

Review

Plant-Derived Nanoparticles in Cancer Therapy: A Comprehensive Review of Recent Advances and Future Prospects

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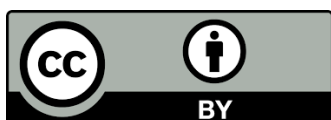
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Abstract

Cancer continues to be one of the leading causes of global death, and conventional therapies have limited efficacy because of their toxicity, drug resistance, and off-target effects. Plant-derived nanoparticles (PDNPs) have emerged as suitable alternatives as they have biocompatibility, biodegradability, and multifunctional therapy. In this review, we discussed the recent advancements in PDNPs for cancer therapy, including the green synthesis of PDNPs using phytochemical (flavonoids, terpenoids) reducing and capping agents, subsequent physicochemical characterization, and mechanisms of action. PDNPs take advantage of passive targeting via the enhanced permeability and retention (EPR) effect, and active targeting through ligand-receptor targeting (folate, estrogen receptors). PDNPs also utilize features of the tumor microenvironment (TME) (acidic pH, redox imbalance, protease overexpression, etc.) to mediate stimuli-responsive drug release. PDNPs have potent



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anticancer activity by inducing apoptosis via ROS generation and mitochondrial dysfunction, regulating immune responses (repolarizing tumor-associated macrophages), and reducing metastasis by inhibiting epithelial-mesenchymal transition (EMT). Various PDNP platforms from metallic nanoparticles (Au, Ag, ZnO), to plant virus nanoparticles (TMV, CPMV), to polymeric/lipid carriers promote effective delivery of chemotherapeutics, phytochemicals (curcumin, quercetin), and gene-editing technologies (CRISPR/Cas9). Despite their better biosafety and selective cytotoxicity, challenges remain with scalability, pharmacokinetics, and long-term toxicity, and all these will need to be further addressed. Future opportunities are anticipated in AI-assisted design, utilizing CRISPR integration for precision gene editing, and developing tailored PDNP formulation strategies unique to the tumor's molecular profile (precision medicine). PDNPs would be a disruptive, sustainable delivery vehicle for conventional therapies and represent a transformative surface-initiated approach that would certainly advance cancer nanomedicine and could symbolize the necessary shift in the current paradigm.

Keywords

Plant-derived nanoparticles; cancer therapy; targeted drug delivery; green synthesis

1. Introduction

Cancer continues to be among the leading causes of mortality globally, provoking the search for novel and effective therapeutic interventions [1, 2]. Traditional anticancer therapies, e.g., chemotherapy and radiotherapy, are severely limited by significant drawbacks, e.g., systemic toxicity, off-target effects, and drug resistance. These treatments are non-specific, resulting in collateral destruction of normal, dividing cells such as those in the gastrointestinal tract, bone marrow, and hair follicles [3, 4]. This non-selective cytotoxicity not only decreases patient quality of life but also weakens the immune system, thereby decreasing the body's ability to produce an antitumor response [2, 3, 5]. On the molecular level, cancer cell resistance includes overexpression of drug efflux transporters like P-glycoprotein (P-gp), mutation of drug target enzymes (e.g., topoisomerase II), upregulation of anti-apoptotic proteins (e.g., Bcl-2), and enhanced DNA repair mechanisms. Such modifications undermine the long-term efficacy of chemotherapy regimens [6].

Nanomedicine has developed as a new and transformative discipline with promising potential to revolutionize cancer treatment. Nanoparticles (NPs) possess well-differentiated physicochemical characteristics, including size tunability (1–100 nm), large surface-area-to-volume ratio, and surface functionalization [7-10]. These characteristics enable precise drug loading, controlled release, and active tumor tissue targeting, thereby maximizing therapeutic efficacy and minimizing systemic toxicity. Among the many NP platforms, plant-derived NPs (PDNPs) have drawn interest due to their unique set of biocompatibility, biodegradability, and ecological sustainability [11, 12].

The PDNPs are synthesized by green chemistry techniques involving phytochemicals derived from plants, such as flavonoids, alkaloids, terpenoids, and phenolic acids, as natural reducing and capping agents. These molecules often possess inherent anticancer activities, such as quercetin's inhibition of the PI3K/AKT pathway or curcumin's inhibition of the NF- κ B and STAT3 pathways [13,

14]. This allows PDNPs to possess multimodal anticancer activities like apoptosis induction, immune modulation, and anti-angiogenesis [15-17]. In addition, the molecular conformation of phytochemicals can allow targeting of specific receptors on the surface of cancer cells, including the folate receptor- α or estrogen receptor- α , through ligand-receptor interactions [18].

Additionally, PDNPs can be designed to leverage the unique aspects of the tumor microenvironment (TME), such as acidic pH, oxidative stress, and enzyme activity, to achieve site-specific delivery of therapeutic payloads [19]. The molecular tunability of PDNPs allows them to be conjugated with targeting ligands, chemotherapeutic drugs, and even gene-editing tools like CRISPR/Cas9 to ensure optimal specificity and customization in the treatment of cancer [20]. The present review tries to rationally survey the recent advances in the field of PDNPs, from their synthesis to structural and physicochemical characterization, molecular mechanisms of anticancer action, and drug delivery.

2. Fundamentals of Planet-Derived Nanoparticles in Cancer Therapy

NPs can target tumors via passive and active mechanisms, both governed by dissimilar biological and physicochemical principles that enable preferential TME accumulation. Passive targeting leverages the increased permeability and retention (EPR) effect, a qualitative feature of solid tumors [21]. Due to pathologic angiogenesis, the vasculature of tumors contains poorly organized, leaky capillaries with large fenestrations (100–800 nm), defective basement membranes, and poor pericyte coverage. These properties allow systemically injected NPs to extravasate out of circulation and infiltrate into tumor tissue. Contributing to this effect is the impaired lymphatic drainage of tumors, which hinders NP clearance and allows for long-term retention [22, 23].

Passive targeting efficiency is mainly dependent on physicochemical properties such as particle size, geometry, and surface characteristics. PDNPs with sizes between 10 and 100 nm achieve a practical compromise: small enough to pass through fenestrated tumor capillaries, yet too large to undergo rapid renal clearance (which usually occurs for particles <8 nm) [24]. Shape also serves a molecular purpose; i.e., elongated plant viruses like tobacco mosaic virus (TMV) utilize anisotropic geometry to align with shear flow and enable more efficient navigation of dense extracellular matrices. This allows more penetration into tumor tissue and more extensive diffusion, which is significant in solid tumor targeting [25].

Active targeting, however, involves molecular-scale changes in PDNP surfaces to engage in ligand-receptor interactions specific to cancer cells. Functional ligands, such as antibodies, aptamers, peptides, or phytochemical moieties, are attached to PDNP surfaces to target overexpressed cancer tissue receptors. For example, folate-targeting PDNPs can bind to the overexpressed folate receptor- α in ovarian and breast cancers [26, 27]. Notably, naturally occurring phytochemicals contained in PDNPs, such as flavonoids (apigenin, luteolin, genistein), may perform multiple functions, both anticancer and targeting functions [28]. Flavonoid-estrogen receptor interaction, specifically in estrogen receptor-positive (ER⁺) breast cancers, can mediate receptor-specific endocytosis and thereby enable uptake and intracellular delivery of therapeutic cargos [29].

The TME presents unique biochemical stimuli that can be exploited for stimuli-responsive drug delivery by PDNPs. Among the hallmark features is extracellular acidosis (pH 6.5–6.9 versus pH 7.4 in normal tissues) caused by increased anaerobic glycolysis (Warburg effect) and lactate production. PDNPs can be engineered with pH-sensitive linkers (e.g., hydrazone, imine bonds) or surface

coatings that hydrolyze at acidic pH, leading to site-specific release of therapeutics that are encapsulated. For instance, gold nanoparticles (AuNPs) synthesized with *Trachyspermum ammi* seed extract show acid-induced disassembly for drug activation primarily at the cancer locations [30].

Besides acidity, TME also houses a redox imbalance in the form of elevated levels of reactive oxygen species (ROS) and intracellular glutathione (GSH). Cancer cells house up to 10 times higher GSH concentrations than normal cells (1–10 mM vs. ~2 mM), which makes it a redox-responsive PDNP-friendly environment. These systems are often disulfide crosslinks or thiol-reactive polymers that are cleaved in the presence of GSH to allow for drug release in cancer cells [31]. ROS-responsive elements like thioketal or boronic ester groups can be introduced in PDNP design for oxidative-induced release [32].

The proteolytic signature of the TME is also a targetable feature. Proteases such as matrix metalloproteinases (MMP-2, MMP-9) are often overexpressed in metastatic tumors [33]. PDNPs can be engineered with peptide substrates that are MMP-cleavable, providing localized payload release with enzymatic digestion. This strategy not only enhances tumor-specificity but also operates in concert with the molecular heterogeneity of cancer, providing site-specific activation of therapeutics within invasive or aggressive regions of the tumor [34].

Cumulatively, these active and passive strategies allow PDNPs to navigate complex biological barriers to deliver anticancer therapeutics with precision, decreased systemic exposure, and maximized therapeutic outcome. Through the integration of molecular responsiveness and targeting specificity, PDNPs provide a dynamic platform with the promise of overcoming the multifarious shortcomings of conventional cancer therapies [21].

3. Synthesis of Plant-Derived Nanoparticles

Green synthesis of NPs has emerged as an environmentally friendly and sustainable alternative to traditional chemical and physical methods. It utilizes plant extracts as reducing and stabilizing agents without needing toxic chemicals and minimizes environmental pollution. Various plant parts, including leaves, fruits, seeds, and roots, can be used as the source for the green synthesis of PDNPs [35]. These parts of plants have diverse phytochemicals such as polyphenols, flavonoids, terpenoids, alkaloids, and saponins that can participate in redox reactions and surface capping. The biosynthetic pathway generally involves the reduction of metal ions (e.g., Ag^+ , Au^{3+} , Zn^{2+}) to their zero-valent forms by electron-donating phytochemicals and subsequent stabilization of the so-formed NPs through capping by the same or different bioactive molecules. The rate of nucleation and growth of NPs is influenced by the concentration and reactivity of these phytochemicals, which also controls the morphology, size distribution, and surface functionality of the as-synthesized PDNPs [36].

Leaves are among the most exploited plant sources for PDNP synthesis due to their easy availability and extraction. As an example, aloe vera leaf extract is used to synthesize silver NPs (AgNPs) because of the excellent antimicrobial activity [37]. Aloin and emodin are two compounds from aloe vera that contain hydroxyl groups and carbonyl groups and are capable of reducing silver ions and stabilizing the subsequently formed NPs. Fruits, for example, *Citrus aurantiifolia* (lime), one of the many species with bioactive agents, such as ascorbic acid and flavonoids, are also used since these bioactive agents are particularly effective reducing agents due to their ability to donate electrons to metal ions and stabilize and mitigate the formation of the metal cores [38]. Seeds, such

as *Trachyspermum ammi* (ajwain), have also been used to synthesize AuNPs that exhibited pH-responsive drug release capabilities with phytoconstituents thymol and carvacrol [39]. Roots, such as *Panax ginseng* (ginseng), have also been used to synthesize PDNPs that exhibited immunomodulatory activity likely mediated by ginsenosides that have reductant characteristics as well as surface-active traits [40].

Phytochemicals present in plant extracts play key roles in the green synthesis of PDNPs. Phenolic acids, such as gallic acid and catechins, act as reducing agents, which decrease metal ions to NPs through redox reactions [41]. Terpenoids, including limonene and linalool, are responsible for NP stabilization by forming hydrophobic interactions surrounding the particle core that inhibit agglomeration. Peptides and proteins can be used as capping agents, adhering to the NP surface through amine, carboxyl, or thiol groups to control the size, morphology, and dispersion of NPs in water. The phytochemical composition of the plant extract can have a profound effect on the nucleation kinetics and stability of the resulting PDNPs, so it is necessary to select appropriate plant sources and extraction and synthesis conditions to achieve reproducible physicochemical properties (Figure 1) [42].

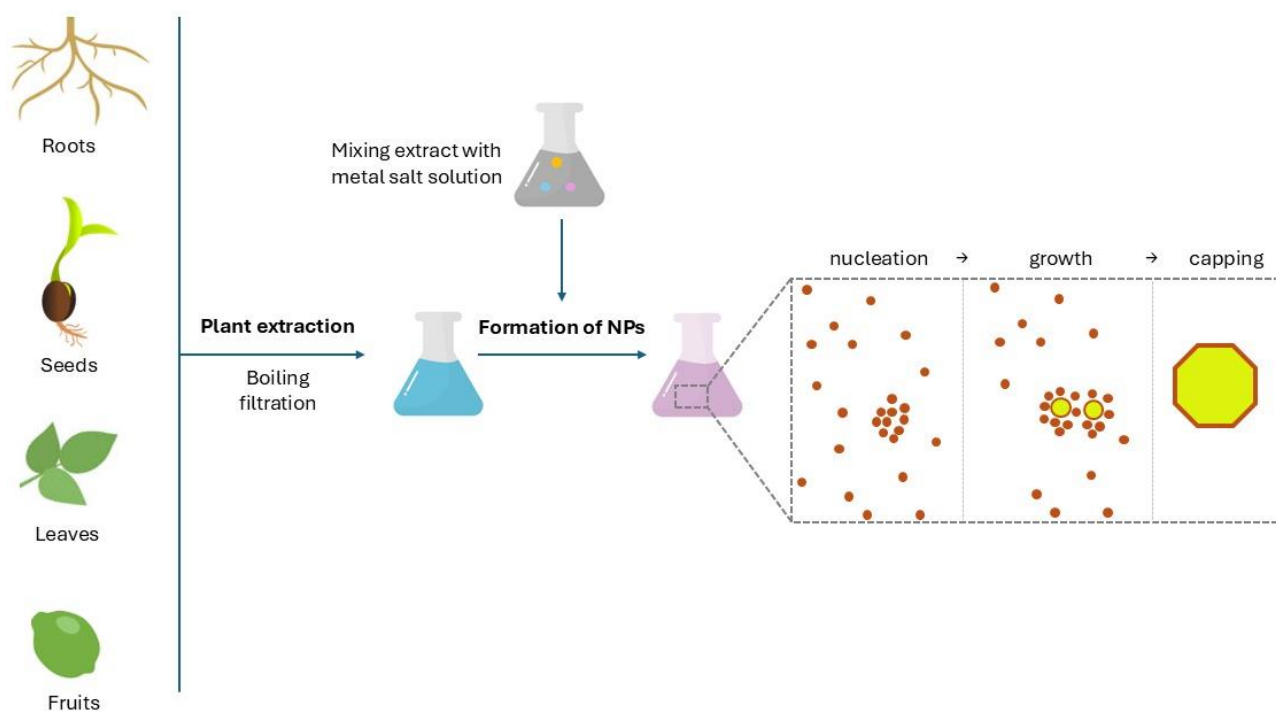


Figure 1 Schematic representation of green synthesis for plant-derived nanoparticles. The process involves plant extraction (leaves, fruits, seeds, roots), mixing with metal salt solutions, and subsequent reduction/stabilization by phytochemicals to form capped nanoparticles through nucleation, growth, and capping stages.

It is essential to fully characterize PDNPs to determine their physical and chemical properties and to anticipate their potential interactions in biological systems. There are sophisticated techniques that will provide descriptions of the size, shape, surface charge, composition, and stability of PDNPs. High-resolution transmission electron microscopy (HR-TEM) will provide detailed structural descriptions of PDNPs, including their size, shape, and crystallinity. It also enables imaging of lattice fringes that define the crystallinity and uniformity of the NPs. Fourier transform infrared

spectroscopy (FTIR) will be used to determine the functional groups that exist on the PDNP surface to help elucidate the specific phytochemicals involved in NP production, and how they are bound to the surface [43, 44].

Dynamic light scattering (DLS) is used to determine the hydrodynamic size distribution and also the colloidal stability of PDNPs in suspension, which are relevant to the prediction of their in vivo circulation half-life and biodistribution. Zeta potential analysis provides information on the surface charge of PDNPs, influencing their aggregation behavior, cell uptake, and serum protein interaction [45]. A highly positive or negative zeta potential generally leads to improved colloidal stability via electrostatic repulsion. X-ray diffraction (XRD) is used to analyze the crystalline nature of PDNPs, with characteristic peaks suggesting the formation of specific metal or metal oxide phases. These methods of characterization collectively provide a comprehensive view of the physicochemical profile of PDNPs that is necessary for designing them for biomedical applications and also for predicting their pharmacokinetics and therapeutic activity in vivo [46].

The scalability issue persists as a significant barrier. Translation from academia to industrial processes entails combining the principles of green chemistry with those of advanced manufacturing. Industrial bioproduction methods will need to involve continuous flow bioreactors, standardization of phytochemicals, and modular systems for purification to replace batch processes to deliver annual production of ton-scale quantities [47]. Initiatives such as the EU Nanomedicine Characterization Lab (EUNCL) are addressing regulatory matters through the development of GMP protocols for PDNPs [48]. In comparison, cost/benefit studies have shown that PdNPs made from plant sources offer a price reduction from chemical synthesis of between 30-50%, primarily through the removal of toxic solvents. Giving priority to these scalable and environmentally sustainable platforms is the best option for moving PDNPs from the benchtop to become a clinical reality [47].

4. Types of Plant-Derived Nanoparticles

4.1 Metallic NPs

Metallic NPs like AuNPs, AgNPs, and zinc oxide NPs (ZnONPs) have attracted significant research interest to treat cancer due to their physicochemical nature and multi-dimensional anticancer activities. AuNPs, which are synthesized from the leaves of *Cassia auriculata*, show anti-angiogenic effects by modulating the signaling pathways associated with vascular endothelial growth factors (VEGF). Remarkably, AuNPs can inhibit the phosphorylation of VEGF receptor-2 (VEGFR2) on endothelial cells, inhibit PI3K/AKT and MAPK/ERK cascades, which play a critical role in endothelial cell proliferation and vessel formation. The anti-angiogenic effect, when restricted, puts tumors under duress of limited oxygen and nutrients and inhibits tumor growth and metastasis [18, 46, 49, 50].

Plant-derived AgNPs like *Medicago sativa* (alfalfa) are particularly potent in their antimicrobial activities due to their disruption of microbial cell membranes and generation of ROS. In anticancer therapy, AgNPs cause cytotoxicity through a variety of mechanisms, including direct interactions with nuclear DNA, which causes genotoxic stress, induces mitochondrial membrane depolarization, and activates intrinsic apoptotic pathways. On the molecular level, AgNPs increase intracellular ROS levels, which induce p53-dependent apoptosis signaling, Bax upregulation, and anti-apoptotic proteins such as Bcl-2 downregulation, resulting in caspase-3 activation and induced cell death [51].

ZnONPs, which were synthesized from *Camellia sinensis* (green tea), have primarily been found to produce very high intracellular ROS in cancer cells. This oxidative stress overwhelms the antioxidant defense mechanisms of the cancer cell, leading to damage to lipids, proteins, and nucleic acids. The heightened levels of ROS also trigger endoplasmic reticulum (ER) stress and mitochondrial dysfunction, which induce apoptosis by the unfolded protein response (UPR) and cytochrome c release into the cytosol [52]. ZnONPs have exhibited selectivity by inducing such effects mainly in cancer cells, which are already known to possess a high intrinsic level of oxidative stress, and sparing healthy cells with more efficient antioxidant systems [53].

4.2 Plant Virus NPs

Plant viruses such as TMV, cowpea mosaic virus (CPMV), and potato virus X (PVX) have been used as multifaceted building blocks for the development of new nanocarriers for drug delivery and imaging [54, 55]. These viruses are non-pathogenic to humans and possess highly organized capsid structures that can be chemically or genetically modified for the release of targeting ligands or for the delivery of therapeutic payloads. TMV, for instance, consists of a rigid rod structure of repeating coat proteins where high drug loading density is achievable. TMV has been surface-functionalized with doxorubicin via pH-sensitive linkers for controlled drug release in acidic tumor microenvironments [54, 56].

CPMV, with its surface-exposed lysine residues and icosahedral geometry, allows easy conjugation of imaging agents such as near-infrared dyes or radiolabels. It will enable intravital imaging for monitoring NP biodistribution and therapeutic response in real time. CPMV capsid structure also allows endocytosis through binding to surface integrins that are overexpressed on cancer cells, enhancing cellular uptake [55, 57].

PVX, a filamentous plant virus, may be genetically engineered to display specific peptides on its surface, like RGD (arginine-glycine-aspartate), which is specific to integrin $\alpha v \beta 3$ receptors found predominantly in tumor neovasculature. Specific receptor targeting allows enhanced vaccine homing to tumors as well as targeted drug delivery of encapsulated or conjugated anticancer drugs, thus making plant viruses a tunable and immunologically silent platform for targeted cancer treatment [58].

4.3 Polymeric/Lipid NPs

Polymeric and lipid NPs serve as an alternative for the delivery of anticancer plant-derived compounds with higher efficacies. Chitosan, alginate, and starch are naturally occurring polymers that have vast applications due to their biocompatibility, biodegradability, and ability to be shaped into NPs via ion gelation or nanoprecipitation methods. Curcumin, a polyphenolic compound with a well-established inhibitory activity on NF- κ B, STAT3, and mTOR pathways, exhibits poor water solubility and bioavailability [59]. When loaded into chitosan NPs, curcumin shows improved aqueous solubilization, prolonged systemic circulation, and increased cellular uptake via endocytosis, and hence an amplified anticancer action [60].

Flavonoids, another class of bioactive plant components, can be entrapped in liposomes, phospholipid bilayer vesicles with a spherical structure [61]. Liposomal entrapment prevents flavonoids from being metabolically degraded, enhances their bioavailability by traversing cell membranes, and facilitates receptor-mediated uptake by cancerous tissues [62]. For example,

liposomes loaded with quercetin may utilize overexpressed folate receptors or LDL receptors on cancer cells to target delivery [63]. Additionally, polymeric and lipid carriers can be PEGylated with PEG chains to ensure improved circulation stability and reduced uptake by the mononuclear phagocyte system (MPS), enhancing the pharmacokinetic properties. These platforms provide an efficient method to overcome physicochemical limitations of plant compounds and deliver drugs effectively into tumors (Figure 2, Table 1) [64].

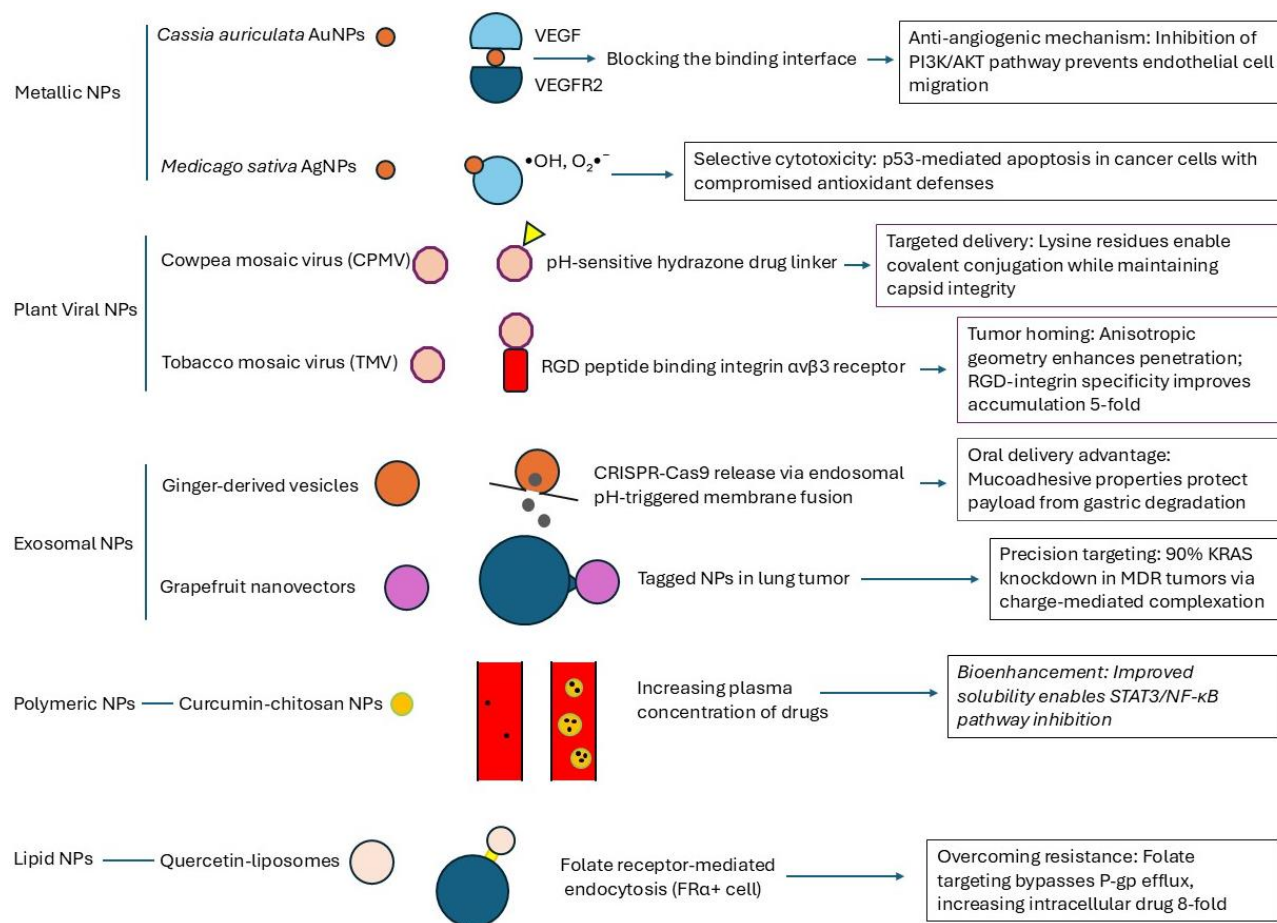


Figure 2 Nanoparticle-based therapeutics: targeted mechanisms for enhanced drug delivery. This figure illustrates various nanoparticle (NP) types—metallic, plant viral, exosomal, polymeric, and lipid-based—and their mechanisms of action in therapeutic applications. Each NP example demonstrates how specific properties, such as targeting receptors, enhancing drug stability, or overcoming resistance, can be leveraged for more effective treatments in cancer.

Table 1 Comparative overview of plant-derived nanoparticles applicable in cancer therapy.

NP Type	Source	3D Shape	Brief Description	Ref
Gold NPs (AuNPs)	Leaves of <i>Cassia auriculata</i>	Spherical	Inhibit VEGFR2 phosphorylation; block PI3K/AKT and MAPK/ERK signaling to exert anti-angiogenic effects, starving tumors of blood supply	[18, 46, 49]
Silver NPs (AgNPs)	<i>Medicago sativa</i> (alfalfa)	Spherical	Generate ROS, induce p53-dependent apoptosis (Bax upregulation/Bcl-2 downregulation), mitochondrial depolarization, and caspase-3 activation	[51]
Zinc Oxide NPs (ZnONPs)	<i>Camellia sinensis</i> (green tea)	Spherical	Overproduce intracellular ROS, trigger ER stress, and mitochondrial stress dysfunction via UPR, leading to selective apoptosis in cancer cells	[52, 53]
Tobacco Mosaic Virus (TMV) NPs	Tobacco mosaic virus capsids	Rigid rod	Filamentous rods of repeating coat proteins; high drug-loading capacity; surface-attached doxorubicin via pH-sensitive linkers for tumor-specific release	[54, 56]
Cowpea Mosaic Virus (CPMV) NPs	Cowpea mosaic virus capsids	Icosahedral	Surface lysines enable conjugation of imaging/radiolabel agents, and integrin-mediated uptake for real-time biodistribution monitoring	[55, 57]
Potato Virus X (PVX) NPs	Potato virus X capsids	Filamentous	Genetically display RGD peptides targeting $\alpha_v\beta_3$ integrins on the tumor neovasculature; tunable for vaccine/drug delivery	[58]
Chitosan-based NPs	Curcumin-loaded chitosan	Spherical	Enhance curcumin solubility, prolong circulation, boost endocytic uptake, and anticancer efficacy via NF- κ B/STAT3/mTOR inhibition	[60]
Flavonoid-liposomes	Quercetin-loaded liposomes	Spherical	Protect flavonoids from degradation, enhance bioavailability, and leverage folate/LDL receptor-mediated uptake in cancer cells	[61, 62]

5. Anticancer Activity of PDNPs

5.1 Induction of Apoptosis

As mentioned above, apoptosis is one central mechanism for the elimination of damaged or unwanted cells, and its dysregulation is a feature of cancer. PDNPs cause apoptosis in cancer cells through various molecular mechanisms, primarily by the generation of ROS and disruption of mitochondrial integrity [65]. ZnONPs, for example, may cause intracellular ROS levels higher than the antioxidant capacity of cancer cells, leading to oxidative damage in DNA, lipids, and proteins. This ROS stress activates the intrinsic pathway of apoptosis through MOMP, release of cytochrome c, and subsequent activation of the apoptosome complex of Apaf-1 and caspase-9 [66]. Activation of executioner caspases like caspase-3 yields DNA fragmentation and apoptotic cell death. AgNPs from *Brassica juncea* (mustard) have been found to block the mitochondrial electron transport chain complexes, especially Complex I and III, resulting in mitochondrial depolarization and increased membrane permeability. This is believed to improve the release of cytochrome c and initiate caspase-mediated apoptosis in cancer cells [67].

5.2 Immune Modulation

Immune response is essential for recognizing and eliminating cancer cells, and PDNPs can modulate the immune response to trigger antitumor immunity. PDNPs can reprogram TAMs to shift their phenotype from the M2 immunosuppressive to the pro-inflammatory M1 phenotype. M1 macrophages release cytokines such as IL-12, TNF- α , and IFN- γ , which stimulate cytotoxic T cell activation and promote antigen presentation. Polarization is often mediated by ROS production and NF- κ B activation pathways triggered by PDNP internalization. PDNPs can also disrupt immune checkpoint signaling. For instance, phytochemicals on PDNP surfaces can downregulate programmed cell death protein-1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) expression either by transcriptional downregulation or post-translational interference. The immunomodulatory effect produced can reactivate exhausted T cells such that the immune system can mount a more substantial and prolonged attack on tumor cells [19, 68].

5.3 Anti-Metastatic

Metastasis, the spread of cancer cells from the primary tumor to other sites, is responsible for the majority of deaths from cancer. PDNPs suppress metastasis by suppressing the epithelial-mesenchymal transition (EMT), a process central to the development of migratory and invasive cell properties in cancer cells [69]. Molecularly, PDNPs suppress key EMT transcription factors such as Snail, Twist, and Zeb1, and induce epithelial markers such as E-cadherin. Furthermore, PDNPs can interfere with signaling pathways like TGF- β , Wnt/ β -catenin, and Notch that are very well known to trigger EMT [69]. Additionally, PDNPs are capable of binding and degrading specific long non-coding RNAs (lncRNAs) involved in metastasis regulation. With CRISPR/Cas9 delivery systems encapsulated in PDNPs, it becomes possible to edit or knockdown lncRNAs like MALAT1 or HOTAIR, which have critical functions in EMT and metastatic progression, thus efficiently preventing metastasis of cancer cells [20, 70].

6. Drug Delivery Applications

PDNPs can be loaded with various anticancer therapeutic payloads, including chemotherapeutic agents, plant-derived phytochemicals, and gene editing reagents, to enhance their anticancer efficacy and specificity. Chemotherapeutic agents such as doxorubicin can be conjugated or encapsulated within PDNPs through the incorporation of pH-sensitive or redox-sensitive linkers [71]. This strategy allows for site-specific drug delivery in acidic or oxidative tumor microenvironments and reduces systemic toxicity. Phytochemicals like curcumin and berberine, which suffer from low solubility and wide metabolism, can be loaded into PDNPs to increase their intracellular retention and bioavailability. Such molecules possess anticancer actions through modifying signaling pathways, NF- κ B, STAT3, and AMPK [72].

Gene-editing tools like CRISPR/Cas9 can also be delivered efficiently by employing PDNPs. Plant-based nanocarriers protect the ribonucleoprotein complexes from nuclease digestion and facilitate endosomal escape into the cytoplasm or the nucleus. Site-specific knockout of drug targets in cancer, such as oncogenes or drug resistance genes such as MDR1 or KRAS, is facilitated by this delivery system. Multidrug resistance (MDR) remains a primary obstacle to cancer treatment, and P-gp remains a key efflux pump [73]. Quercetin-loaded PDNPs were also shown to inhibit P-gp expression and activity, allowing the chemotherapeutic drugs to penetrate drug-resistant cancer cells and render the cells drug-sensitive again [74].

Theranostic applications combine therapeutic and diagnostic modalities within a single PDNP platform. Dual-functional AuNPs synthesized from plant extracts can function as imaging agents and therapeutic agents. Once functionalized with imaging contrast agents, these AuNPs can be helpful in several computed tomography (CT) or photoacoustic imaging (PAI) procedures for tumor localization. Upon illumination by near-infrared (NIR) light, such NPs deposit localized heat on surface plasmon resonance, which results in the killing of cancer cells through photothermal ablation. The combined approach allows real-time monitoring in addition to personalized regulation of the treatment regimen based on tumor feedback [75, 76].

7. Toxicity and Biosafety of Planet-Derived Nanoparticles

Biosafety is a concern when developing any nanomedicine, and PDNPs are less toxic than artificial NPs due to their biogenic origin and bio-compatibility. For example, ZnONPs from *Cassia auriculata* have been reported to be selectively cytotoxic with apoptosis induction in breast cancer cells without causing damage to non-tumorigenic epithelial cells. This selective toxicity is believed to be mediated via differential ROS and antioxidant defense mechanisms between cancer and normal cells. ZnONPs generate ROS such as superoxide anions and hydroxyl radicals, leading to oxidative damage to DNA and mitochondrial dysfunction in cancer cells with already elevated basal oxidative stress. In contrast, normal cells with a functional antioxidant system (e.g., glutathione, superoxide dismutase) can better neutralize these radicals and thus survive [77, 78].

The pharmacokinetic fate and profile of PDNPs, including their absorption, distribution, metabolism, and excretion (ADME), also play vital roles in drug efficacy and systemic safety [79]. Small PDNPs (<10 nm) are usually cleared rapidly by renal filtration via glomerular excretion, which decreases their circulation time and therapeutic effect. Larger PDNPs (larger than 100 nm), however, are found to accumulate in the MPS organs of the liver and spleen by opsonization and Kupffer cell and splenic macrophage uptake [48]. The accumulation in these organs could present a risk of

chronic toxicity or immune stimulation if properly controlled. Surface functionalization strategies such as PEGylation can increase circulation half-life through reduced protein corona formation and phagocytic clearance. Surface charge and hydrophilicity also must be optimized to facilitate effective biodistribution and prevent off-target interaction. Tuning of PDNP size, shape, and surface chemistry is hence essential to promote optimal pharmacokinetics with minimal off-target accumulation and toxicity [13].

PDNPs usually elicit lower levels of immunogenicity than synthetic nanoparticles. However, specific formulations can elicit immune reactions based on the formulation and methods of administration. Structured plant viral nanoparticles (for example, CPMV, TMV) elicit immune activation (via Toll-like receptors (TLR2/4)) and also elicit complement activation that can lead to hypersensitivity or enhance clearance of plasma if repeated doses are administered. For example, intravenous administration of CPMV leads to IgG/IgM production within 7 days. Plant-derived nanoparticles, for instance, PDNPs that make use of lectin to possess carbohydrate-binding domains (for example, those derived from *Sambucus nigra*), may initiate dendritic cell activation via these domains. Orally derived ginger exosomes appear to induce immune tolerance due to GI tract homeostasis. There are three central mitigation strategies [80, 81].

While current studies demonstrate favorable acute safety profiles of PDNPs, long-term toxicity assessments remain critically underexplored. Existing research primarily focuses on short-term exposures (≤ 4 weeks), leaving significant gaps in understanding chronic effects such as organ accumulation (particularly liver/spleen retention of metallic PDNPs), delayed immunogenicity of plant viral components, and potential generational impacts. Future investigations should implement OECD Guideline 452-compliant chronic toxicity studies (6-12 months) incorporating multi-organ histopathology, oxidative stress biomarkers (8-OHdG, MDA), and genotoxicity assays (micronucleus, COMET) [82].

8. Future Perspectives in Precision Oncology

The amalgamation of CRISPR-Cas9 systems and PDNPs is a novel approach toward precision gene editing and cancer therapy [20]. It has been shown that exosomes derived from ginger (i.e., PENs) can successfully encapsulate and coat CRISPR components for oral delivery, thereby protecting them from degradation in the GI tract. These PENs then use passive drug release methods (pH and enzyme responsive) to release gene editing parcels at tumor sites, as demonstrated by a successful KRAS knockout in preclinical models of colorectal cancer with very low off-target events [83]. The natural tropism that plant-derived nanocarriers have for specific tissues (tumor in this case) allows for localized, mutation-specific therapies, in combination with their ability to protect their payload [84]. Artificial intelligence has become a prerequisite for optimizing PDNP formulations and predicting their potential *in vivo* behavior. Advanced machine learning (ML) algorithms are now able to parse complex datasets of physicochemical properties of nanoparticles, biodistribution properties, and therapeutic outcomes to identify ideal design parameters. For example, some of the predictive models developed from the machine learning algorithms have identified that citrus-derived nanoparticles ranging from 40-60 nm in size with a slight negative surface charge (-15 to -20 mV) achieved the best tumor accumulation in HER2-positive breast cancer, while simultaneously eluding rapid clearance. Using a predictive model for design significantly decreases the time spent on typical trial and error processes, which can be incredibly challenging, while developing and

optimizing a targeted PDNP system workaround, since there are so few existing examples to follow [85, 86].

The future of PDNP-based cancer therapy is a genuinely personal therapy via three customizable approaches. First, molecular targeting achieved through surface modification with agents such as anti-HER2 peptides or folate conjugates could allow nanoparticles to target tumor-specific receptors. Second, payload customization, where therapeutic contents can be tailored to match the tumor genotype for a given patient, such as delivering TP53 mRNA for p53-deficient cancers. Third, microenvironment-responsive designs that have only been activated under tumor-specific conditions, such as elevated levels of reactive oxygen species or protease activity. Current proof-of-concept studies have demonstrated the considerable potential these approaches offer, with some formulations showing greater than 5:1 tumor-selective accumulation when compared to healthy tissue. The clinical translation of precision-based PDNP therapies will likewise require the simultaneous advancement of diagnostics, including genomic testing technologies and manufacturing technologies [87-89]. The newest development, liquid biopsy-guided nanotherapy - wherein liquid biopsy analyzes circulating tumor DNA and informs real-time PDNP customization in clinical care settings - is one of the most promising directions for the future of PDNP-based cancer therapy. However, multiple challenges remain in developing a scalable production plan while maintaining the precision and quality to create patient-specific therapies. Achieving workable solutions, however, will require interdisciplinary dialogue, and perhaps even the emergence of new inter-professional domains, to realize the full potential of PDNPs in precision oncology [90].

9. Conclusion

PDNPs show the potential promise of a new cancer therapy tool through their multifunctionality, biocompatibility, and the ability to make a green synthesis. Dual-characterization PDNPs can also provide localized delivery of therapeutic agents in a minimal toxic manner, with a targeted and stimuli-responsive delivery method, maintaining some effectiveness throughout the body. The plant-based phytochemicals also provide intrinsic bioactivity, which can assist with a second layer of therapy with the potential for additional synergy and anticancer efficacy. However, prior confirmation through strong clinical verification needs to be completed to prove the safety, efficacy, and pharmacokinetics in humans. These barriers will need to be crossed through collaboration across multiple scales involving botanists, oncologists, materials scientists, and various regulatory agencies to enable the progression from innovation in the lab to clinical implementation. Scalability, toxicity, and standardization need to be addressed methodologically to produce PDNPs at quality and cost uniformity for widespread applications. The rise in cancer-related deaths, together with the accompanying limitations of current treatment options, highlights the need for new approaches—ones that PDNPs are well-positioned to deliver. The future promise of bioinspired, personalized, and integrative cancer care provided by PDNPs is transformative in cancer pharmacotherapy. PDNPs will uniquely position cancer treatments as advances in AI-led design, gene-editing integration, and individualized medicines continue to evolve. With ongoing investment in research, infrastructure, and regulatory pipelines, the translational potential of plant-based NPs in cancer care can be realized. The clinical translation of PDNPs is currently hindered by a lack of large-scale, multicenter clinical trial data to confirm their efficacy and safety in humans. While preclinical studies demonstrate significant potential, the absence of comprehensive human trials

limits their immediate clinical applicability. Future research must prioritize the design of rigorous clinical trials to evaluate PDNP performance across diverse cancer types and patient populations. These trials should focus on standardized PDNP formulations, such as curcumin-loaded chitosan nanoparticles or plant virus-based NPs, and incorporate long-term safety monitoring.

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Author Contributions

Beom-Jin Lee: conceptualization, investigation, writing – review & editing; Manal Hadi Ghaffoori Kanaan: conceptualization, supervision, writing – original draft, writing – review & editing; Sura Saad Abdullah: writing – original draft, investigation; Abdolmajid Ghasemian: writing – review & editing. All the authors critically revised and approved the final version of the manuscript.

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