Drug Design, Development and Therapy

Dovepress
Taylor & Francis Group

Open Access Full Text Article

REVIEW

Phytosome-Enhanced Secondary Metabolites for Improved Anticancer Efficacy: Mechanisms and Bioavailability Review

Lia Mardiana[1,2], Tiana Milanda[3], Yuni Elsa Hadisaputri[3], Anis Yohana Chaerunisaa[4]

[1]Doctoral Program, Faculty of Pharmacy, Universitas Padjadjaran, Sumedang, 45363, Indonesia; [2]Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy, Universitas Islam Kalimantan Muhammad Arsyad Al-Banjari, Banjarmasin, 70123, Indonesia; [3]Department of Biological Pharmacy, Faculty of Pharmacy, Universitas Padjadjaran, Sumedang, 45363, Indonesia; [4]Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy, Universitas Padjadjaran, Sumedang, 45363, Indonesia

Correspondence: Tiana Milanda; Yuni Elsa Hadisaputri, Department of Biological Pharmacy, Faculty of Pharmacy, Universitas Padjadjaran, Sumedang, 45363, Indonesia, Email tiana.milanda@unpad.ac.id; yuni.elsa@unpad.ac.id

Purpose: Phytosome technology, an advanced lipid-based delivery system, offers a promising solution for enhancing the bioavailability and therapeutic efficacy of secondary metabolites, particularly in cancer treatment. These metabolites, such as flavonoids, terpenoids, and alkaloids, possess significant anticancer potential but are often limited by poor solubility and low absorption. This review aims to investigate how phytosome encapsulation improves the pharmacokinetic profiles and anticancer effectiveness of these bioactive compounds.

Patients and Methods: This comprehensive review is based on an analysis of recent literature retrieved from PubMed, Scopus, and ScienceDirect databases. It focuses on findings from preclinical and in vitro studies that examine the pharmacokinetic enhancements provided by phytosome technology when applied to secondary metabolites.

Results: Phytosome-encapsulated secondary metabolites exhibit significantly improved solubility, absorption, distribution, and cellular uptake compared to non-encapsulated forms. This enhanced bioavailability facilitates more effective inhibition of cancer pathways, including NF-κB and PI3K/AKT, leading to increased anticancer efficacy in preclinical models.

Conclusion: Phytosome technology has demonstrated its potential to overcome bioavailability challenges, resulting in safer and more effective therapeutic options for cancer treatment. This review highlights the potential of phytosome-based formulations as a novel approach to anticancer therapy, supporting further development in preclinical, in vitro, and potential clinical applications.

Keywords: phytosome, secondary metabolites, cancer, bioavailability

Introduction

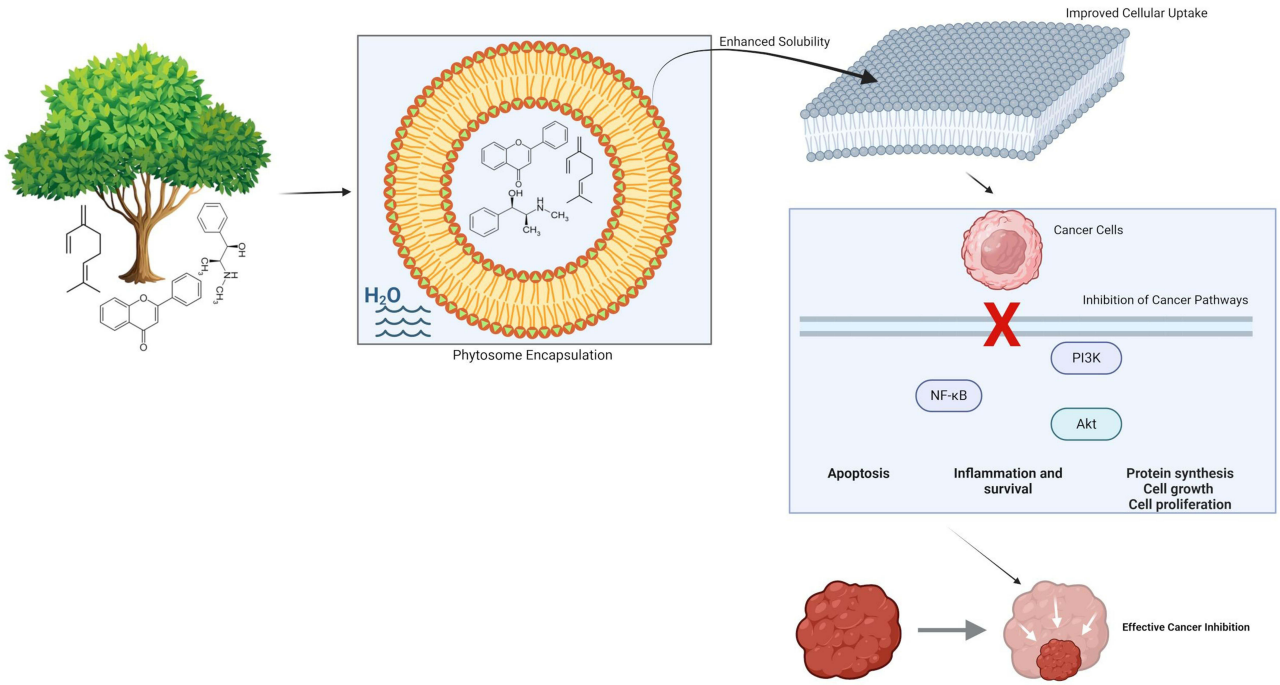
Cancer remains a significant global health challenge, consistently ranking as a leading cause of death worldwide.[1] It is characterized by abnormal cell proliferation, with the ability to invade surrounding tissues and metastasize to other parts of the body, as defined by the National Cancer Institute. The increasing prevalence of cancer significantly impacts both the quality of life and average lifespan globally. By 2040, new cancer cases are projected to rise to 29.5 million annually, leading to approximately 16.4 million deaths.[2,3]

Phytosome technology represents an innovative drug delivery system designed to encapsulate plant extracts or phytochemicals within a phospholipid complex, thereby enhancing their absorption and effectiveness.[4] Unlike traditional phytochemical formulations, which often face challenges related to poor lipid solubility and limited absorption, phytosomes significantly enhance the solubility and bioavailability of polar phytoconstituents.[5] By forming a lipid-compatible complex, phytosomes improve drug absorption, distribution, and targeted delivery, maximizing therapeutic outcomes.[6]

While liposomes and phytosomes both utilize phospholipid-based encapsulation, their structures and applications differ significantly.[7] Liposomes generally form bilayer vesicles that enclose a broad range of pharmaceutical compounds, focusing on general drug delivery. In contrast, phytosomes form a molecular complex with plant-derived

Received: 23 July 2024
Accepted: 24 November 2024
Published: 11 January 2025

Graphical Abstract



secondary metabolites, specifically enhancing their solubility, stability, and targeted bioavailability.[8–11] This distinction allows phytosomes to deliver polar phytoconstituents more effectively, making them more suitable for natural compound therapies.

Secondary metabolites, including flavonoids, terpenoids, alkaloids, and phenolic compounds, are recognized for their potential anticancer properties but often have low water solubility, which restricts their absorption and therapeutic efficacy.[11–13] This limitation presents a challenge in drug development, as higher doses of these compounds are often needed to achieve therapeutic effects, complicating formulation and delivery processes. To overcome these limitations, the use of surfactants has been explored as a strategy to improve the solubility of certain extracts, such as rosemary.[14] Surfactants reduce the surface tension between water and the solute, facilitating the dispersion of poorly soluble molecules, thereby increasing bioavailability.[15,16] However, phytosome technology offers a more advanced solution by not only enhancing solubility but also improving overall pharmacokinetics, including absorption, distribution, and cellular uptake of secondary metabolites.[17,18] Recent studies have demonstrated that secondary metabolites encapsulated in phytosomes, such as quercetin, curcumin, and berberine, exhibit improved solubility and enhanced anticancer efficacy compared to their non-encapsulated forms.[19,20] Phytosome encapsulation enables more effective interactions with cancer pathways, such as NF-κB and PI3K/AKT,[21–23] improving therapeutic outcomes in preclinical cancer models.

This review aims to investigate the transformative potential of phytosome technology in cancer treatment, particularly its ability to improve the absorption and efficacy of plant-derived secondary metabolites. The analysis will focus on key secondary metabolites, including alkaloids, flavonoids, terpenoids, and phenolic compounds, which have demonstrated anticancer properties. By examining advancements in phytosome formulations and their potential impact on cancer treatment, this review seeks to offer insights into future strategies for developing more effective oncological therapies.

Methodology

This review synthesizes studies focused on the use of phytosome for cancer treatment, emphasizing the enhancement of secondary metabolites bioavailability. The literature search targeted publications over the past decade, using databases

such as PubMed, Scopus, Google Scholar, and Web of Science. Keywords used included "phytosome technology", "cancer treatment", "plant secondary metabolites", and "phytochemical efficacy in cancer". The initial search obtained 214 studies, where the inclusion and exclusion criteria were rigorously applied to the results. Inclusion criteria were studies that directly addressed the application of phytosome in cancer treatment, showed the pharmacological benefits of secondary metabolites encapsulated in phytosome, and focused on bioavailability enhancement of these compounds. The exclusion criteria removed studies focusing on non-cancer related phytosome applications, those without clear methodological details, and non-peer-reviewed literature. Additionally, studies that did not include actual biological assessments such as purely computational models without experimental validation were excluded, along with duplicates, resulting in 185 studies. A further review based on abstracts and titles led to the selection of 77 relevant studies, where full-text review identified only 20 that met all the specified inclusion criteria, as shown in Figure 1. All figures in this manuscript, including mechanisms and graphical illustrations, were created by the author using BioRender. The chemical structures shown in the figures were re-drawn utilizing ChemDraw Professional (Version 16.0.1.4, licensed to Supriatno Salam, UNPAD, License ID: 112–920,429-8380) to guarantee precision and clarity in the representation of the studied compounds, with reference to data from the PubChem database, ensuring accurate representation of the compounds.

The inclusion criteria used were:

a. Literature discussing the application of phytosome in treatment of cancer.
b. Studies showing the enhanced bioavailability of secondary metabolites through phytosome.
c. Peer-reviewed studies with full experimental details.

The exclusion criteria were:

a. Literature not related to the application of phytosome in cancer treatment.
b. Non-peer-reviewed studies and those lacking empirical data.
c. Studies focusing on non-biological evaluations of phytosome.

Comprehension and Advancement of Phytosome

Phytosome was first developed in the early 1990s as an innovative advancement in the formulation and delivery of herbal remedies. These intricate formulations primarily comprised the active constituents of herbal extracts that were attached to phospholipids such as phosphatidylcholine, significantly enhancing bioavailability. Generally, complexation improves the hydrophobic properties of the phytoconstituents, facilitating their passage through lipid-rich cell membranes.[24]

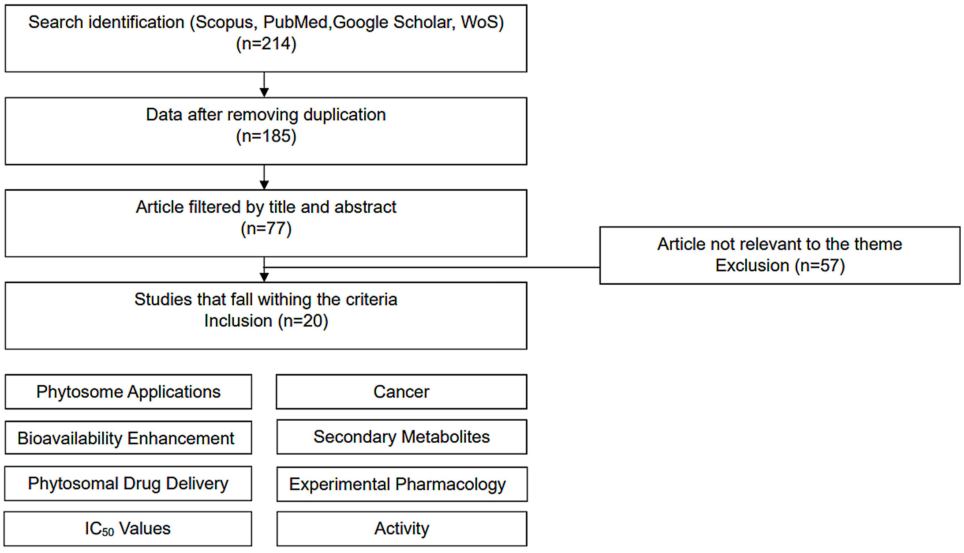


Figure 1 Flow diagram of the method used for screening information sources in the review.

https://doi.org/10.2147/DDDT.S483404

Figure 2 shows the process of enclosing phytoconstituents within phospholipid bilayers in a graphical manner. This encapsulation modifies the hydrophobic characteristics of the phytoconstituents,[25] facilitating their passage through lipid-rich cellular membranes. Phytosome significantly enhances bioavailability of bioactive compounds, leading to improved absorption by the body and increased effectiveness in treating medical conditions.

Phytosome technology has shown the potential to overcome the different limitations often associated with plant extracts, including insufficient absorption, rapid metabolism, and significant systemic excretion.[26] Figure 3 shows the mechanism by which phytosome enhance the transportation of phytoconstituents across cellular barriers. Strategically encapsulating herbal components boosts their bioavailability and allows for regulated release, maintaining sustained therapeutic levels in the bloodstream. The use of controlled release of medication is particularly beneficial in the field of oncology, capable of reducing the need for frequent dosing and minimizing the potential adverse effects associated with high drug concentrations in the body.[27] Furthermore, phytosome structure provides improved solubility and stability, enabling these compounds to effectively and consistently increase anticancer properties.

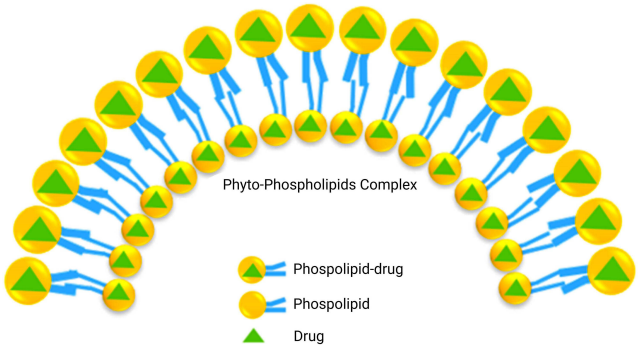


Figure 2 Structural illustration of the phytosome complex, showing phospholipid binding to plant phytoconstituents to enhance bioavailability.
Notes: Created in BioRender. Mardiana, L (2024) BioRender.com/W63W154.

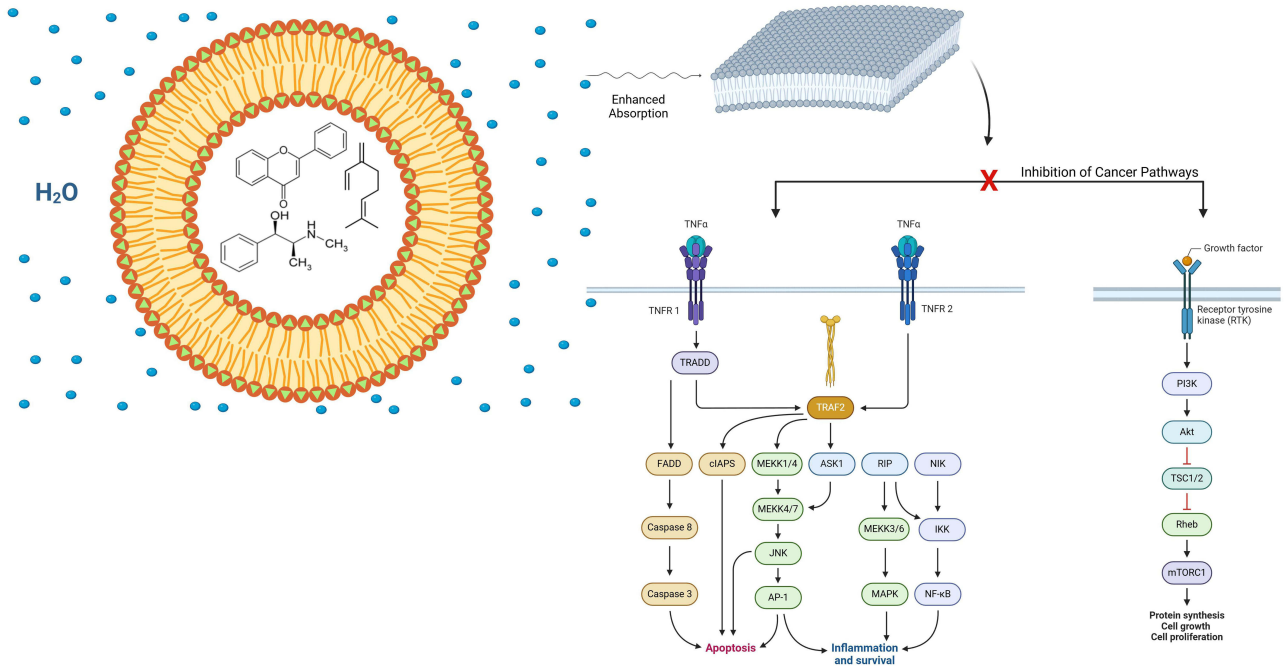


Figure 3 Mechanism of Phytosome-Encapsulated Secondary Metabolites Enhancing Cancer Treatment. The diagram illustrates improved solubility, enhanced absorption, successful cellular uptake, and targeted inhibition of cancer pathways (eg, NF-κB, PI3K/AKT), leading to apoptosis and reduced cell proliferation.
Notes: Created in BioRender. Mardiana, L (2024) BioRender.com/W63W154.

Recent Patents on Phytosomes

Recent patents on phytosomes highlight significant advancements in their development and application for improving the bioavailability of secondary metabolites in cancer treatment. These patents primarily focus on novel formulations that enhance the absorption, stability, and therapeutic efficacy of phytochemicals. For example, patents have been filed for formulations that utilize modified phospholipid structures to increase the solubility and targeted delivery of active compounds, particularly flavonoids, terpenoids, and phenolics.[28,29]

Patent No. WO2022135652A1 (2021) describes genistein-loaded phytosomes aimed at liver cancer treatment through oral administration, using various phospholipid types to improve solubility and bioavailability.[30] Similarly, Patent No. US11207388 (2023) details a phytosomal formulation using *Allium sativum* and *Murraya koenigii* for the treatment of breast cancer, emphasizing sustained release and enhanced delivery.[31] Another notable patent, Patent No. IN201841001612 (2019), focuses on a phytosomal complex combining *Allium sativum* and *Murraya koenigii* for both breast and prostate cancer treatment, aiming to prevent post-therapy recurrence.[32] Additionally, Patent No. IN202341042728 (2023) introduces a phytosome loaded with biosynthesized Ag nanoparticles, designed for bone cancer treatment through second-order targeting, which improves cellular uptake and targeting efficiency.[33] Some patents emphasize the development of synergistic formulations, where phytosomes are combined with other drug delivery systems to achieve enhanced anticancer activity and reduced toxicity. These innovations in phytosome technology offer promising approaches to overcoming the challenges of conventional formulations, setting new benchmarks for future cancer therapies.

Mechanism of Action: Enhancing Bioavailability Through Phytosome

Phytosome has made significant progress in the field of medication delivery by improving bioavailability of phytochemical.[34] This medication delivery method uses specific phospholipid complexes that closely resemble the lipid bilayer of cell membranes. The amphiphilic properties of these complexes facilitate strong and efficient contact with cell membranes,[35] enabling enhanced absorption of phytochemical through the gastrointestinal tract. Figure 3 shows the incorporation of phytosome into biological membranes. Generally, phytosome is designed to imitate the structural properties of cell membranes, protecting phytochemical from the harsh enzymatic conditions of the digestive system and improving precise transportation to specified tissues.[36] It also maintains the quality and effectiveness of the bioactive substances by duplicating cellular structures.[37] These structural alterations guarantee a significantly greater dispersion of active components to targeted regions, thereby boosting therapeutic capacity.[38]

Modified phytochemical within phytosome[39,40] has shown enhanced resistance to digestive enzymes, which increases systemic availability, extending stability and lifespan. This feature is essential to guarantee that therapeutic drug retain efficacy while passing through the body and providing persistent therapeutic effects.[41] Phytosome formulations are more successful than typical herbal extracts due to the ability to increase the amount of phytochemical[42] absorbed by the body and enhances the effectiveness of pharmacological treatment. As a novel advancement in pharmaceutical science, phytosome improves delivery and efficacy of phytochemical treatment by making structural changes, providing protective encapsulation, and increasing availability in the body.[43] This advanced delivery system represents a significant improvement in the more efficient use of natural substances, enhancing therapeutic effects in clinical trials. Phytosome technology enhances the anticancer potential of secondary metabolites through multiple mechanisms. First, the encapsulation of bioactive compounds with phospholipids increases their solubility and absorption across cell membranes, resulting in higher plasma concentrations and better therapeutic outcomes.[44–46] Second, the lipid-compatible nature of phytosomes allows for more efficient penetration of cancer cell membranes,[47,48] leading to increased intracellular concentrations of the active compounds. This improved cellular uptake ensures that secondary metabolites can more effectively interact with key cancer pathways, such as NF-κB and PI3K/AKT, which are critical for cancer cell survival and proliferation.[49,50] By overcoming the bioavailability challenges of these compounds, phytosomes provide targeted inhibition of cancer pathways, ultimately improving their anticancer efficacy.

Comparing Phytosome and Conventional Phytochemical Delivery Methods

Comparative analyses of phytosome and conventional herbal delivery vehicles, such as capsules and tinctures, show a significant enhancement in both bioavailability and the biological efficacy of plant extracts.[17] Phytosome has been shown in clinical trials to increase the absorption rate of phytochemical by approximately two times compared to non-complexed plant extracts. For example, silymarin is a well-known chemical protecting the liver and is obtained from milk thistle, which can be absorbed and used by the body when administered as phytosome,[51] compared to regular milk thistle supplements. Additionally, phytosome has an extended duration of presence in the bloodstream, enabling a sustained therapeutic effect and decreased frequency of dosage. These qualities give phytosome an advantage over traditional methods, as preferred options for delivering phytochemical in clinical trials.

Secondary Metabolites in Cancer Treatment

Secondary metabolites are a wide range of chemical compounds produced by plants through metabolic pathways that are separate from their fundamental physiological functions. These chemicals, comprising more than 50,000 known varieties, provide adaptive benefits, with a substantial impact on the pharmaceutical business.[52] Compounds such as terpenoids, flavonoids, alkaloids, and phenolics are well-known for their antioxidative, anti-inflammatory, antibacterial, and anticancer properties.[53] The categorization and potential uses of secondary metabolites, including terpenoids, flavonoids, alkaloids, and phenolics, are illustrated in Figure 4, available at the end of the manuscript. These metabolites play a significant role in plant defense against diseases, resistance to pests, and attraction of pollinators.[54] The investigation of these metabolites has shown significant progress in plants metabolomics to uncover potential in pharmaceutical study, agriculture, and diverse industrial uses.[55,56] A recent investigation on particular categories of chemicals found in secondary metabolites has shown their considerable capacity as potent anti-cancer agents. Plant-derived chemicals have also been used in many therapeutic and preventive methods to hinder the progression of cancer, showing significant potential as efficacious remedies.[57–60]

Secondary metabolites derived from various plant sources have demonstrated significant promise in cancer therapy due to their diverse pharmacological activities. These metabolites can be broadly categorized into flavonoids, terpenoids, alkaloids, and phenolic compounds, each exhibiting unique anticancer properties. Flavonoids, such as quercetin, kaempferol, and rutin, are known for their ability to induce apoptosis, inhibit cancer cell proliferation, and suppress metastasis.[61–63] See Figure 5 at the end of the manuscript for a detailed visualization of the structures of secondary metabolites identified, including Cynaroside, Astragalin, Isorhamnetin 3-O-glukosida, Quercetin, Rutin, Flavonol, Phellopterin, Bergapten, and Isoquinoline. The encapsulation of flavonoids in phytosomes significantly enhances their solubility and stability, resulting in increased absorption and bioavailability.[18,64] Similarly, terpenoids,

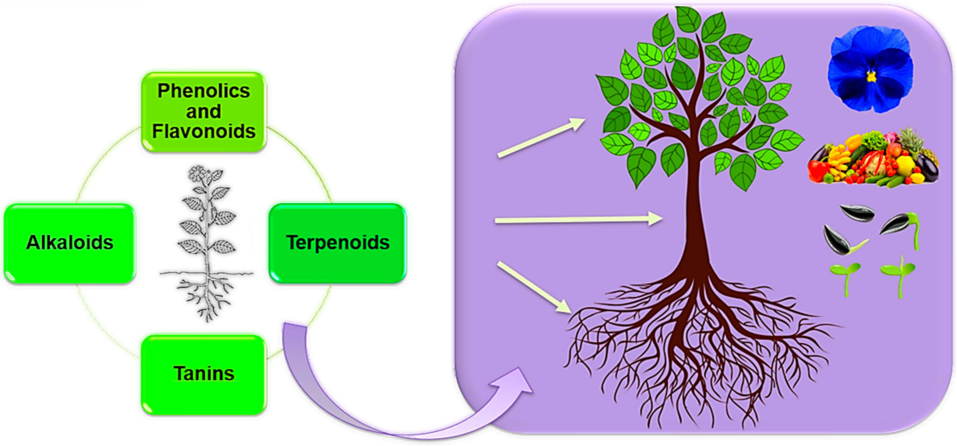


Figure 4 Overview of secondary metabolites and their classifications, including alkaloids, flavonoids, terpenoids, and phenolics, with a focus on anticancer properties.
Notes: Created in BioRender. Mardiana, L (2024) BioRender.com/W63W154.

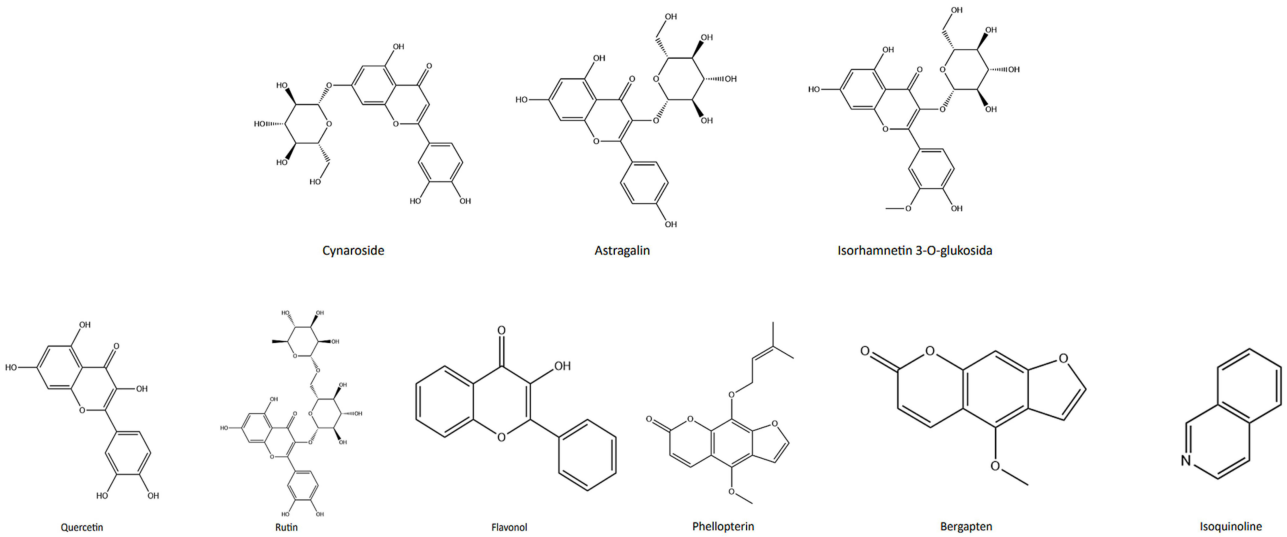


Figure 5 Chemical structures of phytoconstituents used in phytosome-based cancer treatment.

including curcumin,[65] betulinic acid,[66] and ginsenoside Rg3,[65] show broad-spectrum anticancer effects, such as antiproliferative and antiangiogenic activities.[65] Encapsulation in phytosomes further improves the solubility and therapeutic outcomes of these terpenoids.[67,68]

Alkaloids, including berberine, dauricine, and vinblastine, are known for their potent anticancer effects, primarily through apoptosis induction, cell cycle arrest, and autophagy inhibition.[69,70] Phytosome-based formulations of alkaloids have demonstrated enhanced pharmacokinetic properties, leading to improved bioavailability.[17,71] Phenolic compounds, such as resveratrol and pterostilbene, are also effective in preventing cancer cell proliferation and inducing apoptosis.[72,73] Phytosome encapsulation increases the bioavailability of these phenolic compounds, facilitating more effective targeting of cancer cells.[74–76] Recent studies have supported the efficacy of phytosome-encapsulated secondary metabolites, showcasing significant improvements in therapeutic outcomes across various cancer models.

The examination of secondary metabolites in several cancer cell lines shows the significance and potential of plant-derived compounds in the field of oncology. This section provides a more detailed analysis of the consequences of the results, specifically showing their substantial influence on advancement of new medication treatment and methods for cancer treatment. The IC_{50} values in Table 1 show that secondary metabolites, such as flavonoids and alkaloids, have strong effectiveness against a range of cancer types. For instance, efficacy of flavonoids in suppressing cell proliferation in breast, lung, and liver cancer cell lines suggests the capacity to disrupt essential pathways essential for advancement of cancer. Moreover, the impact of alkaloids on melanoma cell lines shows the ability to trigger apoptosis and interfere with cellular proliferation mechanisms.[6,83]

These results emphasize the adaptability of secondary metabolites as versatile agents in cancer treatment. The phytoconstituents show promise for the development of comprehensive cancer therapeutics by targeting important processes such as cell cycle progression,[84,85] apoptosis induction,[86,87] and metastasis inhibition.[88] The variation in IC_{50} values among different cell lines also suggests that secondary metabolites can be customized to selectively target specific forms of cancer, thereby improving the accuracy of oncology.

Flavonoids are secondary metabolites found in plants, with significant health advantages, including strong antioxidant[89] characteristics that protect cells from harm caused by free radicals. The anti-inflammatory characteristics mitigate the possibility of vascular disorders, while anticancer attributes modulate the proliferation of cancer cells. Extensive study also emphasizes the neuroprotective and cardioprotective benefits of flavonoid, which protects the heart and nerves from harm. Moreover, flavonoids possess antibacterial characteristics, underscoring their significance in medicinal contexts for combating microbial infections.[17,90] The classification and specific compounds within each category are essential to identify different roles and therapeutic potentials of secondary metabolites in cancer treatment.

https://doi.org/10.2147/DDDT.S483404

Table 1 IC_{50} Values of Various Phytoconstituents Against Different Cancer Cell Lines, Highlighting the Efficacy of Flavonoids and Alkaloids in Inhibiting Cancer Proliferation

Phytoconstituents (Compound)	Cell Line	IC_{50} Range	Ref
Flavonoids (Quercetin, Kaempferol)	MCF-7 (Breast cancer) A549 (Lung cancer)	22.74 μg/mL 8.74 μg/mL	[77]
Flavonoids (Apigenin)	HepG2 (Liver cancer)	7.6 μM	[78]
	SMMC-7721 (Liver cancer)	3.1 μM	
Flavonoids (Cynaroside and Astragalin)	HeLa (Cervical cancer)	396.0 and 449.0 μg/mL	[79]
Flavonoids (Isorhamnetin 3-O-glukosida)	Lung cancer lines H69 COR-L47 DMS53 DMS79	 125.2 ± 4.5 μg/mL 119.8 ± 6.2 μg/mL 125.3 ± 4.4 μg/mL 89.8 ± 3.2 μg/mL	
Flavonoids (Quercetin 3-O-rutinoside rutin)	Bone cancer lines A-673 CADOES1 HOS SW-1353	 86.4 ± 2.0 μg/mL 124.6 ± 1.9 μg/mL 106.0 ± 4.3 μg/mL 129.7 ± 2.8 μg/mL	
Flavonol	MCF7 (Breast cancer) HeLa (Cervical cancer)	0.96 μM 0.51 μM	[80]
Coumarins (Phellopterin)	Multiple myeloma lines SK-MM-1 RPMI8226 U-266	 69.1 ± 1.2 μg/mL 85.7 ± 1.8 μg/mL 44.3 ± 1.4 μg/mL	[81]
Psoralen (Bergapten)	Breast cancer lines 600MPE AMJ13 AU565 Evsa-T	 109.4 ± 3.9 μg/mL 91.8 ± 4.0 μg/mL 93.5 ± 5.7 μg/mL 249.6 ± 5.3 μg/mL	
Isoquinoline Alkaloids	A375 (Melanoma) SK-MEL-3 (Melanoma)	12.65 μg/mL 1.93 μg/mL	[82]

Figure 6 presents a summary of the four primary categories of secondary metabolites, namely alkaloids, flavonoids, terpenoids, and polyphenols. It also shows essential molecules, indicating the categorization of secondary metabolites including significant anti-cancer compounds. Alkaloids, such as vinblastine,[91] vincristine,[92] and camptothecin,[93] possess potent characteristics for inhibiting cell proliferation. These compounds interfere with cellular processes that are essential for the growth and survival of cancer cells, increasing effectiveness in chemotherapy treatment. Flavonoids, such as apigenin, genistein, and kaempferol, can serve as antioxidants, reduce inflammation, and inhibit the growth of cancer cells.[94,95] The capacity to regulate signaling pathways in cell cycle and apoptosis also contributes to the high potential of inhibiting advancement and dissemination of malignancies. Terpenoids, such as lycopene and gamma-tocopherol, have important functions in preventing the growth of cancer.[96] These compounds are recognized for their ability to inhibit cell division and trigger programmed cell death (apoptosis) in cancer cells, specifically in models of prostate and breast cancer. Polyphenols such as curcumin, resveratrol, and epigallocatechin gallate (EGCG) have shown significant potential in the prevention and cancer treatment.[97,98] The mechanisms include the regulation of oxidative stress and inflammation, along with direct impacts on tumor cell signaling and death.[99,100] The classification facilitates the identification of

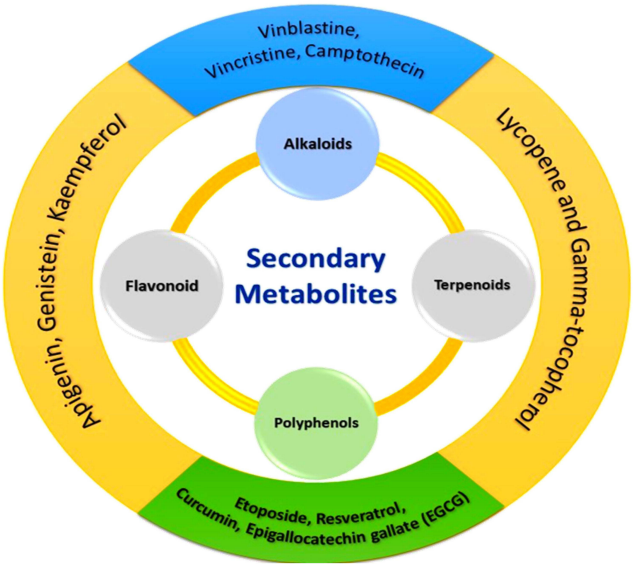


Figure 6 Overview of Secondary Metabolites and Their Classifications, Including Key Compounds with Anticancer Properties. The figure was created by the author using BioRender. Mardiana, L (2024) BioRender.com/W63W154.
Notes: The diagram categorizes secondary metabolites into four groups: Alkaloid Group: Vinblastine, vincristine, and camptothecin. Terpenoid Group: Lycopene and gamma-tocopherol. Polyphenol Group: Etoposide, resveratrol, curcumin, and epigallocatechin gallate (EGCG). Flavonoid Group: Apigenin, genistein, and kaempferol.

possible compounds that can attack cancer and emphasizes the need to improve the ability to be absorbed by the body for effective performance. This can achieved through the use of improved delivery systems such as phytosome, which enhances the solubility, absorption, and therapeutic effectiveness of powerful compounds in clinical applications by enclosing in phospholipid complexes.[101]

The existence of secondary metabolites in medicinal plants, such as alkaloids, flavonoids, and phenols, shows their significant potential in combating cancer due to strong anti-cancer characteristics. These metabolites show anti-proliferative properties against cancer cells and have the ability to control tumor growth, thereby hindering advancement of tumors. Moreover, the presence of bioactive compounds in marine algae improves the effectiveness of standard pharmaceuticals, particularly in treatment of lung cancer. This suggests a possible collaboration between natural compounds and conventional drug.[102,103]

Challenges in Using Phytochemical for Cancer Treatment

Although plant-derived secondary metabolites have the potential to be used in cancer treatment, there are various problems that need to be addressed. The intricate nature of their chemical structures frequently impedes the process of synthesizing and achieving large-scale manufacture. The fluctuation in the content and activity of these compounds in natural sources can impact the uniformity and treatment effectiveness. These compounds have the potential to negatively interact with standard cancer treatment, requiring serious supervision strategies.[11,104]

Investigation and Advancement of Anti-Cancer Compounds Derived from Secondary Metabolites

A comprehensive investigation into chemicals with anti-cancer properties has shown their function through several mechanisms. These include the inhibition of cell proliferation, induction of cancer cell apoptosis, and prevention of angiogenesis, which is essential for tumor metastasis.[105] The compounds often obstruct the function of crucial enzymes that are essential for the survival and growth of cancer cells, thereby inhibiting the proliferation of cancer. This activity emphasizes the potential of plant-derived chemicals to attack cancer by selectively targeting multiple crucial pathways. The continuous advancement of novel compounds is focused on optimizing absorption, distribution, metabolism, and minimizing side effects, improving the effectiveness and safety profiles for application in cancer treatment.[39]

Phytosome with Secondary Metabolites in Cancer Treatment

The use of phytosome technology has significantly revolutionized the administration and efficacy of secondary metabolites in cancer treatment. This novel method includes enclosing herbal constituents in lipid molecules,[106–108] leading to a significant enhancement in absorption and therapeutic efficacy. Furthermore, phytosome technology improves the capacity of hydrophobic compounds to dissolve and remain stable This technology offers innovative opportunities for advancement of therapeutic options that are more efficient and less harmful.

Phytosome technology uses lipid carriers to create compounds with active substances, facilitating precise targeting of cancer cells. The implementation of this technology focuses on enhancing treatment outcomes by enabling the use of lower drug doses and decreasing the probability of experiencing undesirable side effects often associated with greater doses of medicine. Table 2 presents a concise overview of efficacy of several phytosome formulations in treating different cancer cell types, showing their potential therapeutic outcomes.[109,110]

Efficacy of phytosome formulations, such as Sinigrin and Boswellia phytosome, includes offering strong anti-cancer properties and anti-inflammatory benefits, respectively. The synergistic application of Luteolin and Mitomycin, in combination with Luteolin phytosome, shows targeted and potent effects against certain cancer cells. Table 2 also shows the capability of phytosome technology to significantly enhance efficacy of bioactive compounds in cancer treatment. Refer to Figure 7 at the end of the manuscript for the structural visualization of Sinigrin, Luteolin, and Mitomycin, which are among the secondary metabolites discussed for their potential therapeutic effects. Furthermore, phytosome are effective in addressing deficiencies of secondary metabolites, such as flavonoids, which commonly encounter restricted bioavailability and limited interactions with target organs.[83,117]

Phytochemical, such as alkaloids, phenolics, flavonoids, steroids, glycosides, and terpenoids, have shown significant anticancer effects. As shown in Figure 8 at the end of the manuscript, the structures of phytochemicals such as Fisetin, Chrysin, Curcumin, Apigenin, Withaferin, and Glycyrrhizic acid are illustrated. These compounds are utilized in both phytosome and non-phytosome formulations for cancer treatment. However, the implementation of these methods encounters obstacles such as restricted engagement with specific organs and insufficient bioavailability. As shown in Table 3, phytosome technology overcome the problems by improving the absorption into the body and the effectiveness of secondary metabolites. A comparative investigation conducted on a mouse model showed that flavonoids phytosome had enhanced bioavailability and health outcomes compared to ordinary quercetin.[118]

The incorporation of cisplatin and glycyrrhizic acid, a phenolic molecule, into nano-phytosome formulations also showed significant improvement in the effectiveness of the anticancer treatment.[117] Specifically, treatment caused a decrease in the growth of DLD-1 cell line by approximately 44.3% and 95.6% in LIM-2405 cell growth when evaluated in laboratory settings at a dose of 150 μM. The significant enhancement in efficacy was measured as a 124% increase in inhibition from the lowest to highest level in DLD-1 cells. This shows the potential of PEGylated nano-phytosome created using the thin film hydration method.[117] Moreover, the use of PEGylated nano-phytosome led to a substantial increase in DNA damage in DLD-1 cells compared to treatment with cisplatin alone. This emphasizes the system's ability to improve the effectiveness and underlying mechanisms of anticancer activity by delivering phenolic compounds more efficiently. When evaluating the effects of phytosome technology on phytochemical treatment, there is

Table 2 Efficacy of Phytosome-Encapsulated Secondary Metabolites Against Various Cancer Cell Types, Showing Enhanced Therapeutic Outcomes

Metabolite/Compound	Cancer Cell Type / Disease	Effectiveness/Efficacy	Ref
Sinigrin Phytosome	Melanoma	Complete wound healing, potent anticancer activity	[111]
Boswellia Phytosome	General inflammation associated with tumors	Robust anti-inflammatory effects	[112]
Luteolin Phytosome	General	Enhanced drug sensitivity in cancer cells	[74]
Mitomycin and Luteolin Phytosome	Specific cancer cells	Superior targeting and effectiveness	[113]
General Phytosome Technology	Various	Increased bioavailability and pharmacokinetics, reduced dosage requirements	[87,107,114–116]

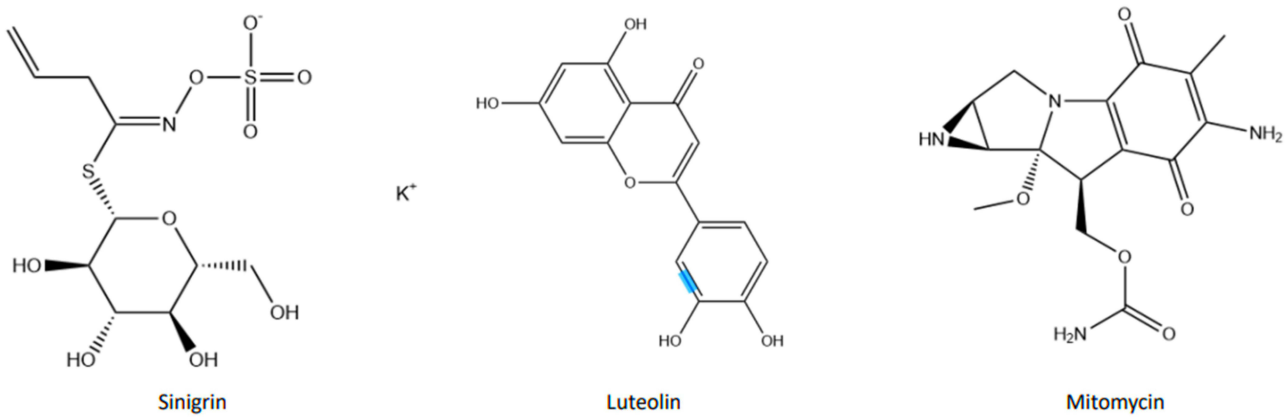


Figure 7 Chemical Structures of Secondary Metabolites Used in Cancer Treatment.
Notes: The figure shows the chemical structures of: Sinigrin: A glucosinolate e known for its anticancer activity. Luteolin: A flavonoid with potential anticancer effects. Mitomycin: An alkaloid commonly used in cancer chemotherapy.

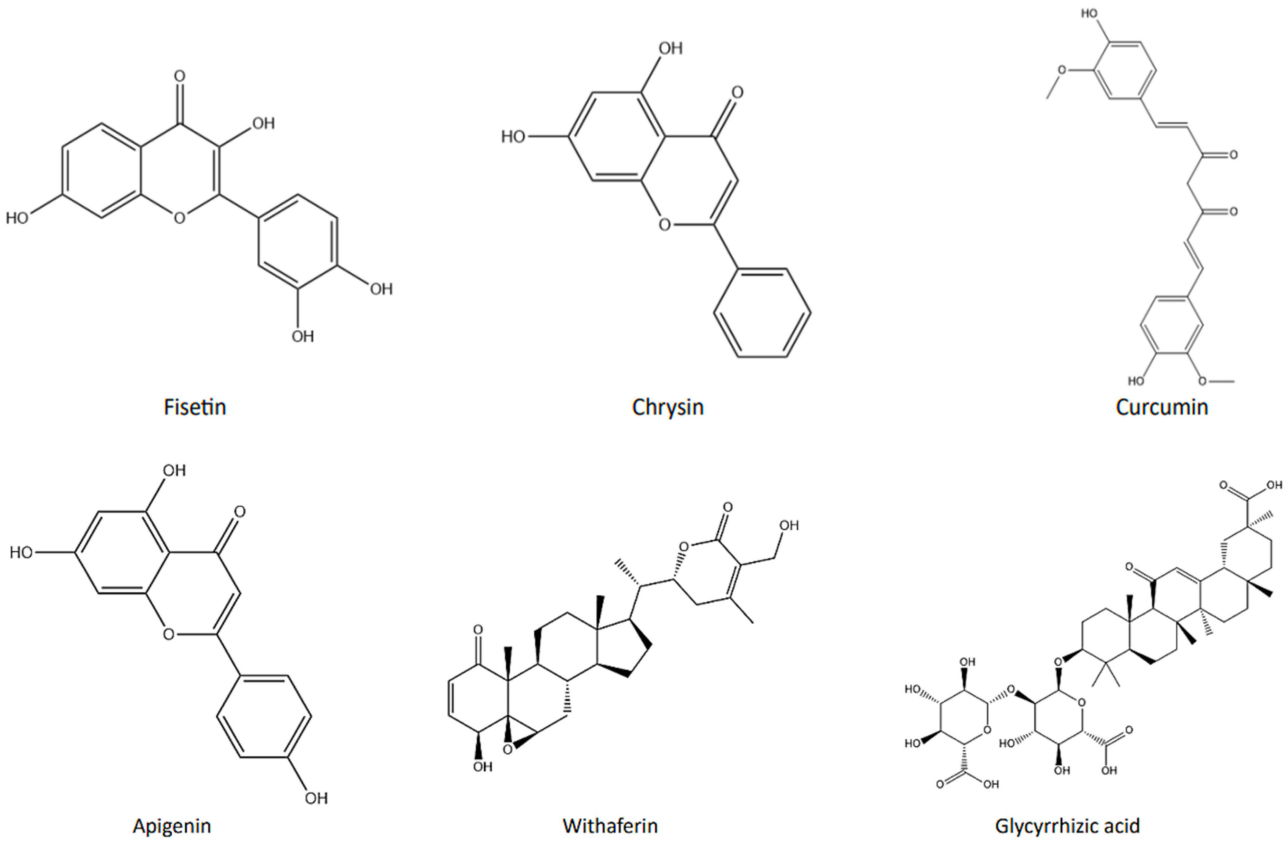


Figure 8 Structures of Phytochemical used in Phytosome and Non-Phytosome Cancer Treatment.

an improvement in effectiveness during formulations comparison between phytosome and non-phytosome. Specifically, polyphenols targeting 4 T1 cancer cells showed the most remarkable enhancement, with a decrease in IC_{50} values from 39.94 µg/mL to 7.73 µg/mL, leading to an 80.67% reduction and a fivefold increase in activity. Chrysin showed a significant decrease in IC_{50} in HT29 cells, resulting in a nearly threefold increase in efficacy. Similarly, Terpenoids and Flavonoids showed major reductions in IC_{50} in Vero cell lines, leading to a threefold increase in efficacy. The Polyherbal mix showed a 35.9% reduction in IC_{50} and a 1.56-fold increase in activity on MCF-7 and MDA MB 231 cells. Polyphenols showed the most significant increase after being encapsulated in phytosome. This suggested the

https://doi.org/10.2147/DDDT.S483404

Table 3 Comparison of IC_{50} Values Between Phytosome and Non-Phytosome Formulations of Secondary Metabolites in Cancer Treatment

Phytochemical	Category	Cancer Cell	In Vivo / In Vitro Test	Method	Non-Phytosome (IC_{50})	Phytosome (IC_{50})	Mechanism	Ref
Polyphenols	Phenolic	4 T1	In-Vitro	Thin-Layer Hydration solvent injection	39.94 ± 0.10 µg/ mL	7.73 ± 2.87 µg/ mL	↑ Apoptosis	[74]
Fisetin	Phenolic	MDA-MB -231	In-Vitro	Thin Film Hydration and Solvent Injection	189.10 ± 3.07 µg/ mL	75.81 ± 2.99 µg/ mL	↓Antiproliferative, ↑Apoptosis and necroptosis, ↓TGF-β1/ MMP-9 molecular pathways of tumorigenesis	[119]
Chrysin	Flavonoids	HT29	In-Vitro	Antisolvent Precipitation	53.21 µg/ mL	17.9 µg/ mL	↓Cell Viability	[120]
Curcumin, Apigenin, Withaferin	Phenolic, Flavonoids, Steroids	MCF-7, MDA-MB -231	In-Vitro	Thin Film Hydration	75 µg/ mL, 80 µg/ mL, 74 µg/ mL	40 µg/ mL, 44 µg/ mL, 42 µg/ mL	↑Cytotoxic effects, ↑Apoptosis	[121]
	Terpenoids Flavonoids	Vero (Normal) Cell Lines	In-Vitro	Solvent Evaporation & Thin Film Hydration	220.2656 µg/ mL	77.67509 µg/ mL	Inhibitory effect ↓Cell Viability	[42]
Polyherbal	Mixed	MCF-7, MDA MB 231	In-Vitro	Thin Film Hydration	35–82 µg/mL	20–55 µg/mL	Synergistic effects, ↑ ROS production	[121]

Notes: Phytosome: refer to secondary metabolites encapsulated in a phospholipid complex, which enhances their bioavailability and efficacy. Non-phytosome: include standardized extracts or solutions that are not encapsulated by a phospholipid complex. ↑ (up arrow): indicates an enhancement in the effect. ↓ (down arrow: indicates a reduction in the effect.

substantial influence of phytosome technology on improving the administration and efficacy of phytochemical in cancer treatment. The results also showed the role of phytosome in converting natural chemicals into powerful anticancer drug, representing an essential breakthrough in the field of oncology. Moreover, this technology improves therapeutic effectiveness of phenolics, which possess anticancer effects. Table 3 shows the ability of phytosome formulations to overcome the harmful effects on cells and restrictions in bioactive compounds processed by the body, resulting in improved effectiveness in causing programmed cell death and reducing resistance to drugs.[84,122]

This review uniquely contributes to the field by exploring the innovative application of phytosome technology for enhancing the anticancer efficacy of secondary metabolites. Unlike previous studies that focus primarily on general pharmacological properties, this review delves into specific mechanisms by which phytosome encapsulation optimizes solubility, absorption, and targeted delivery of natural compounds. The findings presented here provide novel insights into how such advanced delivery systems can overcome longstanding challenges in the clinical application of secondary metabolites for cancer therapy, setting a foundation for more effective, natural-based cancer treatments.

Synthesis of Phytosome Containing Secondary Metabolites

Phytosome production entails enclosing bioactive plant components in lipid matrix, mainly phospholipids, to improve bioavailability and stability. This process commonly uses various methods such as solvent evaporation, thin-layer hydration, and anti-solvent precipitation.[123] The methods promote the development of a connection between the water-loving portion of phytochemical and the water-repelling section of the phospholipid, leading to a well-organized, stable compound that efficiently crosses cell membranes.[124] The selection of the method depends on the physicochemical characteristics of metabolites to be enclosed, suggesting effective incorporation into the lipid framework. To optimize phytosome formulations, there is a need to alter the ratios of phospholipids to secondary metabolites, modify the synthesis parameters to improve encapsulation efficiency, and assess the bioactivity of the resulting phytosome.[125] During this stage of development, it is essential to customize the properties of phytosome, such as particle size, zeta potential, and encapsulation efficiency,[126] to meet therapeutic requirements of certain metabolites. Methods such as

dynamic light scattering (DLS) and scanning electron microscopy (SEM) are commonly used to analyze and improve the properties of these nanoparticles, showing their effectiveness and stability in physiological environments.[127]

Phytosome has essential benefits in terms of enhanced bioavailability and effectiveness, although there are difficulties in stability, scalability, and manufacture. Therefore, appropriate storage conditions and suitable stabilizers are required for long-term stability.[128] Scalability refers to the process of moving from small-scale production in a laboratory to large-scale manufacture in industrial settings. This process requires the development of efficient and affordable methods that can handle a high volume of output, without causing any damage to the structure of phytosome. Moreover, there is a need to overcome regulatory obstacles and ensure adherence to pharmaceutical standards on quality and safety.

Future Perspectives and Directions

Phytosome technology has made progress in developing delivery systems that can specifically transport phytochemical to cancer cells. Currently, various investigations are being carried out to investigate innovations, such as modifying the surface of phytosome with antibodies or ligands that can identify specific markers on cancer cells. These modifications are performed to enhance the selectivity of phytosome, thereby minimizing the effects on healthy cells and improving therapeutic outcomes in the field of oncology. The modular structure of phytosome technology renders it highly versatile for specific treatment to optimize effectiveness and reduce adverse effects by modifying the composition and dosage according to unique patient profiles. Phytosome being included in individualized treatment plans is a potential advancement in precision medicine, particularly in the field of cancer care, where the variability in individual response to treatment is a major obstacle.

Understanding and complying with regulations is crucial for the successful implementation of phytosome technology in clinical trials. Furthermore, there is a need to meet the rigorous demands of the regulatory body, which require thorough documentation of the synthesis process, and verification of safety, and efficacy through clinical trials. To obtain the product into clinical use, it is essential to increase manufacturing on a larger scale, while adhering to Good Manufacturing Practices (GMP). Stability tests must be conducted, along with regulatory permissions before the product can enter the market.

Conclusion

Phytosome technology demonstrates significant potential in augmenting natural chemicals for cancer treatment. Phytosomes enhance the delivery of bioactive compounds, including flavonoids, alkaloids, and terpenoids, efficiently targeting essential cancer pathways including NF-κB and PI3K/AKT, thereby establishing them as a promising asset in oncology. In addition to their anticancer properties, phytosomes mitigate the shortcomings of traditional formulations by creating molecular complexes with secondary metabolites, thereby improving their solubility and bioavailability. Comparative studies demonstrate that phytosome-based formulations attain enhanced absorption and prolonged circulation durations, resulting in increased therapeutic efficacy. This review emphasises phytosome technology as a novel delivery mechanism, facilitating future research and clinical applications in cancer therapy.

Acknowledgments

We express our gratitude to the Rector of Universitas Padjadjaran for the APC. Chemical structures were redrawn utilizing ChemDraw Professional (Version 16.0.1.4), licensed to Supriatno Salam at Universitas Padjadjaran.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Gaidai O, Yan P, Xing Y. Future world cancer death rate prediction. *Sci Rep*. 2023;13(1):1–9. doi:10.1038/s41598-023-27547-x
2. National Cancer Institute. Statistics at a Glance: the Burden of Cancer in the United States. *Cancer Stat*. 2017;2017:1.
3. National Cancer Institute. *Definition of Cancer*; 1997. doi:10.12968/pnur.1997.8.18.27
4. Al-Kaf AG, Nelson NO, Patrick OU, Peace NA, Victor EJ, Alexander I. Phytochemical Analysis and Estimation of Anti Oxidant Potential of Phytosomes Formulations of Morinda Lucida Benth. *Univers J Pharm Res*. 2023;7(6):22–27. doi:10.22270/ujpr.v7i6.865

5. Tungmunnithum D, Thongboonyou A, Pholboon A, Yangsabai A. Flavonoids and Other Phenolic Compounds from Medicinal Plants for Pharmaceutical and Medical Aspects: an Overview. *Medicines*. 2018;5(3):93. doi:10.3390/medicines5030093
6. Riaz M, Khalid R, Afzal M, et al. Phytobioactive compounds as therapeutic agents for human diseases: a review. *Food Sci Nutr*. 2023;11 (6):2500–2529. doi:10.1002/fsn3.3308
7. Silva FL, Da O, Betania M, Marques DF, Kato C, Carneiro G. Expert Opinion on Drug Discovery Nanonization techniques to overcome poor water- solubility with drugs. *Expert Opin Drug Discov*. 2020;2020:1–12. doi:10.1080/17460441.2020.1750591
8. Pote SV, Bavaskar K, Jain A. Solubility Enhancement of Poorly Soluble Drug by using different Techniques. Research Journal of Pharmaceutical Dosage Forms and Technology. 2022;14(04):52711. doi:10.52711/0975-4377.2022.00052
9. Park S, Mun S, Kim Y-R. Influences of added surfactants on the water solubility and antibacterial activity of rosemary extract. *Food Sci Biotechnol*. 2020;29(10):1373–1380. doi:10.1007/s10068-020-00792-w
10. Gali L, Pirozzi A, Donsì F. Biopolymer- and Lipid-Based Carriers for the Delivery of Plant-Based Ingredients. *Pharmaceutics*. 2023;15(3):927. doi:10.3390/pharmaceutics15030927
11. Usman M, Khan WR, Yousaf N, et al. Exploring the Phytochemicals and Anti-Cancer Potential of the Members of Fabaceae Family: a Comprehensive Review. *Molecules*. 2022;27(12):3863. doi:10.3390/molecules27123863
12. Krishnan R, Scholar PG, Vigyana D. Phytosomes: an Advanced Concept To Novel Drug Delivery System Phytosomes: an Advanced Concept To Novel Drug Delivery. *Int J Sci Res*. 2023;2023(January):10–12. doi:10.36106/IJSR/2112616
13. Amit P, Tanwar YS, Rakesh S. Phytosome: phytolipid Drug Delivery System for Improving Bioavailability of Herbal Drug. *J Pharm Sci Biosci Res*. 2013;3(2):51–57.
14. Mazaud A, Lebeuf R, Laguerre M, Nardello RV. Hydrotropic Extraction of Carnosic Acid from Rosemary with Short- Chain Alkyl Polyethylene Glycol Ethers. *ACS Sustain Chem Eng*. 2020;8(40):15268–15277. doi:10.1021/acssuschemeng.0c05078
15. Bhalani DV, Nutan B, Kumar A, Singh Chandel AK. Bioavailability Enhancement Techniques for Poorly Aqueous Soluble Drugs and Therapeutics. *Biomedicines*. 2022;10(2055):1–33. doi:10.3390/biomedicines10092055
16. Bhakay A, Rahman M, Dave RN, Bilgili E. Bioavailability Enhancement of Poorly Water-Soluble Drugs via Nanocomposites: formulation – processing Aspects and Challenges. *Pharm Rev*. 2018;10(86):1–62. doi:10.3390/pharmaceutics10030086
17. Barani M, Sangiovanni E, Angarano M, et al. Phytosomes as innovative delivery systems for phytochemicals: a comprehensive review of literature. *International Journal of Nanomedicine*. 2021;16:6983–7022. doi:10.2147/IJN.S318416
18. Zverev YF, Rykunova AY. Modern Nanocarriers as a Factor in Increasing the Bioavailability and Pharmacological Activity of Flavonoids. *Appl Biochem Microbiol*. 2022;58(9):1002–1020. doi:10.1134/S0003683822090149
19. Ibrahim M, Abdellatif AAH. *Nano- Pharmaceuticals: Principles and Applications*. Yata VK, Ranjan S, Dasgupta N, Lichtfouse E, ed.. Springer;2021. doi:10.1007/978-3-030-44925-4
20. Grilc NK, Sova M. Drug Delivery Strategies for Curcumin and Other Natural Nrf2 Modulators of Oxidative Stress-Related Diseases. *Pharmaceutics*. 2021;13(2137):1–29. doi:10.3390/pharmaceutics13122137
21. Kumar N, Arfin S, Kumar S, Kar R, Dey A. Seminars in Cancer Biology Re-establishing the comprehension of phytomedicine and nanomedicine in inflammation-mediated cancer signaling. *Semin Cancer Biol*. 2022;86(P2):1086–1104. doi:10.1016/j.semcancer.2022.02.022
22. Al-rabia MW, Alhakamy NA, Rizg WY, et al. Boosting curcumin activity against human prostatic cancer PC3 cells by utilizing scorpion venom conjugated phytosomes as promising functionalized nanovesicles. *Drug Deliv*. 2022;29(1):807–820. doi:10.1080/10717544.2022.2048133
23. Fakhri S, Moradi SZ, Yarmohammadi A, Narimani F. Modulation of TLR / NF- k B / NLRP Signaling by Bioactive Phytocompounds: a Promising Strategy to Augment Cancer Chemotherapy and Immunotherapy. *Front Oncol*. 2022;12(March):1–46. doi:10.3389/fonc.2022.834072
24. Rai M, Vikram A, Paudel N, et al. Current Research in Toxicology Herbal concoction Unveiled: a computational analysis of phytochemicals' pharmacokinetic and toxicological profiles using novel approach methodologies (NAMs) Introduction. *Curr Res Toxicol*. 2023;5(June):100118. doi:10.1016/j.crtox.2023.100118
25. Pachuau L, Laldinchhana, Roy PK, Zothantluanga JH, Ray S, Das S. *Encapsulation of Bioactive Compound and Its Therapeutic Potential BT - Bioactive Natural Products for Pharmaceutical Applications*. In: Pal D, Nayak AK, ed.. Springer International Publishing; 2021:687–714. doi:10.1007/978-3-030-54027-2_20
26. Sayed N, Khurana A, Godugu C. Journal of Drug Delivery Science and Technology Pharmaceutical perspective on the translational hurdles of phytoconstituents and strategies to overcome. *J Drug Deliv Sci Technol*. 2019;53(April):101201. doi:10.1016/j.jddst.2019.101201
27. Peers S, Montembault A, Ladavière C. Chitosan hydrogels for sustained drug delivery. *J Control Release*. 2020;326(February):150–163. doi:10.1016/j.jconrel.2020.06.012
28. Martínez IAR, Serafini MR, Alves IA, Novoa DMA, Aragon Novoa DM. Trends in Oral Flavonoid Drug Delivery Systems Based on Current Pharmaceutical Strategies. A Systematic Patent Review (2011–2023. *J Herbs Med*. 2024;43(December 2023):100828. doi:10.1016/j.hermed.2023.100828
29. Hamdard J, Delhi N, Zealand N, et al. Recent Advancement in Clinical Application of Nanotechnological Approached Targeted Delivery of Herbal Drugs. *Nanophytomedicine*. 2020;151–172:1–25. doi:10.1007/978-981-15-4909-0_9
30. Ibrahim K, Refaie W, Abdallah O. WO2022135652A1.
31. Falls I. *States Patent*. 2021;Vol. 2:1–80.
32. Azeezn AV, SD SV. *IN201841001612 - Formulation of Allium Sativum and Murraya Koenigii Based Phytosomal Complex for the Sustained Release and Treatment of Breast Cancer*. 2019:39.
33. Pradeepa SY, Tharani S, Mathu SI, Anandha VRK, Bindhu J. Phytosome Loaded With Biosynthesized Ag Nps For Combating Bone Cancer Through Second-Order Targeting. 2023;22(12).
34. Hu Y, Lin Q, Zhao H, et al. Food Hydrocolloids Bioaccessibility and bioavailability of phytochemicals: influencing factors, improvements, and evaluations. *Food Hydrocoll*. 2023;135(July 2022):108165. doi:10.1016/j.foodhyd.2022.108165
35. Liu Y, Li S, Liu X, et al. Design of Small Nanoparticles Decorated with Amphiphilic Ligands: self-Preservation Effect and Translocation into a Plasma Membrane. *ACS Appl Mater Interfaces*. 2019;11(27):23822–23831. doi:10.1021/acsami.9b03638
36. Jogpal V, Sanduja M, Dutt R, Garg V, Tinku T. Advancement of nanomedicines in chronic inflammatory disorders. *Inflammopharmacology*. 2022;30(2):355–368. doi:10.1007/s10787-022-00927-x

37. Ames CL, Klompen AML, Badhiwala K, et al. Cassiosomes are stinging-cell structures in the mucus of the upside-down jellyfish Cassiopea xamachana. *Commun Biol*. 2020;3(1):67. doi:10.1038/s42003-020-0777-8
38. Paul W, Sharma CP. Inorganic nanoparticles for targeted drug delivery. In: Second E editor. *Sharma CPBT-B of MIM*. Woodhead Publishing; 2020:333–373. doi:10.1016/B978-0-08-102680-9.00013-5.
39. Umashankar DD. Plant secondary metabolites as regenerative medicine. *J Phytopharm*. 2020;9(4):270–273. doi:10.31254/phyto.2020.9410
40. Chauhan D, Yadav PK, Sultana N, et al. Advancements in nanotechnology for the delivery of phytochemicals. *J Integr Med*. 2024;22 (4):385–398. doi:10.1016/j.joim.2024.04.005
41. Pons-Faudoa FP, Ballerini A, Sakamoto J, Grattoni A. Advanced implantable drug delivery technologies: transforming the clinical landscape of therapeutics for chronic diseases. *Biomed Microdevices*. 2019;21(2):47. doi:10.1007/s10544-019-0389-6
42. Murugesan MP, Venkata Ratnam M, Mengitsu Y, Kandasamy K. Evaluation of anti-cancer activity of phytosomes formulated from aloe vera extract. *Mater Today Proc*. 2020;42:631–636. doi:10.1016/j.matpr.2020.11.047
43. Sun Y, Zhang S, Xie F, Zhong M, Jiang L, Qi B. Effects of covalent modification with epigallocatechin-3-gallate on oleosin structure and ability to stabilize artificial oil body emulsions. *Food Chem*. 2021;341(September 2020):128272. doi:10.1016/j.foodchem.2020.128272
44. Semenova M, Antipova A, Martirosova E, Zelikina D, Palmina N, Chebotarev S. Food Hydrocolloids Essential contributions of food hydrocolloids and phospholipid liposomes to the formation of carriers for controlled delivery of biologically active substances via the gastrointestinal tract. *Food Hydrocoll*. 2021;120(May):106890. doi:10.1016/j.foodhyd.2021.106890
45. Rezaei A, Fathi M, Mahdi S. Food Hydrocolloids Nanoencapsulation of hydrophobic and low-soluble food bioactive compounds within di ff erent nanocarriers. *Food Hydrocoll*. 2019;88(June 2018):146–162. doi:10.1016/j.foodhyd.2018.10.003
46. Lu M, Qiu Q, Luo X, et al. Phyto-phospholipid complexes (phytosomes): a novel strategy to improve the bioavailability of. *Asian J Pharm Sci*. 2019;14(3):265–274. doi:10.1016/j.ajps.2018.05.011
47. Babazadeh A, Zeinali M, Hamishehkar H. Nano-Phytosome: a Developing Platform for Herbal Anti-Cancer Agents in Cancer Therapy. *Curr Drug Targets*. 2017;18(999):1. doi:10.2174/1389450118666170508095250
48. Kumar S, Baldi A, Sharma DK. Phytosomes: a Modernistic Approach for Novel Herbal Drug Delivery - Enhancing Bioavailability and Revealing Endless Frontier of Phytopharmaceuticals. *J Dev Drugs*. 2020;9(2):1–8. doi:10.4172/2329-6631
49. Qu J, Li J, Zhang Y, et al. AKR1B10 promotes breast cancer cell proliferation and migration via the PI3K / AKT / NF-κB signaling pathway. *Cell Biosci*. 2021;2021:1–13. doi:10.1186/s13578-021-00677-3.
50. Chen H, Chen S, Zheng Q, Nie S, Li W, Hu X. Genistein Promotes Proliferation of Human Cervical Cancer Cells Through Estrogen Receptor-Mediated PI3K/Akt-NF-κB Pathway. *J Cancer*. 2018;9(2):288–295. doi:10.7150/jca.20499
51. Arya A, Paul S, Gangwar A. Silymarin—A Scintillating Phytoantioxidant: clinical Applications and Bio-delivery Problems. In: *Novel Drug Delivery Systems for Phytoconstituents*. CRC Press; 2019:223–240.
52. Saini P, Saini P, Kaur JJ. *Molecular Approaches for Harvesting Natural Diversity for Crop Improvement BT - Rediscovery of Genetic and Genomic Resources for Future Food Security.* ed. Salgotra RK, Zargar SM, et al.Springer Singapore; 2020:67–169. doi:10.1007/978-981-15-0156-2_3
53. Yoldi MJR. Anti-Inflammatory and Antioxidant Properties of Plant Extracts. *Antioxidants*. 2021;4:7–10.
54. Nurul Huda A, Zariman NA, Omar NA. Plant Attractants and Rewards for Pollinators: their Significant to Successful Crop Pollination. *Int J Life Sci Biotechnol*. 2022;5(2):270–293. doi:10.38001/ijlsb.1069254
55. Li C, Wang Z, Chen W, et al. An Integrative Metabolomic and Network Pharmacology Study Revealing the Regulating Properties of Xihuang Pill That Improves Anlotinib Effects in Lung Cancer. *Front Oncol*. 2021;11(August):1–14. doi:10.3389/fonc.2021.697247
56. Moghimipour E, Handali S. Saponin: properties, Methods of Evaluation and Applications. *Annu Res Rev Biol*. 2015;5(3):207–220. doi:10.9734/arrb/2015/11674
57. Hashemi SM, Naghavi MR, Bakhshandeh E, Ghorbani M, Priyanatha C, Zandi P. Effects of abiotic elicitors on expression and accumulation of three candidate benzophenanthridine alkaloids in cultured greater celandine cells. *Molecules*. 2021;26(5):1395. doi:10.3390/molecules26051395
58. Kim T-J, Seo K-H, Chon J-W, et al. Organoleptic Properties of Cow Milk, Yoghurt, Kefir, and Soy Milk When Combined with Broccoli Oil: a Preliminary Study. *J Dairy Sci Biotechnol*. 2022;40(2):76–85. doi:10.22424/jdsb.2022.40.2.76
59. Shaheen R, Hanif MA, Nisar S, et al. Seasonal variation, fractional isolation and nanoencapsulation of antioxidant compounds of Indian blackberry (Syzygium cumini). *Antioxidants*. 2021;10(12):1900. doi:10.3390/antiox10121900
60. Ojha DK, Jain AP. Streptozotocin-induced Antidiabetic Activity of Vitex negundo, Vitex trifolia and Vitex parviflora Combined Phytosomal Formulation. *J Pharm Res Int*. 2021;33:207–213. doi:10.9734/jpri/2021/v33i60b34606
61. Kopustinskiene DM, Jakstas V, Savickas A, Bernatoniene J. Flavonoids as anticancer agents. *Nutrients*. 2020;12(2):1–25. doi:10.3390/nu12020457
62. Ezzati M, Youse B, Velaei K, Safa A. A review on anti-cancer properties of Quercetin in breast cancer. *Life Sci J*. 2020;248 (September 2019):1–12. doi:10.1016/j.lfs.2020.117463
63. Almatroodi SA, Alsahli MA, Almatroudi A, et al. Potential Therapeutic Targets of Quercetin, a Plant Flavonol, and Its Role in the Therapy of Various Types of Cancer through the Modulation of Various Cell Signaling Pathways. *Molecules*. 2021;26(1315):1–38. doi:10.3390/molecules26051315
64. Yuan D, Guo Y, Pu F, Yang C, Xiao X, Du H. Opportunities and challenges in enhancing the bioavailability and bioactivity of dietary flavonoids: a novel delivery system perspective. *Food Chem*. 2024;430:137115. doi:10.1016/j.foodchem.2023.137115
65. Zhang C, Wang N, Tan H, Guo W, Li S, Feng Y. Targeting VEGF / VEGFRs Pathway in the Antiangiogenic Treatment of Human Cancers by Traditional Chinese Medicine. *Integr Cancer Ther*. 2018;17(3):582–601. doi:10.1177/1534735418775828
66. Scaria B, Sood S, Raad C, et al. Natural Health Products (NHP's) and Natural Compounds as Therapeutic Agents for the Treatment of Cancer; Mechanisms of Anti-Cancer Activity of Natural Compounds and Overall Trends. *Mol Sci*. 2020;21(8480):1–32. doi:10.3390/ijms21228480
67. Nisar S, Masoodi T, Prabhu KS, et al. Biomedicine & Pharmacotherapy Natural products as chemo-radiation therapy sensitizers in cancers. *Biomed Pharmacother*. 2022;154:113610. doi:10.1016/j.biopha.2022.113610
68. Sharma P, Manchanda R, Goswami R, Chawla S. Biodiversity and Therapeutic Potential of Medicinal Plants. *Environ Concerns Sustain Dev*. 2021;26–44. doi:10.1007/978-981-13-6358-0

69. Liang X, Zhang L, Li F, Luan S, He C. Autophagy-regulating N-heterocycles derivatives as potential anticancer agents. *Futur Med Chem*. 2019;12(3):223–242. doi:10.4155/fmc-2019-0294
70. Naeem A, Hu P, Yang M, et al. Natural Products as Anticancer Agents: current Status and Future Perspectives. *Molecules*. 2022;27(23):1–64. doi:10.3390/molecules27238367
71. Alharbi WS, Almughem FA, Almehmady AM, et al. Phytosomes as an Emerging Nanotechnology Platform for the Topical Delivery of Bioactive Phytochemicals. *Pharmaceutics*. 2021;13(9):1–20. doi:10.3390/pharmaceutics13091475
72. Obrador E, Salvador-palmer R, Jihad-jebbar A, et al. Pterostilbene in Cancer Therapy. *Antioxidants*. 2021;3(10):492. doi:10.3390/antiox10030492
73. Shin HJ, Han JM, Choi YS, Jung HJ. Pterostilbene Suppresses both Cancer Cells and Cancer Stem-Like Cells in Cervical Cancer with. *Molecules*. 2020;2(25):228. doi:10.3390/molecules25010228
74. Wanjiru J, Gathirwa J, Sauli E, Swai HS. Breast Cancer Cell Lines. *Molecules*. 2022;27(4430):1–19. doi:10.3390/molecules27144430
75. Grgic J, Selo G, Planinic M, Tisma M, Bucic-Kojic A. Role of the Encapsulation in Bioavailability of Phenolic Compounds. *Antioxidants*. 2020;9(10):932. doi:10.3390/antiox9100923
76. Yang B, Dong Y, Wang F. Nanoformulations to Enhance the Bioavailability and Physiological Functions of Polyphenols. *Molecules*. 2020;202(25):1–36. doi:10.3390/molecules25204613
77. Basim S, Kasim AA. Cytotoxic Activity of the Ethyl Acetate Extract of Iraqi Carica papaya Leaves in Breast and Lung Cancer Cell Lines. *Asian Pacific J Cancer Prev*. 2023;24(2):581–586. doi:10.31557/APJCP.2023.24.2.581
78. Li J, Shen S, Liu Z, et al. Synthesis and Structure–Activity Analysis of Icaritin Derivatives as Potential Tumor Growth Inhibitors of Hepatocellular Carcinoma Cells. *J Nat Prod*. 2023;86(2):290–306. doi:10.1021/acs.jnatprod.2c00908
79. He M. Total flavonoids in Artemisia absinthium L. and evaluation of its anticancer activity aim of the study. *Int J Mol Sci*. 2023;24:16348.
80. Shoaib M, Ghias M, Shah SWA, et al. Synthetic flavonols and flavones: a future perspective as anticancer agents. *Pak J Pharm Sci*. 2019;32(3):1081–1089.
81. Dehnoee A. *Anticancer Potential of Furanocoumarins and Flavonoids of Heracleum Persicum Fruit*. 2023;Vol. 2023:1–14.
82. Tuzimski T, Petruczynik A, Plech T, et al. Determination of Selected Isoquinoline Alkaloids from Chelidonium majus, Mahonia aquifolium and Sanguinaria canadensis Extracts by Liquid Chromatography and Their In Vitro and In Vivo Cytotoxic Activity against Human Cancer Cells. *Int J Mol Sci*. 2023;24(7):6360. doi:10.3390/ijms24076360
83. Nazemoroaya Z, Sarafbidabad M, Mahdieh A, Zeini D, Nyström B. Use of Saponinosomes from Ziziphus spina-christi as Anticancer Drug Carriers. *ACS Omega*. 2022;7(32):28421–28433. doi:10.1021/acsomega.2c03109
84. Elekofehinti OO, Iwaloye O, Olawale F, Ariyo EO. Saponins in cancer treatment: current progress and future prospects. *Pathophysiology*. 2021;28(2):250–272. doi:10.3390/pathophysiology28020017
85. Badavenkatappa GS, Nelson VK, Peraman R. Tinospora sinensis (Lour.) Merr alkaloid rich extract induces colon cancer cell death via ROS mediated, mTOR dependent apoptosis pathway: "an in-vitro study. *BMC Complement Med Ther*. 2023;23(1):1–14. doi:10.1186/s12906-023-03849-5
86. Nassef MZ, Melnik D, Kopp S, et al. Breast cancer cells in microgravity: new aspects for cancer research. *Int J Mol Sci*. 2020;21(19):1–22. doi:10.3390/ijms21197345
87. Alhakamy NA, Badr-Eldin SM, Fahmy UA, et al. Thymoquinone-loaded soy-phospholipid-based phytosomes exhibit anticancer potential against human lung cancer cells. *Pharmaceutics*. 2020;12(8):1–17. doi:10.3390/pharmaceutics12080761
88. Masoomzadeh S, Gholikhani T, Barfar A, Asnaashari S, Javadzadeh Y. Different Types of Naturally based Drug Delivery Carriers: an Explanation and Expression of Some Anti-cancer Effects. *Bentham Sci Publ*. 2023;29(15):1173–1179. doi:10.2174/1381612829666230510090433
89. Zhan X, Li J, Zhou T. Targeting Nrf2-Mediated Oxidative Stress Response Signaling Pathways as New Therapeutic Strategy for Pituitary Adenomas. *Front Pharmacol*. 2021;12(March):1–16. doi:10.3389/fphar.2021.565748
90. Hashemzadeh H, Hanafi-Bojd MY, Iranshahy M, Zarban A, Raissi H. The combination of polyphenols and phospholipids as an efficient platform for delivery of natural products. *Sci Rep*. 2023;13(1):1–20. doi:10.1038/s41598-023-29237-0
91. National Center for Biotechnology Information. PubChem Compound Summary for CID 13342, Vinblastine. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Vinblastine. Accessed May 29, 2024.
92. National Center for Biotechnology Information. PubChem Compound Summary for CID 5978, Vincristine. Accessed May 25, 2024. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Vincristine.
93. Liu Z, Zheng Q, Chen W, et al. Chemosensitizing effect of Paris Saponin I on Camptothecin and 10-hydroxycamptothecin in lung cancer cells via p38 MAPK, ERK, and Akt signaling pathways. *Eur J Med Chem*. 2017;125:760–769. doi:10.1016/j.ejmech.2016.09.066
94. Li G, Ding K, Qiao Y, et al. Flavonoids Regulate Inflammation and Oxidative. *Molecules*. 2020;23(25):1–15. doi:10.3390/molecules25235628
95. Ginwala R, Bhavsar R, Chigbu DGI, Jain P. Potential Role of Flavonoids in Treating Chronic Inflammatory Diseases with a Special Focus on the Anti-Inflammatory Activity of Apigenin. *Antioxidants*. 2019;2(8):1–28. doi:10.3390/antiox8020035
96. Kwatra B. A Review On Potential Properties And Therapeutic Applications Of. *Int J Med Biomed*. 2020;4(10):33–44. doi:10.32553/ijmbs.v4i4.1081
97. Chimento A, Amico MD, Luca A, Conforti FL, Pezzi V, De Amicis F. Resveratrol, Epigallocatechin Gallate and Curcumin for Cancer Therapy: challenges from Their Pro-Apoptotic Properties. *Life*. 2023;2(13):1–24.
98. Almatroodi SA, Almatroudi A, Khan AA, Alhumaydhi FA, Alsahli MA, Rahmani AH. Potential Therapeutic Targets of Epigallocatechin Gallate (EGCG), the Most Abundant Catechin in Green Tea, and Its Role in the Therapy of Various Types of Cancer. *Molecules*. 2020;14(25):1–39.
99. Arfin S, Jha NK, Jha SK, et al. Oxidative Stress in Cancer Cell Metabolism. *Antioxidants*. 2021;5(10):1–28.
100. Lin Y, Jiang M, Chen W, Zhao T, Wei Y. Biomedicine & Pharmacotherapy Cancer and ER stress: mutual crosstalk between autophagy, oxidative stress and in fl ammatory response. *Biomed Pharmacother*. 2019;118:1–10. doi:10.1016/j.biopha.2019.109249
101. Singh S, Patel RJ. Review article: phosphatidylcholine (PCL) Fortified Nano-Phytopharmaceuticals For Improvement Of Therapeutic Efficacy Dr. Dayaram Patel Pharmacy College, Bardoli-394601 Gujarat, India. *Res J Pharm Technol*. 2023;2(13):880–903. doi:10.17179/excli2023-6345

102. Alhakamy NA, Fahmy UA, Badr-Eldin SM, et al. Optimized icariin phytosomes exhibit enhanced cytotoxicity and apoptosis-inducing activities in ovarian cancer cells. *Pharmaceutics*. 2020;12(4):346. doi:10.3390/pharmaceutics12040346
103. Song Z, Yin J, Xiao P, et al. Improving breviscapine oral bioavailability by preparing nanosuspensions, liposomes and phospholipid complexes. *Pharmaceutics*. 2021;13(2):1–20. doi:10.3390/pharmaceutics13020132
104. Fathi F, Ebrahimi SN, Valadão AIG, et al. Exploring gunnera tinctoria: from nutritional and anti-tumoral properties to phytosome development following structural arrangement based on molecular docking. *Molecules*. 2021;26(19):5935. doi:10.3390/molecules26195935
105. Xu L, Xu D, Li Z, Gao Y, Chen H. Synthesis and potent cytotoxic activity of a novel diosgenin derivative and its phytosomes against lung cancer cells. *Beilstein J Nanotechnol*. 2019;10:1933–1942. doi:10.3762/bjnano.10.189
106. Ramakrishna W, Kumari A, Rahman N, Mandave P. Anticancer Activities of Plant Secondary Metabolites: rice Callus Suspension Culture as a New Paradigm. *Rice Sci*. 2021;28(1):13–30. doi:10.1016/j.rsci.2020.11.004
107. Singla C, Vishal. Phytosomes: system for Delivering Bioactive Plant Extracts and Phytoconstituents. *Int J Med Pharm Sci*. 2020;10(03):01–08. doi:10.31782/ijmps.2020.10301
108. Hegde MM, Lakshman K. Role of Polyphenols and Flavonoids as Anti-Cancer Drug Candidates: a Review. *Pharmacogn Res*. 2023;15 (2):206–216. doi:10.5530/pres.15.2.022
109. Biyani DM, Umekar M, Wakde I. Formulation And Evaluation Of Curcumin And Andrographolide Phytosomes For Their Potent Activities. *World J Pharm Res*. 2022;11(14):643–670. doi:10.20959/wjpr202214-25852
110. Padmakumari P, Mohan Manda R. Design, formulation, biopharmaceutical evaluation and in-vitro screening of boldine phytosomes for breast cancer therapy. *Mater Today Proc*. 2023. doi:10.1016/j.matpr.2023.08.123
111. Alshahrani SM. Optimization and Characterization of Cuscuta reflexa Extract Loaded Phytosomes by the Box-Behnken Design to Improve the Oral Bioavailability. *J Oleo Sci*. 2022;71(5):671–683. doi:10.5650/jos.ess21318
112. Djekic L, Krajišnik D. Rheological behavior study and its significance in the assessment of application properties and physical stability of phytosome loaded hydrogels. *Arh Farm*. 2021;71(2):120–140. doi:10.5937/arhfarm71-30708
113. Giacosa A, Riva A, Petrangolini G, et al. Beneficial Effects on Abdominal Bloating with an Innovative Food-Grade Formulation of Curcuma longa and Boswellia serrata Extracts in Subjects with Irritable Bowel Syndrome and Small Bowel Dysbiosis. *Nutrients*. 2022;14(3):416. doi:10.3390/nu14030416
114. Sasongko RE, Surini S, Saputri FC. Formulation and characterization of bitter melon extract (Momordica charantia) loaded phytosomes. *Pharmacogn J*. 2019;11(6):1235–1241. doi:10.5530/pj.2019.11.192
115. Han HS, Koo SY, Choi KY. Emerging nanoformulation strategies for phytocompounds and applications from drug delivery to phototherapy to imaging. *Bioact Mater*. 2022;14(December 2021):182–205. doi:10.1016/j.bioactmat.2021.11.027
116. Nandayasa WW, Febriyenti, Lucida HF. Optimization and Characterization of Quercetin Vitamin C Nano-Phytosome Formulation. *Int J Appl Pharm*. 2023;15(Special Issue 1):51–55. doi:10.22159/ijap.2023.v15s1.47507
117. Hatami A, Heydarinasab A, Akbarzadehkhiyavi A, Shariati FP. In vitro co-delivery evaluation of PEGylated nano-liposome loaded by glycyrrhizic acid and cisplatin on cancer cell lines. *J Nanopart Res*. 2020;22(9). doi:10.1007/s11051-020-04982-9
118. El-Fattah AI A, Fathy MM, Ali ZY, El-Garawany AERA, Mohamed EK. Enhanced therapeutic benefit of quercetin-loaded phytosome nanoparticles in ovariectomized rats. *Chem Biol Interact*. 2017;271:30–38. doi:10.1016/j.cbi.2017.04.026
119. Talaat SM, Elnaggar YSR, El-Ganainy SO, Gowayed MA, Allam M, Abdallah OY. Self-assembled fisetin-phospholipid complex: fisetin-integrated phytosomes for effective delivery to breast cancer. *Eur J Pharm Biopharm*. 2023;189(February):174–188. doi:10.1016/j.ejpb.2023.06.009
120. Kudatarkar N, Jalalpure S, Kurangi B. Formulation and Characterization of Chrysin Loaded Phytosomes and its Cytotoxic Effect against Colorectal Cancer Cells. *Ind J Pharm Educ Res*. 2022;56(3):S407–S412. doi:10.5530/ijper.56.3s.148
121. Govindaram LK, Bratty M, Alhazmi HA, et al. Formulation, biopharmaceutical evaluation and in-vitro screening of polyherbal phytosomes for breast cancer therapy. *Drug Dev Ind Pharm*. 2022;48(10):552–565. doi:10.1080/03639045.2022.2138911
122. Majnooni MB, Fakhri S, Ghanadian SM, et al. Inhibiting Angiogenesis by Anti-Cancer Saponins: from Phytochemistry to Cellular Signaling Pathways. *Metabolites*. 2023;13(3):323. doi:10.3390/metabo13030323
123. Kim BG, Jang W, Lim JH, Wang DH. Physical engineering of anti-solvents in perovskite precipitation for enhanced photosensitive affinity. *Int J Energy Res*. 2022;46(7):9748–9760. doi:10.1002/er.7843
124. Jabłonowska E, Matyszewska D, Nazaruk E, Godlewska M, Gaweł D, Bilewicz R. Lipid membranes exposed to dispersions of phytantriol and monoolein cubosomes: Langmuir monolayer and HeLa cell membrane studies. *Biochim Biophys Acta Gen Subj*. 2021;1865(1):129738. doi:10.1016/j.bbagen.2020.129738
125. Shriram RG, Moin A, Alotaibi HF, et al. Phytosomes as a Plausible Nano-Delivery System for Enhanced Oral Bioavailability and Improved Hepatoprotective Activity of Silymarin. *Pharmaceuticals*. 2022;15(7):790. doi:10.3390/ph15070790
126. Rajabi H, Jafari SM, Rajabzadeh G, Sarfarazi M, Sedaghati S. Chitosan-gum Arabic complex nanocarriers for encapsulation of saffron bioactive components. *Colloids Surf a Physicochem Eng Aspects*. 2019;578:123644. doi:10.1016/j.colsurfa.2019.123644
127. Solangi NH, Karri RR, Mubarak NM, Mazari SA. Mechanism of polymer composite-based nanomaterial for biomedical applications. *Adv Ind Eng Polym Res*. 2024;7(1):1–19. doi:10.1016/j.aiepr.2023.09.002
128. Allaw M, Manca ML, Castangia I, Manconi M. Journal of Drug Delivery Science and Technology From plants to phospholipid vesicles: a comprehensive review on the incorporation of phytochemicals into phospholipid vesicles designed for skin applications with special focus on scalability and in vitro and in vivo efficacy. *JDDST*. 2022;67(October 2021):103049. doi:10.1016/j.jddst.2021.103049