

Available online on 15.10.2026 at <http://ajprd.com>

Asian Journal of Pharmaceutical Research and Development

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Review Article

Phytometabolites and Targeted Cancer Nanotherapy: Formulation, Therapeutic Applications and Future Aspects

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ABSTRACT

Cancer remains a major global health challenge, with therapeutic failure frequently associated with tumor heterogeneity, drug resistance, systemic toxicity, poor bioavailability, and inadequate drug accumulation at tumor sites. Phytometabolites, including polyphenols, flavonoids, alkaloids, terpenoids, lignans, stilbenes, and other bioactive plant-derived compounds, have emerged as promising candidates for cancer prevention and therapy because of their diverse molecular activities against multiple hallmarks of cancer. However, their clinical translation is often restricted by poor aqueous solubility, chemical instability, rapid metabolism, limited absorption, short systemic circulation, and nonspecific tissue distribution. Targeted nanotherapy offers an advanced strategy to overcome these limitations by improving the physicochemical properties, pharmacokinetic behavior, tumor accumulation, and therapeutic efficacy of phytometabolites. This review provides a comprehensive overview of recent advances in the formulation and targeted delivery of phytometabolite-based nanotherapeutics for cancer management. Different nanocarrier platforms, including polymeric nanoparticles, lipid-based nanoparticles, liposomes, nanostructured lipid carriers, solid lipid nanoparticles, phytosomes, nanoemulsions, dendrimers, metallic nanoparticles, and stimuli-responsive systems, are discussed with emphasis on formulation approaches, physicochemical characterization, drug loading, controlled release, stability, and scalability. Particular attention is given to active and passive tumor-targeting strategies involving receptors, antibodies, peptides, ligands, and tumor-responsive stimuli to enhance selective delivery and minimize off-target toxicity. The therapeutic potential of phytometabolite nanocarriers is further examined across major cancer types, with emphasis on mechanisms involving apoptosis, oxidative stress modulation, cell-cycle regulation, angiogenesis inhibition, metastasis suppression, autophagy, inflammation, and multidrug-resistance pathways. The review also highlights current challenges related to formulation reproducibility, nanotoxicity, pharmacokinetics, tumor heterogeneity, manufacturing, regulatory requirements, and clinical translation. Finally, emerging approaches integrating precision nanomedicine, biomarker-guided targeting, multifunctional nanoplatforms, combination therapy, and artificial intelligence-assisted formulation design are discussed as future directions for developing clinically translatable phytometabolite-based targeted cancer nanotherapies.

Keywords: Phytometabolites; Cancer Nanotherapy; Targeted Drug Delivery; Nanoformulations; Precision Oncology.

ARTICLE INFO: Received 19 May 2026; Review Complete 15 July 2026; Accepted 21 Sept. 2026; Available online 15 Oct. 2026



Cite this article as:

Jain N, Chakraborty H, Das S, Dey D, Sharma S, Chaurasia M, Phytometabolites and Targeted Cancer Nanotherapy: Formulation, Therapeutic Applications and Future Aspects, Asian Journal of Pharmaceutical Research and Development. 2026; 14(5): 108-118
DOI: <http://dx.doi.org/10.22270/ajprd.v14i5.1876>

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INTRODUCTION

Cancer is a major global health challenge characterized by uncontrolled cell proliferation, invasion, metastasis, and complex molecular alterations. Despite advances in chemotherapy, radiotherapy, immunotherapy, and targeted treatments, therapeutic outcomes are often limited by systemic toxicity, poor drug bioavailability, tumor heterogeneity, and acquired drug resistance.

Phytometabolites have gained considerable attention as promising anticancer agents because of their diverse biological activities and ability to modulate multiple cancer-associated pathways¹⁻². However, poor solubility, instability, rapid metabolism, and limited bioavailability restrict their therapeutic application. Nanotechnology-based delivery systems offer an effective approach to overcome these limitations by enhancing phytometabolite stability, tumor accumulation, cellular uptake, and controlled release. Thus, the integration of

phytometabolites with targeted nanocarriers represents a promising strategy for developing more effective and selective cancer therapies³.

Global burden and therapeutic challenges of cancer

Cancer represents one of the most significant global health challenges and remains a leading cause of morbidity and mortality worldwide. The disease encompasses a diverse group of malignancies characterized by uncontrolled cellular proliferation, genomic instability, resistance to apoptosis, abnormal angiogenesis, invasion, and metastatic dissemination. Despite substantial advances in cancer biology, molecular diagnostics, surgery, radiotherapy, chemotherapy, immunotherapy, hormonal therapy, and targeted treatments, effective cancer management remains challenging⁴. Tumor heterogeneity, genetic and epigenetic alterations, differences in the tumor microenvironment, acquired drug resistance, and disease recurrence contribute considerably to therapeutic failure. In addition, the biological behavior of individual tumors can vary substantially between patients, making a uniform treatment approach inadequate for many malignancies. Metastatic disease further complicates treatment because disseminated tumor cells may establish secondary lesions in anatomically distinct organs and acquire resistance to previously effective therapies. The tumor microenvironment, comprising cancer-associated fibroblasts, immune cells, extracellular matrix components, abnormal vasculature, and signaling molecules, can additionally restrict therapeutic penetration and promote tumor progression. Consequently, there is an increasing need for therapeutic approaches capable of selectively recognizing tumor cells, improving intracellular drug delivery, overcoming biological barriers, and minimizing systemic toxicity. The development of precision-oriented therapeutic strategies that integrate molecular targeting with efficient drug-delivery technologies has therefore become an important direction in contemporary cancer research⁴⁻⁵.

Limitations of conventional anticancer therapy

Conventional cancer treatment primarily involves surgery, chemotherapy, radiotherapy, hormonal therapy, immunotherapy, and molecularly targeted agents, either individually or in combination. Although these approaches have significantly improved survival in several malignancies, their therapeutic benefits are frequently accompanied by important limitations. Cytotoxic chemotherapeutic agents generally lack complete selectivity for malignant cells and may affect normal rapidly dividing tissues, resulting in adverse effects such as myelosuppression, gastrointestinal disturbances, mucosal injury, alopecia, and immunosuppression⁶. Many anticancer drugs also exhibit poor aqueous solubility, chemical instability, rapid metabolism, short circulation half-life, and unfavorable pharmacokinetic properties, which can reduce their therapeutic exposure. Furthermore, nonspecific biodistribution may increase drug accumulation in healthy organs and contribute to systemic toxicity. Multidrug resistance represents another major obstacle and may arise through enhanced drug efflux, alteration of therapeutic targets, increased DNA repair, inhibition of apoptosis, and activation of alternative

survival pathways. Even molecularly targeted therapies may eventually lose efficacy because of mutations, heterogeneous target expression, compensatory signaling, and adaptive resistance. Consequently, improving drug selectivity and delivery while maintaining adequate therapeutic concentrations at the tumor site remains an important objective in cancer research. These limitations have stimulated increasing interest in naturally derived bioactive molecules and advanced delivery technologies capable of improving therapeutic efficacy and reducing unwanted systemic effects⁷⁻⁸.

Phytometabolites as promising anticancer agents

Phytometabolites are naturally occurring bioactive compounds produced by plants and represent an important source of structurally diverse molecules with considerable therapeutic potential. Major classes include polyphenols, flavonoids, alkaloids, terpenoids, stilbenes, lignans, saponins, tannins, and other specialized metabolites. Several phytometabolites, including curcumin, resveratrol, quercetin, epigallocatechin gallate, berberine, luteolin, genistein, and sulforaphane, have demonstrated promising anticancer activities in preclinical investigations. Unlike many conventional agents that primarily act through specific molecular targets, phytometabolites can influence multiple interconnected cellular and molecular processes involved in cancer initiation and progression⁹. Their reported mechanisms include induction of apoptosis, regulation of cell-cycle progression, inhibition of tumor-cell proliferation, suppression of angiogenesis and metastasis, modulation of oxidative stress and inflammation, regulation of autophagy, and interference with major oncogenic signaling pathways such as PI3K/Akt/mTOR, MAPK, NF- κ B, STAT3, and Wnt/ β -catenin. Their multitarget activity may provide opportunities for addressing the complex biology of cancer and potentially enhancing the effectiveness of conventional anticancer agents. However, despite their promising pharmacological profiles, many phytometabolites exhibit poor aqueous solubility, chemical instability, low gastrointestinal absorption, rapid biotransformation, extensive first-pass metabolism, and limited systemic bioavailability. These pharmaceutical limitations can result in inadequate concentrations at the tumor site and restrict their translation from experimental research to clinical applications.

Rationale for nanotechnology-assisted delivery

Nanotechnology-assisted drug delivery has emerged as a promising strategy for overcoming the pharmaceutical and biological limitations associated with phytometabolites. Nanocarriers can improve the aqueous solubility, chemical stability, bioavailability, circulation time, and controlled release of poorly soluble or unstable phytometabolites¹⁰⁻¹¹. Various nanosystems, including polymeric nanoparticles, liposomes, lipid-based nanoparticles, solid lipid nanoparticles, nanostructured lipid carriers, polymeric micelles, nanoemulsions, phytosomes, dendrimers, metallic nanoparticles, and hybrid nanocarriers, have been explored for the delivery of plant-derived anticancer compounds. Their nanoscale dimensions and modifiable surface characteristics can facilitate improved interaction with tumor tissues and enhance cellular internalization.

Nanocarriers can support passive tumor targeting through preferential accumulation in tumor tissues and can also be engineered for active targeting using antibodies, peptides, aptamers, carbohydrates, or receptor-specific ligands. In addition, stimuli-responsive nanocarriers can be designed to release phytometabolites in response to tumor-associated conditions such as acidic pH, elevated reactive oxygen species, specific enzymes, hypoxia, or altered redox status¹². Such approaches may improve spatial and temporal control of drug release while reducing exposure to healthy tissues. Multifunctional nanoplateforms can further combine phytometabolites with conventional anticancer drugs, targeting ligands, imaging agents, or immunomodulatory components, providing opportunities for combination therapy and theranostic applications. Therefore, integrating phytometabolites with targeted nanotechnology offers a promising approach to enhance their pharmacokinetic properties, tumor-specific delivery, therapeutic efficacy, and safety. This emerging field provides a strong foundation for developing next-generation phytometabolite-based cancer nanotherapies with improved precision and translational potential¹³⁻¹⁴.

This review provides a comprehensive overview of phytometabolites and their integration with targeted nanotechnology for cancer management. It discusses major classes of phytometabolites, their anticancer mechanisms, and key limitations such as poor solubility, instability, rapid metabolism, and low bioavailability. The article further examines different nanocarrier platforms, including polymeric nanoparticles, liposomes, lipid-based nanoparticles, solid lipid nanoparticles, nanostructured lipid carriers, phytosomes, nanoemulsions, dendrimers, and hybrid systems, with emphasis on formulation, characterization, controlled release, and targeted delivery. Passive and active targeting approaches, receptor-mediated delivery, and stimuli-responsive systems are also discussed. The review highlights the potential of these nanotherapeutic systems across different cancer types and

explores their molecular mechanisms, translational challenges, safety, scalability, regulatory considerations, and future prospects, including precision nanomedicine, biomarker-guided targeting, multifunctional nanoplateforms, combination therapy, and AI-assisted formulation development.

PHYTOMETABOLITES AS EMERGING ANTICANCER THERAPEUTICS

Phytometabolites are diverse plant-derived bioactive compounds with significant potential for cancer prevention and therapy. Major classes include polyphenols and flavonoids, alkaloids, terpenoids and terpenes, lignans, stilbenes, saponins, and other specialized metabolites. Compounds such as curcumin, quercetin, epigallocatechin gallate, berberine, resveratrol, paclitaxel, artemisinin, ginsenosides, and podophyllotoxin have demonstrated promising anticancer activities through diverse molecular mechanisms¹⁵. These phytometabolites can inhibit tumor-cell proliferation, induce apoptosis and cell-cycle arrest, suppress angiogenesis and metastasis, regulate oxidative stress and inflammation, and modulate autophagy and multidrug resistance. Their effects are associated with regulation of important signaling pathways and molecular targets, including PI3K/Akt/mTOR, MAPK, NF-κB, JAK/STAT, Wnt/β-catenin, Nrf2, and p53. The multitarget nature of these compounds provides opportunities for addressing the complex and heterogeneous biology of cancer and for combining phytometabolites with conventional anticancer agents. However, their therapeutic translation is frequently limited by poor aqueous solubility, chemical instability, rapid metabolism, low absorption, and limited systemic bioavailability¹⁶⁻¹⁷. Consequently, integrating phytometabolites with advanced nanocarriers may improve their stability, pharmacokinetic properties, tumor accumulation, cellular uptake, and therapeutic efficacy, supporting their development as targeted cancer nanotherapeutics (Table 1).

Table 1: Major Phytometabolite Classes, Representative Compounds, Molecular Targets, and Anticancer Activities

Phytometabolite class	Representative compounds	Major molecular targets/pathways	Principal anticancer activities	Relevance to nanotherapy	Ref.
Polyphenols	Curcumin, EGCG, chlorogenic acid	NF-κB, PI3K/Akt/mTOR, MAPK, STAT3, Nrf2	Apoptosis, anti-inflammatory, anti-proliferative, anti-angiogenic effects	Improves solubility, stability, bioavailability, and tumor accumulation	[18]
Flavonoids	Quercetin, luteolin, apigenin, kaempferol	PI3K/Akt, MAPK, Wnt/β-catenin, NF-κB	Cell-cycle arrest, apoptosis, oxidative-stress modulation, inhibition of metastasis	Enhances cellular uptake and controlled tumor delivery	
Alkaloids	Berberine, camptothecin, vincristine, vinblastine	Topoisomerases, tubulin, AMPK, PI3K/Akt	Cytotoxicity, apoptosis, cell-cycle arrest, inhibition of proliferation	Enables controlled release and may reduce systemic toxicity	[19]
Terpenoids and terpenes	Paclitaxel, artemisinin, ursolic acid, limonene	Tubulin, PI3K/Akt, MAPK, NF-κB	Apoptosis, anti-angiogenesis, anti-metastatic and anti-inflammatory effects	Improves aqueous dispersibility, pharmacokinetics, and tumor targeting	
Lignans	Podophyllotoxin, matairesinol	Tubulin, cell-cycle regulators, apoptotic pathways	Mitotic arrest, apoptosis, anti-proliferative activity	Facilitates targeted delivery and reduces nonspecific exposure	[20]
Stilbenes	Resveratrol, pterostilbene	SIRT1, NF-κB, PI3K/Akt, STAT3	Apoptosis, anti-inflammatory, anti-metastatic and anti-angiogenic effects	Enhances stability, bioavailability, and sustained release	[21]

Saponins	Ginsenosides, diosgenin, glycyrrhizin	PI3K/Akt, MAPK, NF-κB, caspases	Apoptosis, cell-cycle regulation, immune modulation, inhibition of invasion	Supports improved delivery and synergistic combination therapy
Other phytochemicals	Sulforaphane, coumarins, quinones, organosulfur compounds	Nrf2, NF-κB, STAT3, p53 and related pathways	Antioxidant, pro-apoptotic, anti-inflammatory, anti-metastatic effects	Provides opportunities for multifunctional and stimuli-responsive nanocarriers

Phytochemicals offer substantial anticancer potential through their multitarget and multifunctional mechanisms. However, their poor physicochemical and pharmacokinetic properties remain major barriers to clinical translation. Therefore, integrating these bioactive compounds with advanced nanocarriers and targeted delivery systems may enhance their stability, bioavailability, tumor-specific accumulation, and therapeutic efficacy, supporting the development of next-generation cancer nanotherapies²².

THERAPEUTIC LIMITATIONS AND NEED FOR NANOFORMULATION OF PHYTOCHEMICALS

Despite their promising anticancer activities, the therapeutic application of phytochemicals is often constrained by several physicochemical, pharmacokinetic, and biological limitations. Many phytochemicals exhibit poor aqueous solubility, chemical instability, low bioavailability, rapid metabolism, short circulation half-life, and nonspecific tissue distribution, which can substantially reduce their effective concentration at tumor sites. Furthermore, the complex tumor microenvironment, abnormal vasculature, dense extracellular matrix, and limited cellular uptake can restrict tumor penetration and intracellular delivery²³. These limitations may create a significant gap between the potent anticancer effects observed in experimental studies and their clinical translation. Nanoformulation provides a promising approach to overcome these barriers by improving solubility, stability, bioavailability, pharmacokinetic behavior, tumor accumulation, cellular internalization, and controlled release. Thus, the development of phytochemical-loaded nanocarriers represents an important strategy for enhancing their therapeutic efficacy and improving their potential for targeted cancer treatment.

Poor aqueous solubility and dissolution

Many phytochemicals exhibit poor aqueous solubility due to their hydrophobic or crystalline nature, resulting in slow dissolution and inadequate gastrointestinal absorption. Limited dissolution can substantially reduce the amount of compound available for systemic circulation and consequently decrease therapeutic efficacy. Nanoformulation can improve apparent solubility and dissolution by reducing particle size, increasing surface area, and incorporating phytochemicals into suitable lipidic or polymeric carriers²⁴⁻²⁵.

Chemical and biological instability

Several phytochemicals are chemically or biologically unstable and may undergo degradation because of exposure to light, oxygen, temperature, pH variations, enzymes, or physiological conditions. Such instability can reduce their active concentration during storage, gastrointestinal transit, and systemic circulation. Encapsulation within nanocarriers can provide a protective

environment that improves stability and preserves the biological activity of these compounds.

Low bioavailability and rapid metabolism

Low oral bioavailability is a major limitation for many phytochemicals and is often associated with poor absorption, extensive first-pass metabolism, and rapid biotransformation. Consequently, only a small fraction of the administered dose may reach systemic circulation and target tissues. Nanoformulations can enhance gastrointestinal absorption, protect phytochemicals from premature degradation, and facilitate sustained or controlled release, thereby improving systemic bioavailability²⁶⁻²⁷.

Pharmacokinetic limitations

Phytochemicals may exhibit short plasma half-lives, rapid elimination, variable absorption, and inadequate systemic exposure, resulting in inconsistent pharmacological effects. Their unfavorable pharmacokinetic profiles may require frequent or higher dosing, potentially increasing toxicity. Nanocarriers can modify drug disposition by prolonging circulation time, controlling release, reducing premature elimination, and improving exposure to the desired therapeutic site.

Nonspecific distribution and systemic toxicity

Following conventional administration, phytochemicals may undergo nonspecific distribution throughout the body, limiting their accumulation at tumor sites and potentially increasing exposure to healthy tissues. Although many phytochemicals are considered biologically promising, dose-dependent toxicity and off-target effects may still restrict their therapeutic window. Targeted nanocarriers can improve tissue selectivity through surface functionalization with antibodies, peptides, aptamers, or receptor-specific ligands, potentially reducing nonspecific exposure and systemic toxicity²⁸.

Barriers to tumor penetration and intracellular delivery

The abnormal tumor vasculature, dense extracellular matrix, elevated interstitial fluid pressure, and heterogeneous blood flow can substantially restrict drug penetration into solid tumors. Even after reaching the tumor, limited cellular uptake and inefficient intracellular release may reduce therapeutic activity. Nanocarriers can improve tumor accumulation, facilitate cellular internalization, and provide controlled intracellular release of phytochemicals. Surface modification and stimuli-responsive systems can further enhance tumor-specific and intracellular delivery²⁹.

Nanocarrier Platforms For Phytochemical Delivery

Nanocarrier-based delivery systems have emerged as important platforms for improving the therapeutic performance of phytometabolites with poor solubility, stability, bioavailability, and tumor selectivity. Different nanocarriers provide distinct advantages in terms of encapsulation capacity, protection of the active compound, controlled release, cellular uptake, and tumor targeting. Polymeric nanoparticles can provide sustained and controlled release, whereas liposomes and lipid-based nanoparticles offer high biocompatibility and efficient incorporation of hydrophobic and hydrophilic phytometabolites. Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) improve solubility and protect phytometabolites from degradation³⁰. Phytosomes and nanoemulsions are particularly useful for enhancing the absorption and

bioavailability of poorly water-soluble plant compounds. Dendrimers and polymeric micelles provide high surface functionality and nanoscale drug-loading environments, facilitating targeted delivery and cellular internalization. Metallic and inorganic nanoparticles can additionally provide imaging, photothermal, catalytic, or therapeutic functionalities. More recently, hybrid and multifunctional nanocarriers have been developed by integrating two or more delivery technologies to achieve enhanced drug loading, targeting, controlled release, and combination therapy. Selection of an appropriate platform depends on the physicochemical characteristics of the phytometabolite, intended route of administration, tumor type, targeting strategy, and desired therapeutic outcome (**Table 2**).

Table 2: Nanocarrier Platforms for Phytometabolite Delivery and Their Therapeutic Advantages

Nanocarrier platform	Key characteristics	Advantages for phytometabolite delivery	Potential anticancer applications	Ref
Polymeric nanoparticles	Biodegradable polymers such as PLGA, PLA, chitosan, and PEG-based systems	Controlled release, improved stability, protection from degradation, enhanced cellular uptake	Sustained delivery of curcumin, resveratrol, quercetin and other phytometabolites	[31]
Liposomes	Phospholipid bilayer surrounding an aqueous core	Encapsulation of hydrophilic and hydrophobic compounds, biocompatibility, reduced toxicity	Tumor-targeted delivery and improved intracellular accumulation	[32]
Lipid-based nanoparticles	Lipid matrix with surface-modifiable characteristics	Enhanced solubility, bioavailability, protection from metabolism, controlled release	Delivery of poorly soluble phytometabolites to solid tumors	[33]
Solid lipid nanoparticles (SLNs)	Solid lipid matrix stabilized by surfactants	Improved stability, sustained release, enhanced bioavailability	Prolonged delivery of hydrophobic anticancer phytometabolites	[34]
Nanostructured lipid carriers (NLCs)	Mixture of solid and liquid lipids	Higher drug-loading capacity and reduced drug expulsion compared with SLNs	Improved delivery and sustained release of phytometabolites	[35]
Phytosomes	Phospholipid–phytoconstituent complexes	Enhanced membrane affinity, absorption, bioavailability, and stability	Delivery of polyphenols and flavonoids with poor systemic availability	[36]
Nanoemulsions	Nanosized oil-in-water or water-in-oil dispersions	Improved solubilization, absorption, and dispersion of lipophilic compounds	Oral, topical, or systemic delivery of hydrophobic phytometabolites	[37]
Dendrimers	Highly branched, functionalized polymeric structures	High surface functionality, molecular encapsulation, and targeted delivery	Enhanced cellular uptake and controlled delivery	
Polymeric micelles	Amphiphilic polymers forming hydrophobic cores	Solubilization of poorly water-soluble phytometabolites and prolonged circulation	Systemic and tumor-targeted delivery	
Metallic/inorganic nanoparticles	Gold, silver, iron oxide, silica, and other inorganic cores	Imaging, photothermal activity, surface functionalization, and drug delivery	Combined phytometabolite delivery with imaging or photothermal therapy	[38]
Hybrid nanocarriers	Combination of lipidic, polymeric, inorganic, or other components	Combines advantages of multiple platforms, improved stability and loading	Multifunctional and combination cancer therapy	
Multifunctional nanocarriers	Incorporate drug, targeting ligand, imaging agent, or stimuli-responsive components	Targeted delivery, controlled release, imaging, and synergistic therapy	Precision nanotherapy and theranostic applications	

Formulation Strategies and Characterization Of Phytometabolite Nanotherapeutics

The successful development of phytometabolite-loaded nanotherapeutics requires careful selection of formulation methods and systematic physicochemical, pharmaceutical, and biological characterization. Formulation techniques determine particle size, morphology, encapsulation

efficiency, drug loading, stability, release behavior, and ultimately the therapeutic performance of the nanocarrier. Common approaches include nanoprecipitation, solvent evaporation, thin-film hydration, emulsification, high-pressure homogenization, and ultrasonication³⁹. Characterization is subsequently performed to establish critical quality attributes such as particle size,

polydispersity index (PDI), zeta potential, morphology, encapsulation efficiency, and drug loading. In-vitro release, stability, pharmacokinetic, and biodistribution studies provide further information regarding the behavior of the formulation under physiological conditions. For successful translation, formulation development should also incorporate reproducibility, scalability, process optimization, and Quality-by-Design (QbD) principles⁴⁰.

Nanoprecipitation and solvent evaporation

Nanoprecipitation is a simple and widely used technique for preparing phytometabolite-loaded polymeric nanoparticles, particularly for poorly water-soluble compounds. In this approach, the phytometabolite and polymer are dissolved in a suitable organic solvent and introduced into an aqueous phase containing a stabilizer, resulting in rapid solvent diffusion and nanoparticle formation. Particle characteristics can be controlled by adjusting polymer concentration, solvent-to-water ratio, surfactant concentration, and mixing conditions. Solvent evaporation involves dissolving the phytometabolite and carrier material in a volatile organic solvent, followed by emulsification with an aqueous phase and subsequent removal of the solvent⁴¹. This method facilitates efficient encapsulation and controlled release of phytometabolites; however, residual solvent, thermal or chemical degradation, and scale-up requirements should be carefully considered.

Thin-film hydration and emulsification techniques

Thin-film hydration is commonly employed for the preparation of phytometabolite-loaded liposomes and other lipid-based nanocarriers. In this method, phospholipids and the phytometabolite are dissolved in an organic solvent, which is removed to form a thin lipid film, followed by hydration with an aqueous medium to generate nanosized vesicles. Subsequent sonication or extrusion can further reduce particle size and improve uniformity⁴². Emulsification techniques involve combining oil and aqueous phases containing the phytometabolite and suitable stabilizers to produce nanosized droplets. These approaches are particularly useful for poorly water-soluble phytometabolites because they enhance solubilization, dispersion, absorption, and protection against degradation.

High-pressure homogenization and ultrasonication

High-pressure homogenization is an effective technique for producing lipid nanoparticles, nanoemulsions, and other nanosized systems through intense shear forces, turbulence, and cavitation. The process can provide relatively uniform particle sizes and is advantageous for scale-up. However, excessive pressure and repeated homogenization cycles may generate heat and potentially affect thermolabile phytometabolites. Ultrasonication uses acoustic cavitation to disrupt larger particles, droplets, or aggregates and produce nanosized formulations⁴³⁻⁴⁴. It is frequently applied to liposomes, nanoemulsions, polymeric nanoparticles, and lipid-based systems. Sonication time, intensity, pulse duration, and temperature must be optimized to achieve the desired particle characteristics while minimizing heat-induced degradation and structural instability.

Encapsulation efficiency and drug loading

Encapsulation efficiency and drug loading are important parameters for evaluating the incorporation of phytometabolites into nanocarriers. Encapsulation efficiency represents the percentage of the initially added phytometabolite successfully entrapped within the nanocarrier, whereas drug loading indicates the amount of phytometabolite incorporated relative to the total mass of the nanoparticle formulation. High encapsulation efficiency and drug loading are desirable because they increase the therapeutic payload and reduce the amount of carrier required for effective delivery. These parameters are influenced by phytometabolite solubility, carrier composition, drug-to-carrier ratio, preparation method, and interactions between the phytometabolite and carrier matrix⁴⁵⁻⁴⁶.

Particle size, PDI, zeta potential, and morphology

Particle size, polydispersity index (PDI), zeta potential, and morphology are critical characteristics governing the stability and biological performance of phytometabolite nanotherapeutics. Particle size influences cellular uptake, biodistribution, tissue penetration, and tumor accumulation, while PDI provides information regarding the uniformity of particle-size distribution. Zeta potential reflects the surface charge of nanoparticles and contributes to colloidal stability, protein adsorption, cellular interactions, and biological distribution⁴⁷. Morphological characteristics can be evaluated using transmission electron microscopy, scanning electron microscopy, atomic force microscopy, or related imaging techniques to determine particle shape, surface structure, aggregation, and nanoscale architecture. These parameters collectively provide important information regarding formulation quality and biological behavior.

In-vitro drug release, stability, and pharmacokinetic evaluation

In-vitro drug-release studies are performed to determine the release profile and kinetics of phytometabolites from nanocarriers under physiological or tumor-relevant conditions. Depending on the formulation, nanoparticles may provide immediate, sustained, delayed, or stimuli-responsive release. Stability studies evaluate changes in particle size, PDI, zeta potential, morphology, drug content, and encapsulation efficiency during storage under different environmental conditions. Pharmacokinetic evaluation further determines parameters such as maximum plasma concentration, time to maximum concentration, area under the curve, half-life, clearance, and volume of distribution⁴⁸. Comparison with free phytometabolites can demonstrate whether nanoformulation improves systemic exposure, prolongs circulation, enhances bioavailability, and modifies tissue distribution.

Scale-up, reproducibility, and quality-by-design considerations

Successful translation of phytometabolite nanotherapeutics requires scalable manufacturing processes, batch-to-batch reproducibility, process robustness, and consistent product quality. Formulation variables such as polymer or lipid

concentration, surfactant level, mixing rate, temperature, pressure, processing time, and solvent-removal conditions should be systematically optimized. Quality-by-Design (QbD) provides a structured framework for identifying critical material attributes, critical process parameters, and critical quality attributes that influence the performance of the final nanotherapeutic⁴⁹⁻⁵⁰. Design of Experiments (DoE) can facilitate systematic optimization and reduce formulation variability. Incorporating QbD principles during development can improve reproducibility, stability, manufacturing consistency, scalability, and regulatory acceptability, thereby supporting the translation of phytometabolite nanotherapeutics from laboratory research to clinical applications.

TARGETED AND STIMULI-RESPONSIVE CANCER NANOTHERAPY

Targeted and stimuli-responsive nanotherapy provides an advanced approach for improving the selective delivery of phytometabolites to tumor tissues while minimizing off-target exposure. Passive targeting through the enhanced permeability and retention (EPR) effect, active targeting using antibodies, peptides, aptamers, and ligands, and receptor-mediated uptake can enhance tumor accumulation and cellular internalization⁵¹. Furthermore, tumor microenvironment-responsive and stimuli-sensitive systems can exploit variations in pH, enzymes, redox conditions, hypoxia, and reactive oxygen species (ROS) to achieve controlled drug release. Advanced organelle-specific strategies can further enhance intracellular delivery and improve the therapeutic activity of phytometabolites against cancer cells.

Passive tumor targeting and enhanced permeability and retention

Passive tumor targeting is based primarily on the abnormal vascular architecture and impaired lymphatic drainage characteristic of many solid tumors, collectively described by the enhanced permeability and retention (EPR) effect. Nanocarriers can extravasate through relatively permeable tumor blood vessels and accumulate within tumor tissue because of inadequate lymphatic clearance. Particle size, surface characteristics, circulation time, and tumor vascularization strongly influence the extent of passive accumulation⁵²⁻⁵³. Phytometabolite-loaded nanoparticles can therefore increase local drug concentration while reducing exposure to healthy tissues. However, the EPR effect is highly heterogeneous among tumor types and patients and may be influenced by vascular density, stromal composition, interstitial pressure, and tumor progression, limiting its effectiveness as a standalone targeting strategy.

Active targeting using antibodies, peptides, aptamers, and ligands

Active targeting involves functionalizing the surface of nanocarriers with specific recognition molecules, including antibodies, peptides, aptamers, carbohydrates, or small-molecule ligands, to promote preferential interaction with receptors or biomarkers overexpressed on cancer cells. Following accumulation within the tumor, these targeting moieties facilitate selective binding and receptor-mediated internalization of phytometabolite-loaded nanoparticles.

Antibodies can provide high molecular specificity, whereas peptides and aptamers offer advantages related to size, stability, and ease of surface modification⁵⁴. Ligands such as folate, transferrin, hyaluronic acid, and other receptor-binding molecules have also been explored for targeted phytometabolite delivery. Active targeting can enhance cellular uptake and intracellular drug concentration while potentially reducing nonspecific toxicity.

Receptor-mediated targeting

Receptor-mediated targeting exploits the increased expression of specific membrane receptors on tumor cells compared with normal tissues. Nanocarriers can be functionalized with ligands or antibodies directed toward receptors such as folate receptors, transferrin receptors, epidermal growth factor receptors, integrins, CD44, and other tumor-associated receptors. Binding of the targeted nanocarrier to these receptors can initiate receptor-mediated endocytosis, facilitating intracellular accumulation of the phytometabolite. This approach can improve cellular selectivity, enhance therapeutic efficacy, and promote delivery to tumors that exhibit high receptor expression. However, receptor heterogeneity within tumors and variable expression between patients can influence targeting efficiency and emphasize the importance of biomarker-guided approaches⁵⁵⁻⁵⁶.

Tumor microenvironment-responsive nanocarriers

The tumor microenvironment (TME) possesses distinctive characteristics, including acidic extracellular pH, elevated reactive oxygen species, hypoxia, abnormal enzyme activity, altered redox conditions, dense extracellular matrix, and immunosuppressive signaling. These features can be exploited to develop responsive nanocarriers capable of preferentially releasing phytometabolites within tumor tissues. TME-responsive systems can remain relatively stable during circulation while undergoing structural or chemical changes after reaching the tumor environment. This approach enables spatially controlled drug release and may improve tumor selectivity while reducing premature release and systemic toxicity⁵⁷.

pH, Enzyme-, Redox-, Hypoxia-, and ROS-Responsive Systems

Stimuli-responsive nanocarriers are designed to release phytometabolites in response to specific physicochemical conditions associated with tumors. pH-responsive systems exploit the acidic tumor microenvironment or intracellular endosomal conditions to trigger drug release through protonation, ionization, or pH-sensitive bond cleavage. Enzyme-responsive systems utilize tumor-associated enzymes, such as matrix metalloproteinases, to degrade protective components and facilitate drug release. Redox-responsive nanocarriers respond to differences in reducing conditions, particularly the high intracellular glutathione concentration, whereas ROS-responsive systems utilize elevated reactive oxygen species to induce carrier degradation or drug release⁵⁸⁻⁵⁹. Hypoxia-responsive systems are designed to respond to the low-oxygen environment characteristic of many solid tumors. These approaches can provide controlled and site-specific phytometabolite release.

Therapeutic Applications and Molecular Mechanisms In Cancer

Phytometabolite-based nanotherapeutics have demonstrated promising therapeutic potential against a broad range of malignancies, including breast, lung, colorectal, hepatic, pancreatic, and prostate cancers, as well as brain tumors and other difficult-to-treat cancers. Nanoformulation enhances the solubility, stability, bioavailability, tumor accumulation, and intracellular delivery of phytometabolites, thereby improving their anticancer activity. At the molecular level, these nanotherapeutics can induce apoptosis and cell-cycle arrest through modulation of caspases, Bcl-2/Bax, p53, cyclins, and cyclin-dependent kinases, while also regulating oxidative stress and inflammatory responses through pathways such as Nrf2, NF- κ B, STAT3, and MAPK.

Phytometabolite nanocarriers can further exert anti-angiogenic and anti-metastatic effects by suppressing VEGF, HIF-1 α , matrix metalloproteinases, epithelial-mesenchymal transition, and tumor-cell migration. In addition, modulation of autophagy and major tumor-associated signaling pathways, including PI3K/Akt/mTOR, Wnt/ β -catenin, MAPK, and AMPK, can interfere with cancer-cell survival, proliferation, and metabolic adaptation⁶⁰⁻⁶¹. These systems may also help **overcome** multidrug resistance by enhancing intracellular drug accumulation, modulating drug-efflux mechanisms, and restoring sensitivity to anticancer therapy. Furthermore, combining phytometabolites with conventional anticancer agents can provide synergistic or complementary effects, enhance therapeutic efficacy, suppress resistance, and potentially reduce the required dose and associated systemic toxicity of conventional drugs (**Table 3**).

Table 3: Therapeutic Applications and Molecular Mechanisms of Phytometabolite Nanotherapeutics in Cancer

Therapeutic application / mechanism	Major molecular mechanisms or targets	Potential therapeutic effects of phytometabolite nanocarriers	Ref
Breast, lung, colorectal, hepatic, pancreatic, and prostate cancers	PI3K/Akt/mTOR, MAPK, NF- κ B, STAT3, Wnt/ β -catenin, p53	Enhanced tumor accumulation, inhibition of proliferation, induction of apoptosis, suppression of invasion and metastasis	[62]
Brain and other difficult-to-treat cancers	BBB transport, receptor-mediated uptake, PI3K/Akt, MAPK, apoptotic pathways	Improved drug penetration, enhanced cellular uptake, prolonged retention, and increased therapeutic exposure	
Induction of apoptosis and cell-cycle arrest	Caspases, Bax/Bcl-2, p53, cyclins, CDKs, mitochondrial pathways	Mitochondrial dysfunction, caspase activation, programmed cell death, and inhibition of uncontrolled proliferation	[63]
Anti-angiogenic and anti-metastatic effects	VEGF, HIF-1 α , MMPs, EMT-associated pathways, adhesion molecules	Inhibition of blood-vessel formation, tumor invasion, migration, and metastatic dissemination	
Overcoming multidrug resistance	P-glycoprotein, drug-efflux pathways, apoptosis signaling, survival pathways	Increased intracellular drug accumulation, reversal of resistance, and improved sensitivity to anticancer therapy	[64]
Combination with conventional anticancer agents	Complementary/synergistic signaling, apoptosis, oxidative stress, resistance pathways	Enhanced therapeutic efficacy, synergistic activity, reduced effective drug dose, and improved treatment response	

Translational Challenges, Clinical Perspectives, and Future Directions

The clinical translation of nanotechnology-based therapeutic platforms in cancer management is challenged by several interconnected safety, biological, pharmacokinetic, manufacturing, and regulatory barriers. Nanotoxicity and safety concerns remain major considerations because nanoparticle size, surface characteristics, composition, degradation behavior, and prolonged tissue retention may influence cellular toxicity, immunogenicity, oxidative stress, and off-target effects. Comprehensive long-term toxicological and safety evaluations are therefore essential before clinical implementation. Tumor heterogeneity and targeting limitations further complicate therapeutic outcomes, as variations in tumor vascularization, receptor expression, extracellular matrix composition, and cellular phenotypes can produce inconsistent nanoparticle accumulation and therapeutic responses⁶⁵. In addition, differences in pharmacokinetics and biodistribution can affect circulation time, tissue penetration, tumor accumulation, drug release, and clearance, highlighting the need for rational

optimization of nanoparticle size, surface charge, ligand density, and drug-loading characteristics. From a translational perspective, manufacturing scalability, batch-to-batch reproducibility, quality control, and regulatory barriers remain important challenges for converting laboratory-scale formulations into clinically reproducible products. Moreover, limited large-scale clinical studies, heterogeneous trial designs, and insufficient long-term clinical data contribute to persistent clinical evidence and translational gaps. Future developments are expected to increasingly focus on precision nanomedicine and biomarker-guided targeting, enabling patient stratification according to tumor-specific molecular, genetic, and phenotypic characteristics⁶⁴⁻⁶⁵. Artificial intelligence-assisted formulation optimization may further accelerate nanocarrier development by predicting optimal compositions, physicochemical properties, drug-loading efficiency, stability, and biological performance while reducing experimental requirements. Emerging multifunctional and theranostic nanoplatforms integrating targeted drug delivery, imaging, diagnosis, and therapeutic monitoring may provide more personalized and responsive

treatment strategies. Collectively, overcoming these translational barriers through interdisciplinary collaboration, standardized manufacturing, robust regulatory frameworks, and biomarker-driven clinical validation will be critical for realizing the full potential of next-generation nanomedicine in cancer therapy⁶⁵.

CONCLUSION

Phytometabolites represent a diverse and promising group of plant-derived bioactive compounds with considerable potential for cancer prevention and therapy. Their anticancer effects are associated with multiple mechanisms, including induction of apoptosis, cell-cycle regulation, modulation of oxidative stress and inflammation, inhibition of angiogenesis and metastasis, regulation of autophagy, and modulation of important signaling pathways such as PI3K/Akt/mTOR, MAPK, NF- κ B, STAT3, Wnt/ β -catenin, Nrf2, and p53. However, despite their promising biological activities, the therapeutic translation of many phytometabolites is restricted by poor aqueous solubility, chemical instability, rapid metabolism, low bioavailability, short circulation time, and nonspecific tissue distribution. The present review highlights the potential of nanotechnology-based delivery systems to address these limitations and improve the therapeutic performance of phytometabolites. Polymeric nanoparticles, liposomes, lipid-based nanoparticles, solid lipid nanoparticles, nanostructured lipid carriers, phytosomes, nanoemulsions, dendrimers, polymeric micelles, metallic nanoparticles, and hybrid nanocarriers provide different opportunities for improving drug loading, stability, controlled release, cellular uptake, bioavailability, and tumor accumulation. The incorporation of active targeting strategies using antibodies, peptides, aptamers, and receptor-specific ligands can further enhance selective delivery, while stimuli-responsive systems based on pH, enzymes, redox conditions, hypoxia, and reactive oxygen species offer opportunities for controlled and site-specific drug release. Integration of precision nanomedicine, multifunctional and theranostic platforms, combination therapy, and artificial intelligence-assisted formulation optimization may further support the development of clinically relevant phytometabolite nanotherapeutics. Overall, the integration of phytometabolites with advanced targeted nanocarriers provides a promising approach for improving the delivery, stability, and therapeutic performance of plant-derived anticancer agents, while continued multidisciplinary research and clinical validation remain essential for successful translation into cancer therapy.

Conflict of Interest: The authors declare that they have no conflict of interest, financial or otherwise, that could have influenced the preparation, content, or publication of this review article.

Funding: The authors received no specific grant, financial support, or funding from any public, commercial, or not-for-profit organization for the preparation of this review article.

Acknowledgement: The authors would like to express their sincere gratitude to their respective institutions and

colleagues for their academic support, encouragement, and assistance during the preparation of this review article.

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