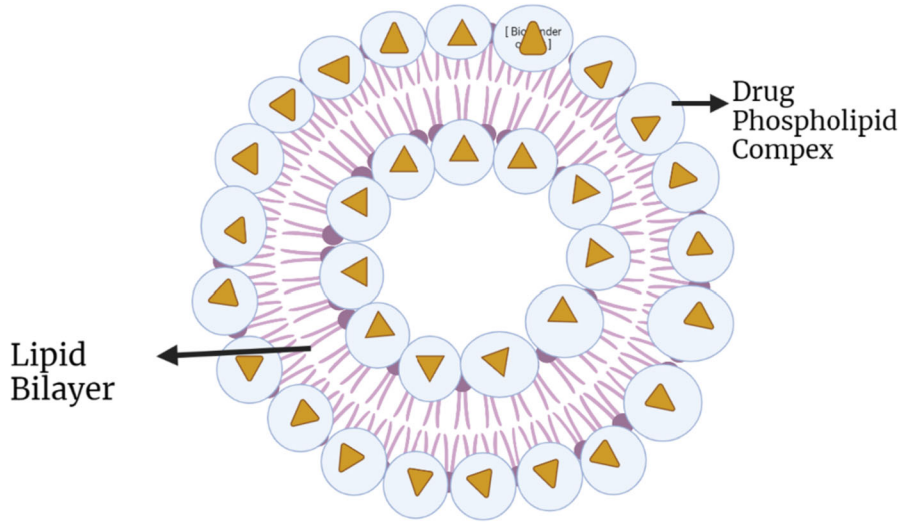

Fig. 1 Structure of phytosomes

as cancer. While many plants are acknowledged for their health-promoting attributes in modern societies, indigenous herbs hold a pivotal role in traditional medicine, particularly in Asia and Africa. As per the World Health Organization (WHO), some nations exclusively rely on plant-based medications, with developing countries also leveraging naturally occurring compounds for therapeutic purposes. Notable compounds isolated from terrestrial plants for their anticancer effects include polyphenols, taxols, and brassinosteroids.

The Indian market offers more than 75 formulations aimed at enhancing human health and vitality. Triphala, a supplement renowned for its potent anticancer properties, is incorporated into over 219 preparations. The capacity of numerous plant extracts to augment treatment outcomes and serve as adjuncts in cancer therapy protocols is widely acknowledged (Koul 2020). In scenarios where conventional biomedical treatments prove ineffective or are unavailable, the Ayurvedic approach, which emphasizes enhancing tissue metabolism, improving digestion, purifying toxins, and inhibiting tumor growth, is deemed beneficial. Nanotechnology emerged as a groundbreaking field several decades ago, providing solutions to various biopharmaceutical challenges. It has revolutionized the pharmaceutical and medical domains by addressing unmet needs. The development of herbal formulations via nanotechnology not only meets these needs but also offers additional advantages such as improved solubility, bioavailability, toxicity management, pharmacological activity, stability, maintenance of release profiles, as well as physical and chemical stability. These benefits contribute to achieving desired levels of safety and efficacy in herbal products. Numerous scientists are engaged in developing novel drug delivery systems, including plant phytosomes, liposomes, microspheres, prolonged and extended-release formulations, transdermal dosage forms, mucoadhesive systems, and orally disintegrating tablets (Kulkarni 2011; Patel et al. 2009). For instance, the initial production of a polyherbal orodispersible tablet has been achieved, with additional formulations currently undergoing laboratory development. Nevertheless, herbal medications present several challenges that necessitate addressing. These challenges encompass conducting clinical trials for herbal drugs, establishing straightforward bio-assays for biotic environments, devising toxicological and pharmacological evaluation methods, determining absorption sites, handling potentially toxic herbal formulations, identifying suitable animal models for assessing toxicity and safety, navigating the complexities of conducting clinical trials with herbal products, and creating bioassays to standardize biological activities (Devi et al. 2010).

Novel approaches for cancer treatment

Immunotherapy

Immunotherapy enhanced the immune system's capacity to combat cancer, often termed as biological therapy, as it harnesses the body's innate defenses to

target and counteract malignancies. Extensive research has been conducted on the application of monoclonal antibodies, which instruct the immune system to identify and eliminate cancer cells as a therapeutic approach. These antibodies target and inhibit the function of specific proteins by binding to cancer cells. This therapy approach is secure (Wang et al. 2018). Immunotherapies often face limitations due to adverse events related to the immune system, including inflammatory responses targeting the host's healthy tissues and immune activation.

Targeted therapy

The popularity of targeted therapeutic drugs in cancer treatment is growing, given their enhanced efficacy and safety when compared to traditional chemotherapy agents. Following the Food and Drug Administration's (FDA) 2001 approval of imatinib, the first tyrosine kinase inhibitor, a number of small-molecule targeted cancer treatments have been developed. The primary classifications of targeted drugs encompass macromolecules and small molecules, encompassing entities such as monoclonal antibodies, polypeptides, antibody–drug conjugates, and nucleic acids (Cross and Burmester 2006). Challenges in targeted cancer therapy include the absence of precise preclinical models for predicting drug efficacy, ineffective clinical development strategies, and limited single-agent activities.

Gene therapy

Clinical trials of gene-based cancer therapies encompass techniques such as Gene transfer of cytokines in ex vivo and in vivo settings, as well as the delivery of prodrugs gene-mediated drug sensitization, and safeguarding bone marrow with drug-resistant genes from high-dose chemotherapy. Two approaches to addressing the genetic alterations in cancer cells involve gene replacement and the deactivation of oncogenes and tumor suppressor genes (Zaimy et al. 2017). The word "gene therapy" refers to a broad category of medical practices that use genetic material to modify cells in vivo or in vitro in order to address and treat various disorders. Numerous preclinical and in vitro animal models have demonstrated exceptional efficacy when used to assess different gene therapy therapies. The advancement of cancer vaccines, the directing of viruses towards cancer cells to induce lysis and elimination, the inhibition of blood flow to tumors, and the introduction of genes into cancer cells to trigger cell death or restore their normal characteristics have all demonstrated enhanced survival outcomes (Cross and Burmester 2006).

Nanocarrier for cancer therapy

Nanotechnology-based cancer therapies are frequently used to promote the safety and efficacy of cancer treatment while also enhancing medication solubility, stability, and multidrug resistance. Effective drug delivery techniques based on nanotechnology include A class of synthetic, non-bioactive, nonviral vectors includes exosomes, polymersomes, dendrimers, nanoparticles, polymeric drug conjugates, and polymeric micelles. They offer a stable method of supplying medicinal materials to cells. Unique benefits of this strategy include low immunogenicity, reduced toxicity, and flexibility for chemical alterations (Mitra et al. 2015).

Hormone therapy

Prostate cancer and breast cancer with oestrogen and progesterone receptors hormone treatment is both safe and effective in successfully treating both conditions. The advancement of the disease occurs as the majority of individuals with metastatic breast and prostate cancer, who initially respond to hormone therapy, eventually develop resistance. The molecular causes of resistance are numerous, varied, and poorly understood. Two potential ways include heightened hormone receptor sensitivity and pathway activation without hormone exposure (Abrahman and Staffurth 2020). In addressing certain cancers that depend on these substances for growth and dissemination, hormone treatment diminishes the levels of hormones within the body. Breast, reproductive system, and prostate cancers are all managed through this approach. The adverse effects vary according to the cancer type, age, sex, and type of medication used in the treatment (Wang et al. 2018).

Nanoparticles

Nanoparticles range in size from 10 to 1000 nm, and their structure is tailored based on the intended

application. In drug delivery, medications are incorporated, enclosed, trapped, or bonded to a nanoparticle matrix to enhance solubility (Ozturk-Atar et al. 2018). Nanoparticles exhibit improved deep tissue penetration, utilizing the enhanced permeability and retention (EPR) effect. Efficiently traversing epithelial fenestration is influenced by their surface properties, affecting bioavailability and half-life. Adjusting particle polymer properties allows for the optimization of medication release rates, influencing the therapeutic impact of nanoparticles in cancer prevention and treatment (Gavas et al. 2021). Despite challenges in formulation, drug loading, and scale-up processes, nanoparticles hold significant potential for FDA/EMA approval. Inorganic nanoparticles, such as nanometer-sized quantum dots, manganese phosphate nanoparticles, noble metals, carbon nanotubes, silica nanoparticles, and magnetic nanoparticles, are particularly noteworthy for their size-dependent physical characteristics and suitability for cancer treatment and diagnosis (Ipar et al. 2019).

Dendrimer

Dendrimers, characterized by a hyperbranched topology, are spherical polymeric macromolecules with well-defined branching architectures (Gavas et al. 2021). These dendrimers possess unique properties, including tunable surface functionality, multi-valency, water solubility, mono-disperse size, and internal drug space, making them advantageous for drug administration (Zaimy et al. 2017).

Micelle

Polymeric micelles, ranging in size from 5 to 100 nm, are effective in transporting poorly water-soluble anticancer medications, enhancing drug stability, and increasing site specificity, thereby improving therapeutic efficacy (Hani et al. 2020). The self-assembly of amphiphilic block copolymers gives rise to the formation of these colloidal nano-constructs with hydrophilic and hydrophobic groups. Polymeric micelles' ability to solubilize poorly water-soluble or hydrophobic drugs within their core enhances bioavailability, making them suitable for cancer drug delivery (Jhaveri and Torchilin 2014).

Cyclodextrins

Interesting macromolecules called cyclodextrins are found to naturally enhance the characteristics and structure of the multifunctional delivery systems that have been described using them. They are an excellent excipient for increasing the apparent solubility, stability, and bioavailability of pharmaceuticals because of their remarkable ability to function as molecular containers, encasing a wide variety of guest molecules within their interior cavity. They are also useful instruments in the creation of innovative drug delivery systems. When it comes to chemotherapy, these qualities are especially useful because most anticancer drugs have both reduced permeability and limited water solubility. It is an effective anticancer therapeutic technique since it has been shown to increase medication apparent solubility, reduce toxic side effects, and increase the bioavailability of the reported anticancer drugs (Santos et al. 2021).

Carbon nanotubes

Extensive research has been conducted on carbon nanotubes (CNTs) for targeted drug delivery in cancer therapy, owing to their unique characteristics. Not only can CNTs be employed as drug carriers for a range of anticancer medicines, but they can also be excellent mediators for radiation therapy due to their intrinsic optical characteristics. Because of their adaptability, CNTs can be used in a variety of therapeutic contexts to treat a variety of tumours. Notwithstanding their advantages, CNT-based treatments continue to encounter a number of difficulties in the clinical context. Not enough research has been done to determine whether CNTs are safe to use in human tissue. Thus, before CNT-based nanotechnology is potentially used in clinics, more research is required to verify its long-term safety in human bodies. Considering how challenging it is to make CNTs on a wide scale (Tang et al. 2021).

Liposomes

Closed colloidal structures made up of lipid layers constitute liposomes that self-assemble, with an outer lipid bilayer encircling a central aqueous region. These lipid-based systems can now be used to operate a range of cancer treatments by utilising different

strategies. Liposomes may be used with Immunoliposomes, which offer improved drug delivery selectivity (Zaimy et al. 2017). Liposomes are a viable delivery system for doxorubicin, paclitaxel, and nucleic acid; they also demonstrate enhanced absorption and increased anti-tumor efficacy (Gavas et al. 2021).

Niosomes

Niosomes and liposomes share a significant bilayer resemblance; however, niosomes also include non-ionic surfactants within an aqueous phase. Better stability, extended shelf life, biodegradability, nonimmunogenicity, biocompatibility, and the ability to gradually deliver a medication to its intended location are among their many advantages. Kulkarni et al. developed niosomes loaded with tamoxifen and doxorubicin were created for the treatment of breast cancer. The reported entrapment efficiencies for doxorubicin and tamoxifen were 72.7% and 74.3%, respectively. Niosome-based breast cancer treatment appears to be feasible (Gautam et al. 2021). Niosomes are a highly effective drug delivery strategy in the therapy regimen of many diseases, and they have the potential to be a more effective treatment than conventional drug-delivery platforms (Yeo et al. 2017).

Ethosomes

Ethosomes are a unique, desirable, and aesthetically pleasing medication delivery technology. Ethamomes can be used to provide medications with little skin penetration. Etosomes are essentially phospholipid-containing lipid vesicles that are ethanolic liposomes; significant amounts of ethanol or isopropyl alcohol can be used (Gautam et al. 2021). The circulatory system and deep skin layers are accessible to medications through the non-invasive transporters known as ethers. Ethamomes are soft vesicles that are intended to improve the passage of active materials, such as medications, through natural channels (Barani et al. 2021). Ethamomes are specifically formulated to deeply penetrate the skin, enhancing drug permeation and deposition for the treatment of various conditions such as alopecia, psoriasis, acne, and skin cancers. This is made possible by the well-known permeation enhancer ethanol (Paiva-Santos et al. 2021).

Transferosomes

Early in the 1990s, a class of elastic or deformable nanocarriers known as transfersomes was identified. Transfersomes have the potential to pierce deeper layers of the skin than normal liposomes, which are limited to the stratum corneum layer. As an enhanced form of liposomes, other lipid carrier types, such as transfersomes, have been created (Barani et al. 2021). Highly deformable vesicles called transfersomes have lately been proposed as innovative medication delivery systems. They have the ability to transport big molecules through intact skin in mammals. A transfersome, in its broadest context, refers to a mechanism that can effectively permeate intact mammalian skin, facilitating the transport of large molecules from the point of application to the desired destination. Transfersomes find application in cancer diagnostics, including the detection of basal cell carcinoma and melanoma. They have the potential to be a useful drug delivery technique for treating skin cancer since they can permeate the skin's layers (Rai et al. 2017).

Exosomes

Exosomes, a type of nanosphere with a bilayered membrane that resembles human cells, are nonimmunogenic and have the ability to carry medications effectively (Hani et al. 2020). These nanoparticles are found in nature and are known to be essential for intercellular communication. They carry a varied load of lipids, proteins, metabolites, and various types of nucleic acids (mRNA, miRNA, tRNA, long non-coding RNA, and DNA). DNA (mt, ss, and ds). The utilization of exosomes in drug delivery has been suggested due to of their ability to transport both large and tiny molecules, which supports their potential as therapeutic agents for a range of disorders, including cancer. Exosomes are involved in complicated biological processes (Aqil and Gupta 2022).

Aquasomes

The submicron, self-assembling vesicles known as aquasomes are used in biotechnology and pharmaceuticals. Its top layer is composed of a polyhydroxy oligomeric film, while its particulate core is composed of ceramic diamond or nano-crystalline calcium phosphate. Greater biological activity is demonstrated

by the drug candidates provided by aquasomes, even in conformationally sensitive ones. Aquasomes have characteristics that protect and retain delicate biomolecules, maintain structural integrity, and expose surface area, making them an excellent delivery mechanism for delivering biological components like peptides, proteins, hormones, antigens, and genes to particular locations (Rana et al. 2020).

Phytosomes

The combination of plant extracts with phosphatidylcholine results in the formation of phytosomes, representing an innovative drug delivery approach technology that improved the phytopharmacological profiles of numerous plant-based medications. According to Beg et al. (2020), the phytosome demonstrated a promising bioavailability of several phytomedicine found in milk thistle, grape seed, green tea, olive, and turmeric. Well-known biocompatible nanocarriers called phytosomes can be used to improve phytopharmaceuticals' permeability and solubility across a range of NDDS (Sundaresan and Kaliappan 2021). Phytosomes have been reported to have higher bioavailability than basic herbal extracts due to their enhanced ability to pass through blood circulation and cross lipid-rich biomembranes (Beg et al. 2020). Phytosomal formulations have noteworthy pharmacological advantages, such as neuroprotective, antioxidant, and anti-inflammatory characteristics. Additionally, they can improve the absorption and availability of phytoconstituents. Despite being researched as an anticancer drug for the treatment of several tumour types (Karpuz et al. 2020). Phyto-phospholipid complexes are easier to synthesise and exhibit a greater drug complexation compared to other types of complexes. Furthermore, they show increased stability as a result of the phosphatidylcholine and plant extracts forming chemical bonds. By making bile more soluble in active ingredients, they improve liver targeting (Lu et al. 2019). One of the emerging nanotechnologies, phytosomes, can be used to overcome the low bioavailability of bioactive phytoconstituents and enhance their miscibility in lipid-rich barriers. (Alharbi et al. 2021a, 2021b).

Phytosome technology

The phytosome method, pioneered by the Italian company Indena s.p.A., involves combining phospholipids with a standardized plant extract to enhance the absorption and effectiveness of specific herbal treatments (Goyal et al. 2011; Shukla et al. 2012; Gandhi et al. 2012). Polyphenols exhibit low solubility in both lipids and water. However, when the charged phosphate head interacts with the polar attributes of the lipophilic component of phospholipids through polar interactions and hydrogen bonding, it results in a unique structure that can be identified using spectroscopy (Sharma and Sikarwar 2005; Bombardelli 1991). Due to its bifunctional nature, phosphatidylcholine possesses both a hydrophilic choline group and a lipophilic phosphatidyl component. The choline head group is connected to the substance, while the phosphatidyl segment envelops the core. To cater to the demands of the contemporary food industry, newer generations of phytosomes are now crafted using a hydroethanolic solvent. The first generation of phytosomes was obtained by combining phospholipids with a specific polyphenolic isolate in a non-polar solvent.

Formulation approach

A stoichiometric number of phospholipids (phosphatidylcholine and lysophosphatidylcholine) as well as a standard plant extract react to form phytosomes in the presence of a solvent that cannot serve as a proton donor. The most widely used phospholipids with plant-based standardised extracts include lysophosphatidylcholine, phosphatidylcholine, phosphatidylethanolamine, and phosphatidic acid. Lysophosphatidylcholine is a bifunctional chemical component, with the hydrophilic choline fraction acting as the tail of the bifunctional complex and the lipophilic phosphatidyl fraction acting as the head.

As a result, hydrophilic phytocomponents are bound by the choline part of lysophosphatidylcholine, and the lipophilic phosphatidyl part is attached to the choline-attached complex (Mascarella 1993; Manach et al. 2004; Bhattacharya and Ghosh 2009; Bhattacharya 2009). To improve solubility in lipids, a phytophospholipid combination is formed. The choline head and the polar phytocomponents must be chemically bonded. To preserve the active phytochemical component from being destroyed by the gastric environment, phytosome technology creates tiny spheres, or microscopic cells (Singh and Awasthi 2018). One fragment of a bifunctional biochemical

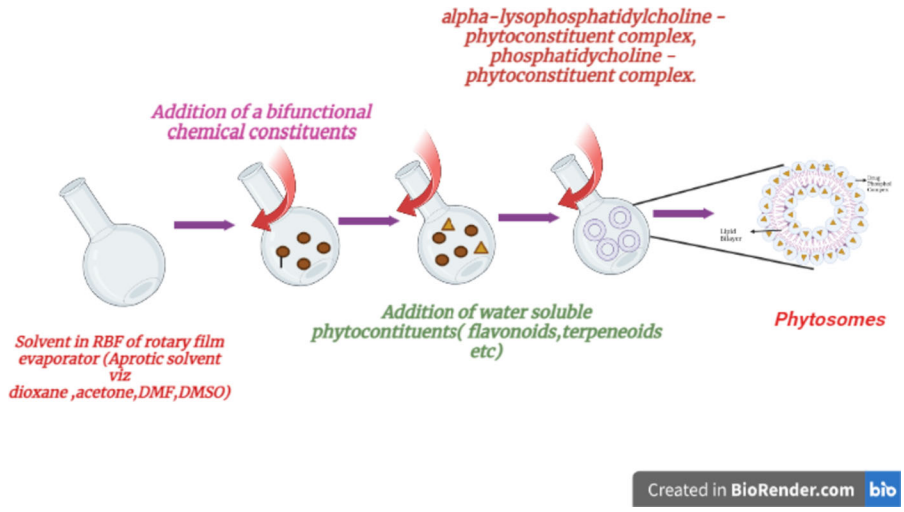

Fig. 2 Illustration of the formulation of phytosomes

composite like phosphatidic acid, lysophosphatidylcholine, terpenoids, or phosphatidylethanolamine is combined with one fragment of an active herbal component belonging to the chemical class of terpenoids or aglycon glycosides in an aprotic solvent that is not capable of acting as a proton contributor, such as acetone, dioxane, or acetonitrile. Then the complexes are isolated by precipitation and spray drying, as shown in Fig. 2. The best ratio of phytocomponents to phospholipids is 1:1. Here are some examples of phospholipids that are regularly used, including phosphatidylethanolamine, phosphatidylcholine, phosphatidic acid, phosphatidyl-L-serine, sphingomyelin, phosphatidyl-DL-glycerol, lysophosphatidylcholine, phosphatidylinositol, and cardiolipin.

Properties of phytosome

- Phytosomes are obtained by reacting a stoichiometric amount of phospholipids with phytocomponents in an aprotic solvent (Sharma and Sikarwar 2005).
- The size of the phytosome ranges from 50 nm to several hundred micrometers (Patel et al. 2013).
- When exposed to water, the phytosome transforms into a liposome-like micellar form, which is visible using photon correlation spectroscopy (PCS) (Jain 2005).
- The extended aliphatic sequences are protected near the active principle, forming a lipophilic shell, based on H1NMR and C13NMR data, it was observed that the fatty chain exhibited consistent signals in both free phospholipids and the complex (Franco et al. 1998).
- Physical characteristics Pharmacokinetic investigations or pharmacodynamic testing in experimental animals and humans have shown that phytosomes are new complexes that are well absorbed and utilised, providing greater bioavailability and better results than typical plant extracts or extracts without complexes (Marena and Lampertico 1991).

Difference between phytosomes and liposomes

A liposome is formed by mixing a water-soluble substance in a specific ratio with phosphatidylcholine under particular conditions, similar to the process for creating phytosomes (Karimi et al. 2015). In this context, the phosphatidylcholine molecules encapsulate the water-soluble substance without forming any chemical bonds (SS 2011; Gandhi et al. 2012; Kumar et al. 2017). As illustrated in Fig. 3 below, a water-soluble component can be encapsulated by numerous phosphatidylcholine molecules. During the phytosomal formation, phosphatidylcholine combines with plant constituents in a 1:1 or 2:1 molecular ratio, depending on the specific complexes involved, including any chemical bonding. Because of this difference, phytosomes are much more easily absorbed than

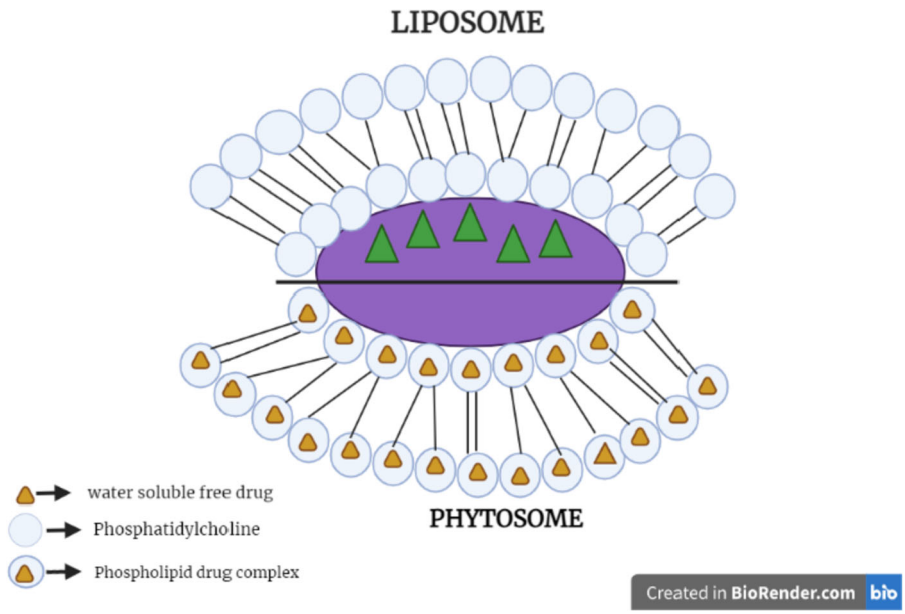

Fig. 3 Difference between phytosomes and liposomes

liposomes and exhibit higher bioavailability. In addition, phytosomes have been found to outperform liposomes in skin care and topical products (Amit et al. 2013; Chauhan et al. 2009; Schandalik et al. 1992).

Distinctive features of phytosomes exhibiting anticancer properties

The development of novel medicines is hampered by concerns about safety, specificity, and efficacy. Unlike conventional treatments that fundamentally rely on pure compounds extracted from natural sources or on artificially manufactured products, which are often associated with side effects and can yield resistance if used in the long term, phytosome-based drug delivery circumvents these issues (Gioia et al. 2020). Collectively, studies have demonstrated that phytosomes have no toxic effect on healthy cells but rather act on abnormal, transformed cells, e.g., cancer cells (Zhang et al. 2016; Raimondo et al. 2015). Consequently, phytosomes represent a developing platform for the plant-based treatment of cancer and the chronic inflammation linked with cancer.

Phytosomes made from fingerroot (*Boesenbergia rotunda* (L.) Mansf.) exhibited an apoptotic impact on colorectal cancer cells in vitro, as indicated in the Table 1 below, but had no adverse effects on healthy colon epithelial cells. After incubating cancer cells for 24 h at a dosage of 50 g/mL, these phytosomes became toxic, but they showed no effect on healthy colon epithelial cells. By absorbing phytosomes, it has been shown that genes linked to apoptosis promotion, such as caspase-3, caspase-9, bax, and bcl-2, are upregulated. Reactive oxygen species (ROS) production and cell death are also intimately related to phytosome absorption (Wongkaewkhiaw et al. 2022). It has been postulated that caveolae-mediated endocytosis and phagocytosis pathways play a role in the internalization of phytosomes. Pre-exposing cells to cellular uptake inhibitors that target the phagocytosis and pinocytosis pathways supported this claim. Three abundant phenolic chemicals in the plant—pinostrobin, pinocembrin, and naringenin chalcone—were linked to the plant's anticancer properties, according to the research. These substances were shown to be the main causes of the anticancer activity that was seen. Nevertheless, additional molecular analyses are need to confirm these results.

Additionally, using receptor-specific blockers, it was discovered that HepG2 human liver cancer cell line absorption of phytosomes produced from garlic (*Allium sativum*) was dependent on the CD98 receptor (Song et al. 2020). The trypsinization of surface proteins on phytosomes from garlic, hindering their internalization, served as additional confirmation. The investigation also revealed a considerable correlation

Table 1 Role of phytosomes with its mechanism involved for treatment of cancer

Phytosomes source	Isolation method	In vitro effect	Mechanism	References
Fingerroot, scientifically known as *Boesenbergia rotunda* (L.) Mansf	Fingerroot was mixed without the addition of extra liquids. The resulting juice was then filtered, subjected to ultracentrifugation, and filtered again through a size-exclusion chromatography column	Phytosomes demonstrated selective cytotoxic and apoptotic effects on cancer cells, sparing normal colon epithelial cells	Disruption of intracellular redox homeostasis and induction of cell apoptosis	Wongkaewkhiaw et al. (2022)
Garlic (*Allium sativum*)	Garlic was homogenized with a blender in cold PBS. The resulting juice underwent a multistep centrifugation process, culminating in ultracentrifugation. The phytosome pellet was then washed and resuspended in PBS	HepG2 cancer cells internalized phytosomes, leading to an anti-inflammatory response, although no anti-cancer effect was observed	Internalization of phytosomes occurred through the CD98 receptor situated on HepG2 cells. This receptor, abundant in mannose motifs, binds to the surface proteins and lectins of phytosomes	Li et al. (2018)
Lemon juice (*Citrus limon* L.)	The fruits were hand-pressed to extract the juice, which was then centrifuged in stages. After filtering the supernatant, it underwent ultracentrifugation, and the resulting phytosomes from the sediment were purified using a 30% sucrose gradient	Phytosomes inhibited cancer cell growth without affecting normal cells	Phytosomes promoted the demise of cancer cells by initiating TRAIL-mediated apoptosis. TRAIL specifically triggered apoptosis in cancer cells while leaving normal cells unaffected	Raimondo et al. (2015)
Corn (*Zea mays* or Maize plant)	A homogenized mixture of the blended edible portion of corn with water was created, followed by step-centrifugation to eliminate debris. The resulting supernatant underwent filtration and ultracentrifugation. The obtained pellet was then resuspended in PBS to yield phytosomes	Phytosomes selectively inhibited proliferation of colon26 cancer cells	–	Sasaki et al. (2021); Sasaki et al. (2022)
Tea leaves (Yongchuan Xiuya)	Fresh tea leaves were blended with PBS in a mixer. The resulting juice underwent a series of centrifugation steps to eliminate any debris. Subsequently, the supernatant was subjected to sucrose density gradient ultra-centrifugation, and phytosomes were harvested from the interface of the 30/45% sucrose layers	Internalization of phytosomes led to reduced viability and increased cytotoxicity in three breast cancer cell lines	Phytosomes elevated intracellular levels of reactive oxygen species (ROS), resulting in mitochondrial damage and initiating cell cycle arrest and apoptosis	Chen et al. (2023)

between CD98 receptor-mediated endocytosis and the presence of lectin family proteins on phytosome surfaces. Interestingly, garlic phytosomes suppressed proinflammatory factors to have an anti-inflammatory effect, but they did not show any anticancer or cell-modifying effects when fed to HepG2 cells. Despite the fact that these data suggest that the garlic phytosome payload has little effect on liver cancer cells, the low dosage that was used (micrograms) may have contributed to the outcomes. Nevertheless, the study offered valuable insights into the specificity of garlic phytosome internalization by target cells expressing the CD98 receptor, a characteristic shared by various cancer types. Allicin, a well-defined bioactive anticancer agent found in garlic, has been extensively investigated to unveil its mechanism of action on cancer cells (Li et al.2018). Hence, undertaking a thorough assessment of the intracellular cargo transported by garlic phytosomes and their subsequent interactions with HepG2 cells will be of utmost importance.

Lemon juice (*Citrus limon* L.) phytosomes have been demonstrated to have antiproliferative and apoptotic effects on cells both in vitro and in vivo (Raimondo et al. 2015) In a mouse model implanted with chronic myelogenous leukaemia cells (LAMA84 cell line), they were also shown to decrease tumour size. A dose of 20 g/mL of phytosomes was reported to be beneficial. Activation of TNF-related apoptosis-inducing ligand (TRAIL) and its receptor, heightened expression of Bad and Bax genes, and reduced expression of antiapoptotic genes, particularly survivin and Bcl-xl, were all associated with the antitumorigenic events. In vivo biodistribution analyses found that injected labeled Citrus limon phytosomes specifically accumulated in cancer cells; while some were absorbed by other organs, no significant anomalies were observed (Raimondo et al. 2015).

Sasaki et al. (2021) successfully isolated phytosomes from the edible portion of corn (also called *Zea mays* or maize plant) using a simple ultracentrifugation-based method that enabled large-scale extraction. The phytosomes demonstrated antiproliferative and apoptotic effects in vitro on a murine colon adenocarcinoma cell line (colon26) and were preferentially taken up by cancer cells compared with normal non-cancer cells, suggesting an affinity for the lipid rafts abundant on cancer cells (Sasaki et al. 2021; 2022). In a syngeneic mouse model, they showcased an anti-cancer effect on subcutaneous murine colon adenocarcinoma tumors, with minimal impact on body weight. However, the specific apoptotic pathways or genes involved were not investigated. Additionally, the content encapsulated within the corn phytosomes, harboring potential anticancer biomolecules, was not explored. However, a previous investigation reported inhibited proliferation and induced apoptosis of colon adenocarcinoma and suggested the presence of the carotenoids zeaxanthin and lutein in corn (Grudzinski et al. 2018).

One edible plant that can be utilized to make cakes, candies, chocolates, and beverages is cannabis (*Cannabis sativa* L.). Though its medical uses are less widespread, its phytosomes have shown encouraging anti-cancer potential. To extract and purify cannabis phytosomes with a high CBD content and low levels of tetrahydrocannabinol (THC), the main psychoactive component in this plant family, researchers used differential centrifugation using a sucrose gradient (referred to as H.C-EVs). HepG2 and Huh-7 liver cancer cell lines showed dose- and time-dependent anti-cancer effects from the isolated phytosomes. Cancer cells underwent apoptosis when exposed to phytosomes at concentrations as low as 25 µg/mL, and their viability was reduced by 50% at 100 µg/mL. No cytotoxic effects were observed on non-cancerous cells such as the HUVEC line (Tajik et al. 2022).

Tea leaves (Yongchuan Xiuya), referred to as TLNTs, have been found to possess potent anticancer properties that can be attributed to phytosomes carrying well-documented anti-cancer polyphenols and flavonoids, such as epigallocatechin-3-gallate (EGCG), vitexin2-O-rhamnoside, vitexin, myricetin-3-O-rhamnoside, kaempferol-3-O-galactoside, and myricetin (Chen et al. 2023). Breast cancer-bearing mice received tea leaf phytosomes intravenously or orally, which aggregated at the tumour's site and stopped tumour growth after just five hours. Studies conducted in vitro demonstrated that the phytosomes entered the cytoplasm of malignant cells and caused the generation of ROS, which caused cell damage. There was evidence of toxicity and side effects following oral administration of phytosomes, but intravenous injection of high doses of phytosomes was found to enhance liver markers, indicating that oral treatment with phytosomes is a safer method. Interestingly, phytosomes augmented the number of favourable bacteria inside the gastrointestinal tract (GIT) while reducing pathogenic bacteria.

Applications of phytosomes in cancer therapy

In contrast to most drug carrier formulations, the process for creating phytosomes is straightforward and uncomplicated. Since the plant components used in phytosome production also act as the active therapeutic agents, this method stands out for its ingenuity and feasibility. The prospects for further advancements in phytosome technology are substantial (Azeez et al. 2018). The antioxidant qualities of medicinal plant chemical constituents, such as flavones, isoflavones, flavonoids, anthocyanins, coumarins, lignins, catechins, and isocatechins, primarily contribute to their anticancer potential. Numerous side effects are associated with the currently available, pricey traditional cancer therapies, including radiotherapy and chemotherapy, which may have a significant negative impact on life quality. This way phytosomes have shown the impact on improvising the treatment for cancer. Figures 4 and 5 show the trends in publications of "Phytosomes" and "Phytosomes AND cancer" from past 23 years, respectively using the search engine "PubMed" (Feb 9, 2024). These figures reflect how phytosomes have found broad ground within the past 2 decade.

The bipolar moiety helps plant-derived pharmaceuticals become more soluble, dispersible, and permeable, making them an effective anti-cancer agent (Chivte et al. 2017). Various active herbal constituents showing anticancer activity on different cancer cell lines are mentioned in Table 2.

Alhakamy et al. the researcher developed optimized phytosomes and assessed their ability to eliminate MCF-7 cells. Additionally, they designed quercetin phytosomes integrated with scorpion venom properties targeting breast cancer treatment. Their analysis revealed that the refined phytosomes had vesicles sized at 116.9 nm and a zeta potential of 31.5 mV. Cell cycle evaluations indicated that the improved QRT formulation notably halted the cell cycle at the S phase post-treatment. The research suggests that a QRT phytosome configuration could be a promising therapeutic strategy for breast cancer. The insights from this investigation hold considerable practical implications (Alhakamy et al. 2020a, 2020b). Additionally, doxorubicin's effectiveness at inhibiting the proliferation of MCF-7 human breast cancer cells was enhanced by quercetin phytosomes (Gavas et al. 2021) Yasmiwar Susilawati et al. reported in their article that the phytosomal drug delivery system performed exceptionally well in enhancing quercetin performance; erythema was significantly (P 0.003) reduced; redness, itching, and inflammation were reduced; skin layers were improved; hydration was increased; and quercetin solubility and absorption were also increased (Susilawati et al. 2021). Dina A. Hafez et al. In a separate controlled research, it was noted that a lecithin-curcumin phytosomal complex (Meriva®) was given to 160 patients. The lecithinized curcumin effectively minimized the side effects associated with radiotherapy and chemotherapy, highlighting the beneficial role of curcumin phytosomes in cancer treatment (Hafez et al. 2020). To evaluate the anticancer potential of phytosomal curcumin, Reyhaneh Moradi Marjaneh et al. exposed CT26 cells to escalating doses of curcumin (0–1000 M) and 5-FU (1–50 mg/ml) for 24, 48, and 72 h, both individually and in combination. They showed how 5-FU and phytosomal curcumin induced dose-dependent suppression of cell proliferation. Additionally, the 5-FU IC50 value was lowered by co-treating with 5-FU and phytosomal curcumin. They came to the conclusion that phytosomal curcumin boosted the anti-proliferative effects of 5-FU in both in vitro and in vivo systems (Marjaneh et al. 2018). Ibrahim et al. investigated the efficacy of curcumin conjugated with phosphatidylcholine in the treatment of mammary gland tumors. Panahi et al. examined the efficacy of utilising phytosomal curcumin in addition to chemotherapy in patients with solid tumours (Mirzaei et al. 2017). Zhenqing Hou et al. developed Phytosomes loaded with Mitomycin (MMC) and soybean phosphatidylcholine complex were developed. The formulation of the MMC drug delivery system involved the creation of phytosomes through a combination of solvent evaporation and nanoprecipitation methods. The study's findings highlighted the remarkable anticancer potential of MMC-loaded phytosomes. In comparison to free MMC, these phytosomes displayed a more potent and dose-responsive inhibition of tumor growth without inducing weight loss. These outcomes suggest that MMC-loaded phytosomes could be a promising and efficient strategy for cancer therapy and drug delivery. A streamlined and effective method was introduced to produce an innovative MMC-loaded phytosome formulation, characterized by enhanced properties like reduced size, narrower size distribution, elevated zeta potential, and improved stability.

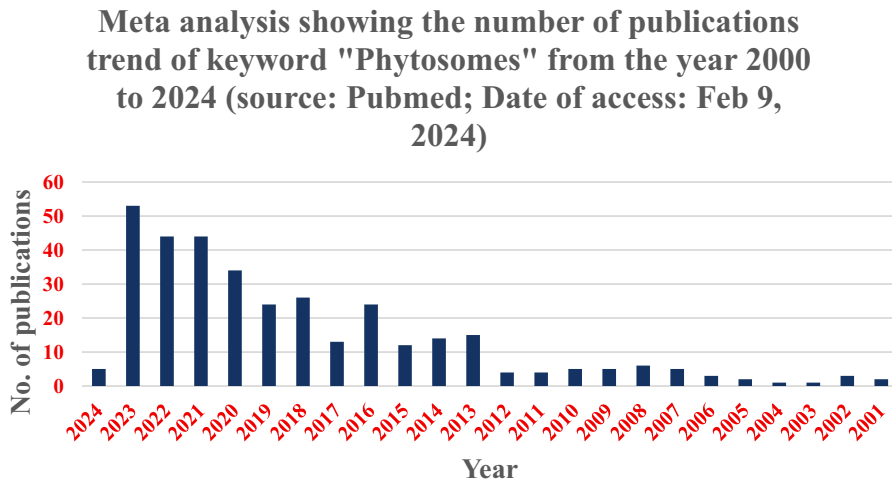

Fig. 4 Meta-analysis showing the number of publications trend of keyword "Phytosomes" from the year 2000 to 2024 (*Source* Pubmed; Date of access: Feb 9, 2024)

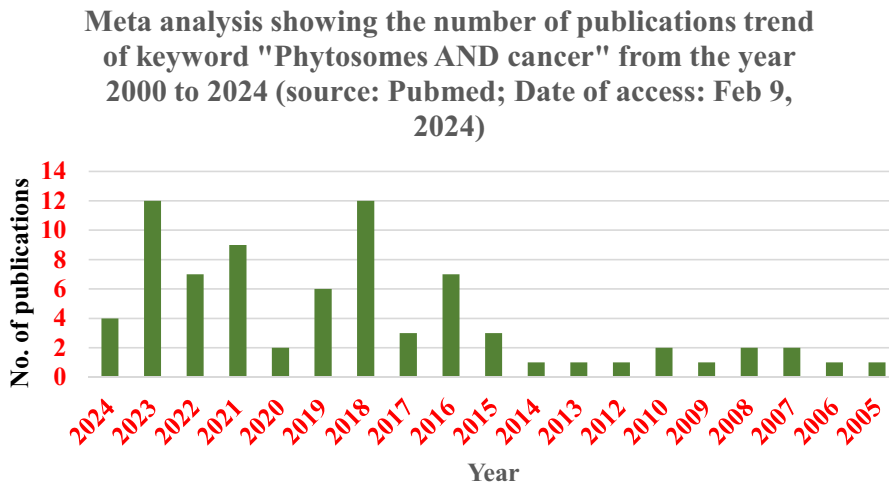

Fig. 5 Meta-analysis showing the number of publications trend of keyword "Phytosomes AND cancer" from the year 2000 to 2024 (*Source* Pubmed; Date of access: Feb 9, 2024)

Notably, the MMC-loaded phytosomes exhibited significantly increased cytotoxicity and a more pronounced inhibitory impact compared to MMC alone (Hou et al. 2013).

Silibinin phytosome

Ochi et al. The researchers encapsulated two plant-derived anti-cancer agents, glycyrrhizic acid and silibinin, within nanophytosomes to enhance their limited bioavailability. They then assessed the impact of these compounds on hepatocellular carcinoma (HCC) cell lines, specifically HepG2. Silibinin, a component naturally found in silymarin, has demonstrated anti-cancer effects by reducing N-nitrosodiethylamine levels in hepatocellular carcinomas (Ramakrishnan et al. 2006). A herbal medicine called glycyrrhizic acid, which is derived from the plant *Glycyrrhiza glabra* (L.), has been shown to have anti-cancer properties due to its potent MMP inhibitory properties and ability to protect DNA in malignant cells (Verschoyle et al. 2008). A 48-h sustained release of 14% (w/w) of silibinin and 88% (w/w) of glycyrrhizic acid was demonstrated in an in vitro release investigation. The co-encapsulated nano-phytosomes of silibinin and glycyrrhizic acid were three times more powerful than those of individual silibinin (25% w/v) and glycyrrhizic acid (75% w/v), according to cell viability research on HepG2 cell lines. In another word, phytosomes improved the bioavailability of silibinin, and results demonstrated the capability of phytosome technology in providing co-

Table 2 Different cancer cell lines demonstrating anticancer effect of various active herbal components

Active herbal constituents	Biological source	Preparation techniques	Major findings	Type of cancer	References
Curcumin	*Curcuma longa*	Rotary evaporation technique	The curcumin-loaded phytosome demonstrates the ability to effectively regulate the release of the medication	Pancreatic cancer	Sachin et al. (2019)
Emodin	Rhubarb	Solvent evaporation	Solubility and dissolution rate of emodin was increased	Anticancer	Singh et al. (2013); Khan et al. (2013)
Aloe	*Aloe vera* extract	Thin film hydration	The aloe vera loaded phytosome are biocompatible and had a growth inhibiting impact on MCF-7 cancer cell line	Anticancer	Murugesan et al. (2020)
Quercetin	*Terminalia arjuna* bark	Anti-solvent precipitation	The optimised QRT formulation have potential to treat breast cancer	Breast cancer	Alhakamy et al. (2022); Sharma et al. (2015)
Genistein	Dyer's *Genista tinctoria* L	Solvent evaporation method	Phytosomes with breast cancer-specific Gen demonstrate enhanced chemotherapeutic effects against breast cancer	Breast cancer	Komeil and Abdallah (2022)
Thymoquinone	*Nigella sativa* L	Anti-solvent precipitation method	The apoptotic capability of TQ-phytosomes on A549 lung cancer cells was enhanced by a factor of three	Lung cancer	Alhakamy et al. (2020a, 2020b)

encapsulated systems, which enhanced the therapeutic effects of silibinin through the synergistic effects of glycyrrhizic acid (Ochi et al. 2016). By diminishing the HIF-1 protein expression, this anticancer medication showed promising inhibitory effects on PC-3 and LNCaP cells (human prostate cancer cell lines) (Jung et al. 2009). Recent studies indicate that the efficacy of silibinin for prostate cancer treatment was enhanced when combined with other anti-cancer drugs, including doxorubicin (Marena and Lampertico 1991) and mitoxantrone (Flaig et al. 2007a, 2007b), cisplatin, carboplatin, etc. Thomas W. Flaig and colleagues examined the impact of a high oral dose of silibinin, administered without phytosomes, on prostate cancer patients in the two weeks leading up to prostatectomy. While silibinin phytosomes can attain elevated plasma concentrations, the levels of silibinin in prostate tissue remain low. The limited duration of the study could account for the suboptimal effects of silibinin on prostate cancer. Additionally, the size of the phytosomes, particularly if they are on a nanoscale, might also be a significant factor influencing their efficacy (Dhanalakshmi et al. 2003). In another study, Matteo Lazzeroni et al. investigated the presurgical effects of silybin nanophytosomes (SNPs) that were orally administered to early breast cancer patients. Although all of the patients performed the therapeutic programme, no toxicity was reported. An important result of this study was the finding that the distribution of SNPs in tumour tissues was nearly four times greater than that of the free Silybin.

Sinigrin phytosome

Managing malignant wounds, especially those stemming from skin cancers, is essential for overall health maintenance. Medications that not only address wound treatment but also exhibit cytotoxic effects on cancer cells are highly valued. Sinigrin, a natural compound and primary glucosinolate, is sourced from the Brassicaceae family and has demonstrated anticancer capabilities (Flaig et al. 2010; Rungapamestry et al. 2008). Addressing malignant wounds, notably those associated with skin cancers, is pivotal for human well-being. We prioritize treatments that not only heal wounds but also display cytotoxic properties against cancerous cells. Derived from the Brassicaceae family, sinigrin, a key glucosinolate, has been identified for its anticancer attributes (Bhattacharya et al. 2010).

Arjuna phytosome

Arjuna (TA), belonging to the Combretaceae family, possesses bark abundant in flavonoids and exhibits antimutagenic and anticancer properties (Mazumder et al. 2016a, 2016b). The primary challenge with TA bark extract is its limited bioavailability, which hampers its clinical use. In an effort to address this issue, Shalini and colleagues developed a nanophytosome complex using a methanolic extract of TA bark, with particle sizes ranging from 30 to 80 nm. They then examined its antiproliferative properties on human breast cancer cell lines (MCF-7). Results from cell proliferation tests on MCF-7 cells demonstrated that TA bark phytosomes outperformed the standard TA bark extract, exhibiting approximately 1.6 times greater efficacy than the free extract (Kaur et al. 2002).

Mitomycin phytosome

Since it has demonstrated strong anticancer properties, mitomycin C (MMC), a natural molecule with a carbamoyl chain and an aziridine ring, is used in a variety of malignancies (Shalini et al. 2015). A significant barrier to the clinical application of MMC is its rapid uptake into the systemic circulation, leading to reduced drug concentrations at the target sites and consequently diminishing its therapeutic benefits. To tackle this challenge, Hou and colleagues developed a delivery system for the mitomycin-C-loaded soybean phytosome PC (MMC SPC) complex, with an average particle size of 210 nm. In vitro release studies revealed a sustained release of MMC following an initial rapid release phase. These findings indicate that phytosomes can effectively shield MMC from quick uptake into the systemic circulation by enhancing its lipophilic properties. In vivo studies on mice with H22 solid tumors demonstrated that the tumor suppression rate achieved with MMC-loaded phytosomes was sixfold greater than that observed with MMC injections (Bradner 2001).

Luteolin phytosome

Luteolin (Lut), a natural compound, exhibits anticancer properties by targeting multiple molecular pathways to induce cancer cell death. Its ability to selectively inhibit the Nrf2 signaling pathway enhances the responsiveness of cell lines from non-small cell lung cancer (NSCLC A549) to anticancer treatments (Hou et al. 2012; Tang et al. 2011). The expression level of Nrf2 in cancer cells is high, and the role of Nrf2 in drug resistance in cancer treatment is confirmed (Zhao et al. 2011). Sabzichi and colleagues enhanced the sensitivity of human breast adenocarcinoma cells (MDA-MB 231) to doxorubicin (dox) by treating them with luteolin-loaded nanophytosome complexes, which effectively inhibited Nrf2-mediated signaling. Cytotoxicity studies revealed that the combination of luteolin phytosomes with doxorubicin outperformed the effects of nano-dox alone on MDA-MB 231 cells. In essence, by boosting the bioavailability of luteolin, phytosomes amplified the therapeutic impact of dox, further enhancing luteolin's ability to inhibit Nrf2 (Wang et al. 2008). Some examples are shown in Table 3 below.

Current phytosomal delivery against various cancer types

Lung cancer ranks as the second most common cancer type. Among the studied phytochemicals for potential lung cancer treatments are elemene, dioscin, docetaxel, hydroxycamptothecin, paclitaxel, and vinorelbine. Meanwhile, breast cancer stands as the leading cancer among women. Phytochemicals showing promise in breast cancer treatment encompass curcumin, docetaxel, paclitaxel, piperine, and resveratrol. Colorectal cancer ranks as the third most frequently diagnosed cancer globally. Phytochemicals such as luteolin, berberine, curcumin, and galbanic acid show promise in combating this type of cancer. For leukemia treatment, key phytochemicals employed include curcumin, phytol, quercetin, and vincristine. Additionally, cervical cancer stands out as a primary cause of mortality among women. Podophyllotoxin, resveratrol, and curcumin exhibit promising potential in addressing cervical cancer. As per the WHO, liver cancer ranks as the fourth leading cause of cancer-related deaths globally. Phytochemicals like 6-gingerol, betulinic acid, resveratrol, and triptolide are being explored for their efficacy against hepatocellular carcinoma. Pancreatic cancer refers to the formation of malignant growths in pancreatic tissue. Curcumin, gemcitabine, and paclitaxel showed potential to treat pancreatic cancer. Phytochemicals such as vincristine and doxorubicin have the potential to treat brain cancer.

Table 3 Examples of nano-phytosome application in cancer treatment

API	Type of study		Response indication	References
Silibinin or Silybin	In vitro	HepG2 cell line	Improve in oral bioavailability of silibinin	Ochi et al. (2016)
	In vivo	Skin cancer		Sabzichi et al. (2014)
	In vivo	Prostate cancer		Kumar et al. (2015)
	Clinical trials (phase I)			Verschoyle et al. (2008)
	Clinical trials (phase I)		Enhancement in oral bioavailability without concurrent improvement in the accumulation of the phytosome complex in prostate tissue	Dhanalakshmi et al. (2003)
	Clinical trials (Phase I)	Breast cancer	Enhance oral bioavailability and accumulate effectively in cancer tissue	Flaig et al. (2007a, 2007b)
Sinigrin	In vivo	Skin cancer	Enhanced anti-cancer efficacy and potential for wound healing	Bhattacharya et al. (2010); Lazzeroni et al. (2016)
T. arjuna	In vitro	MCF-7 cell lines	Enhance oral bioavailability and exhibit improved anti-cancer activity	Kaur et al. (2002)
Mitomycin	In vivo	H22 solid tumor-bearing mice	Improve in oral bioavailability and accumulation in cancer tissue	Bradner (2001)
Luteolin	In vitro	MDA-MB 231 cell lines	Enhance in oral bioavailability	Wang et al. (2008)

Phytosome formulations development

A variety of oral and topical dosage forms can be derived from phytosome complexes. To fully leverage the advantages of this technological advancement, such as enhanced bioavailability and formulation versatility, multiple products can be formulated.

Soft gelatin capsules

As a substitute, soft gelatin capsules are perfect for creating phytosome complexes. The phytosome complex can be encapsulated in soft gelatin capsules after being suspended in fatty carriers. For this use, vegetable or semi-synthetic oils are suitable options. A 100% granular consistency is what Indena suggests using for the best possible capsule formation. As far as Indena is aware, different phytosome complexes behave differently depending on whether they are applied to greasy surfaces or whether the greasy dispersion is contained in soft gelatin capsules. Hence, preliminary feasibility tests are essential to determine the most suitable carrier (Mazumder et al. 2016a, 2016b).

Hard gelatin capsules

These capsules can be formulated using phytosomes. The inherent low density of the phytosome complex might restrict the quantity of powder that can be accommodated in a capsule. Nevertheless, a direct volumetric filling approach, without the need for pre-compression, is feasible, typically allowing for less than 300 mg in a 0-size capsule. Utilizing a piston-tamp capsule filling method allows for a greater quantity of powder to be encapsulated in a capsule; yet, pre-compression might reduce the disintegration rate. Indena recommends closely monitoring relevant parameters as the product or procedure evolves. A preliminary dry granulation approach outlines the preferred manufacturing technique (Rani et al. 2007).

Table 4 A brief summary of phytosomal drug delivery complexes

S. no	Trade name	Daily dose (mg)	Indications	Phytoconstituents complex
1	Silybin phytosomes	120	Antioxidant	Silybin from *Silibrium marianum*
2	Ginseng phytosomes	150	Immunomodulator	Ginsenoside from *Panax ginseg*
3	Curcumin phytosomes	200–300	Cancer chemo preventive agent	Polyphenol from *Curcuma longa*
4	Green phytosomes	50–300	Anti-cancer, antioxidants	Epigallocatechine from *Thea sinesis*
5	Ginko phytosomes	120	Antiaging, protects the brain	Flavonoids from *Ginko biloba*
6	Hawthorn phytosomes	100	Antipertensive	Flavanoids from *Crataegus* species
7	Silyphos milk thistle	150	Antioxidant	Silybin from *Silibrium marianum*
8	Olea phytosomes	120	Anti-inflammatory	Polyphenols from *Oleaeuropea*

Tablets

The most dependable method for creating tablets with greater individual dosages while maintaining ideal technical and biological characteristics is dry granulation. A direct compression procedure should only be utilized for low unitary doses of the phytosome complex due to its restricted flow capacity, probable stickiness, and low apparent density; additionally, to maximize its technical features and produce tablets with an appropriate formIt is advised to dilute the phytosome complex with 60–70% excipients for best results. The stability of the phospholipid complex is compromised by exposure to heat and moisture during processes like granulation or drying; therefore, it's advisable to refrain from wet granulation (Rathore and Swami 2012).

Topical dosage forms

Furthermore, Topical application is feasible for the phytosome complex. To incorporate the phytosome complex into the emulsion, it should be dispersed in a minimal amount of the lipid phase and then added to the pre-formed emulsion at temperatures below 40 °C. Phytosome complexes readily dissolve in commonly employed lipid solvents for topical applications. For formulations with low lipid content, the phytosome complex should be dispersed using an aqueous method and subsequently incorporated into the final mixture at temperatures not exceeding 40 °C. (Semalty et al. 2007).

Advantages of phytosome-loaded herbal medication delivery

Recent studies indicate that phytosomal drug delivery offers a distinct approach to enhance the bioavailability and uptake of plant extracts, potentially allowing for reduced dosage. As a result, numerous plant extracts are garnering increased interest for their potential pharmacological effects. Examples encompass silymarin, andrographolide, curcumin, hesperidin, quercetin, grape seed extract, and silymarin. The flexibility of this drug delivery approach enhances the benefits of herbal medicine, particularly given the growing demand for treating numerous ailments in the contemporary world (Singh and Gangadharappa 2016). A summary of phytosome-loaded plant drug delivery is shown in Table 4.

Recent marketed products

Ginkgoselect®

It is a standardized extract of Ginkgo biloba leaves designed for enhanced absorption. Primarily indicated for peripheral vascular disease and cerebral insufficiency, it serves as a beneficial supplement for supporting brain function under impaired conditions. It offers a favorable choice for prolonged treatment given its improved oral absorption and tolerability. This is a more diluted version of the generic *G. biloba* leaf extract. Common indications include peripheral vascular disease and cerebral insufficiency, potentially assisting with compromised cerebral circulation. It is an ideal ginkgo formulation for prolonged use due to

its enhanced oral acceptability and bioavailability (Upase et al. 2019).

Greenselect®

It comprises a consistently uniform polyphenolic component, making up at least 66.5%, extracted from green tea leaves. Epigallocatechin and its derivatives are the key markers for its identification. In vitro studies have shown that these compounds effectively modulate various biochemical pathways linked to the development of significant chronic degenerative conditions, including cancer and atherosclerosis. The binding of green tea polyphenols with phospholipids significantly improves their oral bioavailability. Derived from green tea leaves, the majority of this consistently uniform polyphenolic fraction, constituting at least 66.5%, is composed of epigallocatechin and its derivatives. These compounds act as potent regulators of homeostasis-related biochemical processes and demonstrate efficacy in treating conditions such as cancer and atherosclerosis. The combination of phospholipids with green tea polyphenols significantly enhances their typically restricted oral bioavailability (Lamare 2019).

Mirtoselect®

The bilberry extract contains anthocyanosides, potent antioxidants known for improving capillary strength and reducing irregular blood vessel permeability. These compounds hold promise for addressing issues like venous insufficiency and irregular retinal blood circulation (Sriya et al. 2020).

Sabalselect®

The product features a saw palmetto berry extract obtained through supercritical CO_2 (carbon dioxide) extraction. It contains fatty acids, alcohols, and sterols, all of which contribute to the well-being of the prostate. Specifically, this extract may offer advantages for addressing noncancerous prostate enlargement. (Gaurav et al. 2021).

Lymphaselect™

It yields an extract from Melilotus officinalis. This remedy is employed for managing venous conditions, including chronic venous insufficiency in the lower extremities (Gharia et al. 2019).

Oleaselect™

This formulation is a modern derivation from the polyphenols present in olive oil. These compounds act as potent antioxidants, effectively neutralizing free radicals, and frequently exhibit anti-inflammatory effects. Additionally, they help inhibit the harmful oxidation of LDL cholesterol (Sahu 2020).

Polinacea™

Derived from Echinacea angustifolia, this immunomodulatory product comprises echinacosides along with a unique high-molecular-weight polysaccharide. When confronted with a potential threat, this supplement enhances the immune response. The innovative phytosome technology facilitates efficient distribution of these cutting-edge phytomedicines, leveraging the synergistic benefits of naturally occurring phospholipid nutraceuticals (Mahapatra et al. 2020).

Phytosomes in cancer therapy: challenges and future aspects

The advancement of phytophospholipid complex technology represents a significant step forward in understanding the systemic absorption of herbal extracts. This approach effectively dispels unwarranted apprehensions surrounding plant-derived medicines. Such groundbreaking compounds offer promising prospects for optimized therapeutic dosing. While initially employed in the realm of cosmetics, phytosomes have now become integral in addressing conditions like cancer, heart ailments, inflammation, tumors, and various liver disorders. Through this innovative formulation technique, phytosomes underscore the enduring relevance of herbal components in contemporary drug delivery strategies (Kumar et al. 2020). Because phyto-phospholipid complexes bind particular ligands and antigens to cellular structures, they can be strong candidates for both passive and active targeting. This expands the range of illnesses that phyto-phospholipid complexes can be used to treat, including rheumatism, osteoarthritis, and cancer. Using more modern methods, including supercritical

fluid systems, and optimizing variables like temperature, pressure, and a few more, can manipulate product dimensions within different restricted ranges. Products with controlled sizes offer enhanced precision in targeting specific microbiological areas, including inflammation and tumors, due to their improved penetration and prolonged retention. By leveraging statistical tools such as factorial design, spherical symmetric design, among others, one can optimize the molar ratios of drug candidates with phospholipids, along with adjusting factors like temperature and other parameters (Khan et al. 2013) to achieve the highest level of entrapment efficiency and the best drug release profile. The emergence of nanotechnology-driven phytosomes is poised to revolutionize drug delivery by overcoming challenges related to by enhancing the bioavailability of essential phytochemicals like silybin, ginkgo, and polyphenols present in olive oil, and addressing the challenge of poor lipid solubility. Many phytochemicals have already been effectively formulated into phytosomes, suggesting the potential for expanding this approach to include more phytochemicals. Subsequent research might uncover synergistic advantages by pairing phytosomes with other phytochemicals or by co-encapsulating a drug with a phytochemical within a nanovesicle (Alharbi et al. 2021a, 2021b). Phospholipids markedly enhance bioavailability in comparison to chemically equivalent, non-complexed forms. The potential of phyto-phospholipid complexes holds great promise for application in the pharmaceutical sector with the collaboration of healthcare professionals and researchers (Lu et al. 2019). Such advancements could open up a substantial opportunity for extending the drug's applications in various medical contexts. Indeed, harnessing the potential of safe phytoconstituents like curcumin, combined with innovative drug delivery techniques, could lead to the creation of safe and environmentally friendly treatments for common human diseases. Exploring the use of complete curcumin nanoparticles for specific targeting of various organs, including tumors, represents a promising area for future research (Ipar et al. 2019).

To summarize, Phytosomes® serve as a valuable solution for naturally occurring extracts with limited bioavailability, benefiting from established analytical methodologies and well-defined processing methodsCompared to traditional forms of medicine, Phytosomes® provides a broad spectrum of advantages. Numerous pharmaceutical products with registered patents are currently available in the market. This research demonstrates that Phytosomes® have introduced a new dimension to pharmaceutical research and development, with a wealth of untapped potential (Agarwal et al. 2012). Another crucial factor for successful product commercialization is its widespread acceptance. The growing demand for treatments that are biocompatible, cost-effective, and safe has heightened interest in natural products. Leveraging phytosome technology for the nano-formulation of nutraceuticals could transform the application of hydrophilic plant compounds in cancer therapy (Baba Zadeh et al. 2018). The use of phytosomes in combination with other phytochemicals or the combination of a medicine and a phytochemical in a nanovesicle in a future study could have stimulatory effects (Alharbi et al. 2021a, 2021b).

Despite the promising advantages of phytosome technology, there remains a limited number of studies exploring its use as a carrier in cancer therapy. As a result, only a handful of products, like Meriva® (curcumin phytosomes) and Siliphos® (Silybin phytosomes), have made their way to the market. Another critical aspect to consider is the scalability of nanophytosome production. While the straightforward manufacturing processes of phytosomes suggest they could be easily scaled up, industrial implementation remains limited. One primary obstacle to industrial scaling could be the pH sensitivity inherent to phytosome structures. Addressing this issue is crucial as it impacts the physicochemical stability of phytosomes, a prerequisite for their large-scale production in the future. An interesting consideration related to phytosomes is the potential for food-grade production methods. Such approaches could mitigate potential adverse effects associated with non-food-grade production techniques. By utilizing food-grade solvents like ethanol, which are approved for food applications, it's feasible to produce food-grade phytosomes by combining them with phosphatidylcholines (PCs) (Ghanbarzadeh et al. 2016; Khan et al. 2013). In conclusion, despite limitations in the manufacturing process, the benefits of phytosomes make them a viable candidate for industrial production, particularly in the context of cancer therapy.

Nanotechnology has revolutionized the delivery of anticancer agents, offering advantages like precise drug distribution, controlled release, evasion from the

reticuloendothelial system, and the passive targeting of tumors through the enhanced permeability and retention (EPR) effect. Recognizing these benefits, the FDA has granted approval for a select number of nanoparticulate drug delivery systems designed for cancer treatment. Among the array of nanocarriers available, lipid-based nanoparticles stand out due to their superior biocompatibility, biodegradability, cost-effectiveness, abundant raw material sources, and extensive research history. While herbal remedies like flavonoids have garnered significant attention in cancer treatment, their limited oral bioavailability hampers their clinical utility. Additionally, lipid-based nanoparticles may not offer sufficient encapsulation capacity for hydrophilic flavonoids or other water-soluble anticancer agents. Phytosomes address these challenges by providing multiple complexation sites for the effective encapsulation of polar active ingredients.

A significant hurdle in the commercialization of phytosomes lies in ensuring their safety post the development of an effective formulation. Prior to their introduction to the market, various criteria such as bioaccumulation, biocompatibility, metabolism, and excretion need thorough evaluation. Additionally, following the formulation of a phytosome, it is essential to assess its pharmacokinetic and pharmacodynamic characteristics in both animals and humans to establish its superiority over pure phytoconstituents. Another step in the marketing process is determining the best dosage form to improve the finished product's absorption and efficacy (Barani et al. 2021). The main reason for the non-industrial scale-up may be the pH sensitivity of phytosome structures. Addressing this issue is crucial for ensuring the physicochemical stability of phytosomes, especially if they are to be produced on a large scale in the future. While advancements in industrial-scale manufacturing techniques, like extruding technologies, hold promise for the commercial production of these nanocarriers, the persistent high cost of raw materials remains a challenge. Pegylated soy phosphatidylcholine (Baba Zadeh et al. 2018) is one potential hazard to this development.

Recent research on phytosomes

Experts are actively pursuing various studies, and recent research indicates that phytosome technology is a revolutionary approach to enhance the bioavailability and uptake derived from plant extracts, thereby substantially decreasing the necessary dosage. The relevance of this method, coupled with increasing interest in herbal remedies for diverse conditions, has spurred additional recent studies. Below, we delve into a literature review of some recent advancements in phytosome formulations.

Georgiev et al. studied involving 180 patients diagnosed with Carpal Tunnel Syndrome (CTS) examined the therapeutic effectiveness of an oral supplement containing a blend of curcumin, alpha-lipoic acid, and B vitamins (Georgiev et al. 2017). For patients with CTS undergoing surgical decompression of the median nerve, the supplement appears to offer potential clinical benefits, as evidenced by high levels of patient satisfaction and adherence both pre-and post-surgery.

To assess the beneficial effects of Green Select Phytosome, a caffeine-free green tea extract combined with proprietary lecithin, on catechin absorption, Belcaro et al. conducted a study involving 50 asymptomatic individuals exhibiting borderline metabolic disorder markers and elevated plasma oxidative stress levels (Belcaro et al. 2013). In comparison to the control group that underwent lifestyle and dietary modifications, Green Select Phytosome exhibited notable efficacy in inducing changes in weight and waist measurement. The findings underscore the value of addressing various metabolic syndrome risk factors with apheliotropic medications, which can amplify the advantages of dietary and lifestyle adjustments, thereby fostering a comprehensive enhancement in individuals' health profiles.

Using a (1:2) molar ratio of curcumin to phospholipids, Zaveri et al. were able to produce a curcumin-phospholipid combination (Zaveri et al. 2011). DSC analysis and FTIR spectroscopy were utilized to confirm the formation of the complex. When comparing the skin permeation of curcumin to that of the complexed form, the latter demonstrated a 60% increase in penetration through the rat skin. The study suggests that the phospholipid complex enhances skin penetration more effectively than pure curcumin.

Cuomo et al. studied the comparative absorption of a standardised mixture of curcuminoids and a corresponding composition of lecithin in a randomised, double-blind, crossover trial in humans (Meriva) (Cuomo et al. 2011). They stated that Meriva increased the curcuminoid plasma profile and

Table 5 List of patents for phytosomes and other related technologies

Title	Innovation	Patent no	References
Phospholipid complexes with enhanced bioavailability derived from extracts of olive leaves or fruits	Extracts or compositions containing phospholipids complexes of olive leaves or fruits that have increased bioavailability	EP/ 1844785	Raimondo et al. (2015)
Sorbitol furfural fatty acid monoesters and formulations for dermatologic along with cosmetic purposes	Fatty acid monoesters of sorbityl furfural can be found in two distinct compound series, each featuring a side chain that is either linear or branched, and containing at least one ethylenic unsaturation	EP1690862	Wongkaewkhiaw et al. (2022)
Ginko biloba derivative-containing formulations for the treatment of allergic and atopic rhinitis	Compositions with Ginkgo biloba fragments that can be used to treat allergy and asthmatic disorders	EP1813280	Song et al. (2020)
A supplement containing antioxidants and plant extract-based remedies for the treatment of circulatory issues and obesity	Plant extracts form the basis for treating circulatory issues such as varicose veins, phlebitis, high blood pressure, atherosclerosis, and hemorrhoids, exhibiting antioxidant effects	EP1214084	Li et al. (2018)
Phospholipid and saponin complexes, as well as medicinal and chemical formulations containing them	High lipophilicity and increased bioavailability of saponin complexes with natural or synthesized phospholipids make them acceptable for usage as an active component in pharmacological, cosmetic and dermatological compositions	EP0283713	Sasaki et al. (2021)
Compositions containing soluble isoflavones	Enhanced solubility, flavor, color, and texture features of isoflavone formulations as well as production methods are described	WO/2004/ 045541	Sasaki et al. (2022)

increased absorption at a dose that was significantly lower than the over-the-counter curcuminoid mixture.

Cuomo et al. compared the absorption of a standardized curcuminoid blend and its lecithin formulation, Meriva, in a randomized, double-blind crossover human research. Even at a dosage far lower than that of the unformulated curcuminoid mixture, Meriva demonstrated a superior plasma curcuminoid profile and enhanced absorption, according to the findings.

Some patented technologies related to phytosomes

Numerous university scientists and industrial laboratories have conducted much advanced research on formulations and processes in the field of phytosomes. Table 5 below provides a list of patents on phytosomes and other related technologies, as well as their uses and progress.

Phytosomes in clinical trials

To further investigate drug safety and its interactions within the human body, numerous formulations based on phytosomes have progressed to clinical trials. This phase is crucial for obtaining the FDA's ultimate approval. The inaugural clinical trial involving a phytosome-based formulation was conducted in 2007. (ClinicalTrials.gov Identifier: NCT00487721, accessed date: August 28, 2021) (Clinical trial 2014a). Silybin, which has been linked to anti-cancer activities (Crema et al. 1990), was added to phytosomes for use by patients undergoing prostatectomy for prostate cancer. The initial findings showed that a high oral dose of silybin-phytosome results in a transiently high blood concentration, and they suggested that this phytosomal formulation may one day be employed as an alternative therapy for the treatment of patients with prostate cancer (Agarwal et al. 2007; Flaig et al. 2010). The second clinical trial involving a silybin-phytosome formulation was also initiated (ClinicalTrials.gov Identifier: NCT02146118, accessed date: August 3, 2022) (Clinical trial 2014b).The phytosome formulation, named Siliphos, was examined in conjunction with the drug erlotinib (Tarceva). Preliminary findings suggest a potential synergistic effect in treating patients with EGFR mutant lung adenocarcinoma, though the

Table 6 Phytosome-based formulations tested in clinical trials

Phytosomes formulation	Condition	Clinical trial phase and no	Study outcome	References
Silybin	Prostate cancer	Phase II (NCT00487721)	Elevated silybin levels in the bloodstream	Gilardini et al. (2016)
Green tea extract	Obesity	PhaseIV (NCT02542449)	Sustaining weight after losing weight	Yanyu et al. (2006)
Bergamot	Hypercholesterolemia	Not applicable (NCT04697121)	Activity against hypercholesterolemia	Alharbi et al. (2021a, 2021b)
Grape seeds extract	Early stages lung cancer	Phase II (NCT04515004)	Postpone the scheduled surgery of > 14 days	Pawar et al. (2022)
Quercetin	COVID-19	Phase III (NCT04578158)	Currently being examined	Bosch-Barrera and Menendez (2015)
Silybin	EGFR mutant lung adenocarcinoma	Phase II (NCT02146118)	Currently being examined	Fanoudi et al. (2020)

research is ongoing. Additionally, a 2014 study investigated the efficacy of green tea extract encapsulated in phytosomes for combating obesity. (ClinicalTrials.gov Identifier: NCT02542449, accessed date: August 28, 2021) (Clinical trial 2015). In individuals who had previously shed weight, the given formulation was employed to manage weight control, and this investigation is presently in its fourth clinical trial phase. Results highlighted a significant role of the green tea extract phytosomal preparation in aiding obese patients in sustaining their weight post-weight reduction (Flaig et al. 2007a, 2007b). Furthermore, when formulated as a phytosome-based product, grape seed extract underwent clinical trials to assess its potential efficacy against early-stage lung cancer (ClinicalTrials.gov Identifier: NCT04515004, accessed date: August 8, 2022) (Clinical trial 2023). The research results revealed that the phytosomal formulation postponed the planned surgery by more than 14 days. In individuals with mild hypercholesterolemia, the potential of the bergamot-phytosome preparation as an anti-hypercholesterolemic agent was explored in combination with artichoke leaf dry extract (ClinicalTrials.gov Identifier: NCT04697121, accessed date: August 8) (Clinical trial 2022a). The outcome shows that the administration of the developed formulation has a favourable impact on lipid and metabolic parameters, leading to the achievement of considerable anti-hypercholesterolemic activity. The most current research, which included a clinical trial, examined the adjuvant advantages of quercetin phytosome in the treatment of COVID-19 patients (ClinicalTrials.gov Identifier: NCT04578158, accessed date: August 8, 2022) (Clinical trial 2022b). The hypothesis suggests that quercetin phytosomes may enhance participants' innate immunity and halt the progression of the COVID-19 condition, potentially averting the need for hospitalization. Research on this topic is currently underway. Details of the phytosome-based formulations examined in clinical trials can be found in Table 6 below.

Bioavailability of phytosomes

Several studies have indicated that phytosomes offer greater bioavailability and absorption compared to traditional methods. The majority of these research efforts have centered on milk thistle, specifically *Silybum marianum*, a plant recognized for its hepatoprotective properties due to its fruits containing water-soluble phytoconstituents known as flavonoids (Kulkarni 2011). Nevertheless, the absorption rate of these flavonoids remains modest. Silybin stands out as the primary and most potent component of Silybum marianum. Cream et al. (1990) discovered that the absorption of silybin phytosomes, consisting of silybin directly bonded to phosphatidylcholine in a single oral dose, was roughly sevenfold higher compared to a standard milk thistle extract containing 70–80% silymarin (Crema et al. 1990). The silymarin

Table 7 Phytosomes available for purchase in stores

S.no	Phytosomes	Indications	Phytoconstituents complex	References
1	Silybin	Hepatoprotective, antioxidant	Silybin from milk thistle seed	Bijak et al. (2017)
2	Ginseng	Immunomodulator	Ginsenosides from *Panax ginseng*	Wan et al. (2021)
3	Curcumin	Cancer	Polyphenol from *Curcuma longa*	Aggarwal et al. (2003)
4	Green tea	Systemic antioxidant anticancer	Epigallocatechin from *Theasinesis*	Chu et al. (2017)
5	Sericoside	Skin tonic	Sericosides from *Terminalia sericea*	Sati et al. (2019)
6	Ginkgo	Anti-aging, safeguards the vascular lining and brain	Flavanoids from *Ginkgo biloba*	Chu et al. (2011)
7	Bilberry	Antioxidants	Anthocyanosides extract	Hamza et al. (2020)
8	Hawthorn	Anti-hypertensive and cardio protective	Flavanoids from the species of *Crataegus*	Rode et al. (2003)
9	Palmetto berries	Antioxidant, non-cancerous prostate enlargement	Alcohols, sterols, and fatty acids	Gandhi et al. (2012)
10	Visnadine	Circulation improver	Visnadine from *Ammi visnaga*	Ho et al. (2018)
11	Centella	Skin and vein conditions	*Centella asiatica* terpenes	Penugonda and Lindshield (2013)

phytosome was created by Janu et al. (2006), who also studied the pharmacokinetics of the drug in rats (Yanyu et al. 2006). Following oral administration to the tested rats, there was a notable enhancement in the bioavailability of silybin, attributed to a remarkable boost in the lipophilic characteristics of the silybin-phospholipid complex and an uptick in silybin's biological activity. Various phytosomes are commercially accessible, with details provided in Table 7 below.

Critical analysis of phytosomes in treating the cancer

The utilization of herbal phytosomes in cancer treatment remains a subject of ongoing debate within the scientific and medical communities. Phytosomes, intricate molecular complexes formed through the fusion of phospholipids and herbal extracts, hold promise for enhancing the bioavailability and efficacy of herbal compounds, thereby potentially augmenting their anti-cancer properties. This rationale underpins their exploration for therapeutic application in cancer management.

Scientific evidence underscores the considerable antitumor potential of phytochemicals. Notably, a substantial proportion (approximately 50%) of approved anticancer medications developed between 1940 and 2014 are sourced from natural products or their derivatives (Newman and Cragg 2016). This review outlines several notable phytochemicals exhibiting anticancer attributes, extensively studied both in vitro and in vivo. Through mechanisms such as scavenging free radicals, these compounds demonstrate complementary and overlapping pathways, effectively impeding the carcinogenic process. Careful use of preclinical screening models can lead to potential lead compounds for anticancer drug development, with extensive data on preliminary efficaciousness, toxicity, pharmacokinetic, and safety information that help determine whether a molecule should proceed to clinical trials. This process is part of the bench to bedside drug development process. The list of several investigations on the phytosomal transport of herbal extracts is displayed in the Table 8 below.

Challenges

More emphasis should be placed on the quantitative and qualitative investigation, optimization, and comprehensive characterization of phytosomal drug delivery systems and their impact on various medical disorders (Kumar et al. 2020). While this field has

Table 8 List of various studies related to phytosomal delivery of herbal extracts

Phytosome	Herbal extract	Findings	References
Greens elect Phytosome	Green tea extract	The improvements in weight and BMI were accompanied by enhancements in molecular markers including growth hormone, insulin-like growth factor-1, insulin, and cortisol levels across both groups	Lazzeroni et al. (2016)
Silybin phytosome	milk thistle (*Silybum marianium*) extract	Participants eligible for prostatectomy due to localized prostate cancer were enrolled. Among them, six patients and six volunteers were administered a daily dose of 13 g of silybin-phytosome, while another six volunteers served as the control group. Despite enhancements in oral bioavailability, there was no observed improvement in prostate tissue buildup	Franceschi and Giori (2007)
Leucoselect Phytosome	Grape seed extract	The antioxidant properties of polyphenols present in grape seed extract may offer benefits in scenarios of smoking-induced oxidative stress	Mazumder et al. (2016a, 2016b)
Curcumin phytosomes	Curcumin extract	Plasma concentrations of three curcuminoids—curcumin, demethoxycurcumin, and bisdemethoxycurcumin—found in turmeric were measured at baseline and at intervals over a 12-h period following oral therapy. This intervention resulted in hepatic accumulation, enhanced oral bioavailability of curcumin, and a significant reduction in plasma levels	Vigna et al. (2003)
Allium sativum phytosome	*Allium sativum*	In another investigation, researchers explored the development of cost-effective phytosomes derived from *Allium sativum* as a potential alternative to conventional cancer treatments. Given the plant's phenolic components' ability to both treat and inhibit the growth of cancer cells, the produced phytosomes exhibited remarkable efficacy, demonstrating 100% lethality to cancer cell lines during in vitro testing	Vandana and Suresh (2008)
Sinigrin's phytosome	*Brassica nigra* (mustard seeds) extrat	Studies assessing the wound-healing potential of HaCaT cells revealed a 50% improvement in wound closure across various doses and time intervals. This study suggests that sinigrin-loaded phytosomes may substantially enhance therapeutic outcomes in cancer therapy and the management of malignant wounds	Merizzi (2002)

undergone considerable research, further attention is warranted towards addressing formulation process challenges. The formulation of phyto-phospholipid complexes aims to ensure stability and demonstrate clinical superiority in these drug delivery systems. Currently, the solvent evaporation method, a labor-intensive procedure involving numerous unit operations, is commonly employed. However, the drying technique used often influences the final product's quality, including particle size, appearance, and hygroscopicity, and remains unoptimized in existing research.

The utilization of supercritical fluid techniques may offer a solution by allowing for precise control of particle size and dispersion at low temperatures, thereby overcoming limitations of current technologies. Despite significant interest in the pharmacokinetic properties of phyto-phospholipid complexes, there is a lack of studies establishing correlations between improved in vivo and in vitro pharmacokinetic properties and the pharmacological efficacy of pharmaceuticals in their phospholipid complex forms (Khan et al. 2013). Additionally, therapeutic aspects of created formulations have received less attention, necessitating further research to bridge the gap between enhanced bioavailability and clinical efficacy.The second challenge lies in large-scale phytosome synthesis while maintaining product attributes during scaling up, particularly concerning practical laboratory techniques in an industrial setting. Although the formulation procedure for many types of phytosomes is often straightforward, the commercial production of pH-sensitive phytosomes is hindered by low physicochemical stability, prolonging the time from product development to effective commercialization. Safety assurance following the

development of an effective formulation poses a significant barrier to phytosome commercialization. Factors such as bioaccumulation, biocompatibility, metabolism, and excretion should be assessed prior to marketing. To establish the superiority of phytosomes over pure phyto-constituents, pharmacokinetic and pharmacodynamic properties in humans and animals should be evaluated post-production. Finding the ideal dosage form to enhance absorption and efficacy of the final product is another crucial stage in the marketing process (Barani et al. 2016). Despite the apparent potential of phytosome technology, few anti-cancer studies have utilized phytosomes as carriers in cancer therapy. This has resulted in limited products, such as Meriva® (curcumin phytosomes) and Siliphos® (Silybin phytosomes), entering the market. Addressing the challenge of pH susceptibility in phytosome structures is crucial for their industrial-scale production. The high cost of raw materials remains a concern, although recent developments in industrial-scale production of vesicular systems offer promising prospects for commercial manufacturing, with technologies like extrusion showing potential (Baba Zadeh et al. 2018).

Future outlook

The evolution of phytophospholipid complex technology represents a systematic approach to assessing the absorption of herbal extracts by the body, effectively dispelling unfounded fears surrounding plant-based medicines. These novel compounds hold great promise for enhancing drug dosage therapy. Originally employed in cosmetics, phytosomes are now widely utilized in treating various medical conditions such as cancer, heart disease, inflammation, tumors, and liver-related illnesses, redefining the significance of herbal medicine in modern drug targeting approaches (Kumar et al. 2020). By attaching specific ligands and antigens to cellular structures, phyto-phospholipid complexes emerge as promising candidates for active targeting alongside passive targeting, broadening the spectrum of treatable illnesses. Through the use of modern techniques such as supercritical fluid systems and optimization of factors like temperature and pressure, the size of these products can be tailored to restricted values, facilitating more precise targeting of microbiological regions such as inflammation and tumors due to enhanced retention and penetrability. Optimization of molar ratios of drug candidates with phospholipids, temperature, and other variables using statistical tools like factorial design and spherical symmetric designing can achieve the optimal drug release profile and highest entrapment efficiency (Khan et al. 2013). The advent of nanotechnology-based phytosomes has the potential to revolutionize medication administration by overcoming barriers associated with inadequate lipid solubility and enhancing the bioavailability of beneficial phytochemicals such as silybin, ginkgo, and polyphenolic compounds found in olive oil.

While many phytochemicals have been successfully formulated as phytosomes, future research may explore synergistic effects from combining phytosomes with other phytochemicals or conventional medications in nano-vesicles (Alharbi et al. 2021a, 2021b). Phospholipids significantly enhance bioavailability compared to non-complexed forms, offering promising prospects for the use of phyto-phospholipid complexes in the pharmaceutical industry with the collaboration of medical professionals and researchers (Lu et al. 2019). This could open up opportunities for treating additional medical conditions. Furthermore, combining safe phytoconstituents like curcumin with innovative medication delivery methods could lead to the development of safe, effective, and environmentally friendly remedies for a wide range of human ailments. One promising area for research is the utilization of complete curcumin nanoparticles for targeted distribution to various organs, including cancers (Ipar et al. 2019). Phytosomes®, in essence, represent a breakthrough for naturally occurring extracts with low bioavailability, backed by well-established analytical and processing techniques. Compared to traditional forms of medicine, they offer numerous advantages and are supported by a multitude of registered patents in the market. According to Agarwal et al. (2012), Phytosomes® have introduced a new dimension and a wealth of untapped potential to pharmaceutical research and development, reflecting their growing popularity as part of an efficient commercialization strategy.

Recent years have witnessed a significant surge in the demand for natural products due to their biocompatibility, affordability, and safety. The commercialization of phytosomes is facilitated by their straightforward manufacturing process and evident support for widespread industrial-scale application of

phytosomal technology. Pharmaceutical companies have extensively explored the advantages and biological functions of phytosome compositions, particularly the enhanced bioavailability of polar phytoconstituents. The accumulating evidence supporting these formulations encourages further fieldwork and clinical research on standardized products to raise awareness of their technological advancements (Brani et al. 2016). Phytosomes emerge as the primary choice for enhancing effectiveness and evolving into a promising strategy for cosmeceutical products, given their ability to facilitate targeted delivery systems, controlled release systems, and increased stability of active compounds (Susilawati et al. 2021). Several nanoparticulate drug delivery devices have received FDA approval for cancer treatment, with lipid-based nanoparticles offering distinct advantages over conventional drug carriers in terms of biocompatibility, biodegradability, cost-effectiveness, and extensive research history. The integration of synthetic and natural anti-cancer drugs into nanophytosomes has shown promise in increasing oral bioavailability and inhibiting tumor growth, indicating potential growth and development of nanophytosomal delivery systems for cancer therapy in the foreseeable future. Moreover, the application of phytosome technology to the nanoformulation of nutraceuticals presents a promising prospect that could revolutionize the utilization of hydrophilic plant compounds in cancer treatment (Baba Zadeh et al. 2018). Future research may explore the synergistic effects of using phytosomes in conjunction with other phytochemicals or combining medications with phytochemicals in nano-vesicles, offering stimulating avenues for further investigation (Alharbi et al. 2021a, 2021b).

Conclusion

Phytosomes bridge the gap between traditional and modern delivery systems for herbal extracts. Representing an advanced form of herbal extract, phytosomes offer enhanced absorption and efficacy compared to their conventional counterparts. Their improved pharmacological and pharmacokinetic properties make them suitable for treating a range of diseases. When compared to standard plant extracts, phytosome-based nutraceuticals achieve equivalent or better therapeutic outcomes in organs like the liver, kidney, brain, and heart, even at reduced doses. By combining plant extracts—particularly polar phytoconstituents like terpenoids, flavonoids, xanthones, and tannins—with phospholipids such as phosphatidylcholine, phytosomes emerge as a novel drug delivery technology. This innovation boasts significantly enhanced absorption rates upon oral intake, owing to the improved lipid solubility that facilitates better membrane permeation. When compared to traditional plant extracts or isolated phytoconstituents, phytosomes ensure a higher concentration of the active ingredient reaches target organs like the liver, heart, brain, and kidneys, even when administered at similar or reduced doses. This heightened bioavailability translates to enhanced therapeutic outcomes that are more pronounced and sustained. A thorough literature review indicates that specific plant extracts, whether in their crude, fractionated, or semi-purified forms, exhibit a range of valuable pharmacological or health-promoting properties. These include anti-inflammatory, cardiovascular, immunomodulatory, antidiabetic, and anticancer effects, positioning them as valuable nutraceuticals for both preventive and medicinal applications over time.

Declarations

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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