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Therapeutic Applications of Plant Virus Nanoparticles in Cancer Treatment and Nanomedicine

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ABSTRACT

Plant virus nanoparticles (VNPs) are inexpensive to produce, dependable, and reusable and have emerged as a versatile and promising platform in nanomedicine, particularly cancer therapy. These biogenic nanostructures possess unique physicochemical properties, including biocompatibility, biodegradability, and structural uniformity, making them ideal candidates for targeted drug delivery. The ability of such nanoparticles to encapsulate chemotherapeutic agents and functionalize with tumor-specific ligands facilitates precise delivery to cancerous tissues, minimizing off-target effects and enhancing therapeutic efficacy. In addition, plant viral vectors (VLPs) are an attractive option for causing anti-tumor immunity because they are undoubtedly secure, harmless, and suitable for mass manufacture and pharmacological adaptation. This review delves into the molecular architecture of plant virus nanoparticles, their functional modifications, and the mechanisms by which they interact with cancer cells. Additionally, it highlights preclinical studies and emerging clinical applications, addressing both the opportunities and challenges in translating VNPs from bench to bedside. By exploring the anticancer potentials of VNPs, this paper aims to underscore their role in shaping the future of sustainable, plant-derived nanotechnology for oncology.

INTRODUCTION

Cancer represents one of the primary drivers of death globally, demanding the constant advancement of innovative and efficient therapies [1]. The quest for effective and targeted cancer therapies has driven the exploration of innovative platforms in nanotechnology (Table 1). Among these, plant virus nanoparticles (VNPs) have emerged as a promising class of biogenic nanomaterials, offering unique opportunities for cancer treatment. Unlike synthetic nanoparticles, VNPs are derived from naturally occurring plant viruses and possess exceptional features such as precise nanoscale architecture, inherent biocompatibility, and ease of functionalization [2]. These attributes make VNPs an attractive alternative for addressing some of the critical limitations of conventional cancer therapies, including nonspecific drug delivery and systemic toxicity. Plant VNPs can be engineered to encapsulate chemotherapeutic agents or conjugated with tumor-specific ligands, enabling precise targeting of cancer cells while sparing healthy tissues. Additionally, their intrinsic immunogenic properties can be harnessed for cancer immunotherapy, potentially enhancing the body's immune response against tumors. Beyond drug delivery, VNPs serve as platforms for diagnostic imaging and theranostics, offering a multifunctional approach to oncology. However, despite their promising

applications, the use of plant VNPs in cancer therapeutics faces challenges such as limited scalability, potential toxicity concerns, and the lack of clinical studies, which must be addressed to translate these nanomaterials into clinical practice [3]. This review provides a comprehensive overview of the anticancer potentials of plant virus nanoparticles, focusing on their structural features, functional applications, and mechanisms of action in cancer treatment. It also examines recent advancements and discusses future directions to bridge the gap between laboratory research and clinical implementation. By exploring these aspects, this review aims to shed light on the transformative role of plant VNPs in advancing cancer therapeutics.

The field of nanomedicine is a nascent area of research across disciplines that exhibits the potential to become a revolutionary and inventive development. Numerous drugs are now undergoing clinical trials, and some are even available for purchase in select pharmacies worldwide. However, due to the relatively high cost of these novel treatments, the number of users is relatively low [4]. It is important to note that while much has been offered regarding the potential effectiveness of nanomedicines, perspectives tend to differ regarding the point at which a crucial cost-benefit analysis is necessary before nanomedicines may be made available for use in the treatment of cancer and other illnesses [5]. A wonderfully diverse category of materials, nanomedicines encompass a wide range of nanoparticles with sizes of particles ranging from 1 nm to more than 400 nm. They can consist solely of metal, as in the instance of gold and silver tiny particles, or they can be composed entirely of liquids or ternary systems, which are made up of a variety of compatible materials and, in most cases, result in a multifunctional entity with stimuli-responsive properties that allow it to react to minute changes in variables like pH and temperature deviations [6]. Additionally, basic polymeric materials like cellulose and chitosan can be used to produce nanoparticles. In the context of cancer treatment, immunotherapy simply refers to a tactic used to stimulate the patient's immune system to fight against the implanting of malignant cells [7, 8]. There are other ways to accomplish the goal. One strategy is to disable immunological checkpoints by using medications referred to as "immune checkpoint inhibitors." Typical components of the immune system, checkpoints work to moderate the immune response to prevent it from being overly robust. Ultimately, this therapeutic approach allows the immune system to react to cancer more potently by blocking these checkpoints [9]. The potential of plant virus-based nanoparticles (VNPs) as a special kind of nanocarriers for biological uses has been investigated. Plant virus VNPs are an affordable, harmless, and biodegradable substitute for synthetic nanoparticles, not to mention how simple they are to make and maintain quality control for. The ability of plant virus nanoparticles to respond to stimuli has been considerably enhanced [10].

Table 1
Applications of Plant-Virus Nanoparticles in Cancer Therapy

Application	Mechanism	Example Virus	References
Drug Delivery	Encapsulation and targeted delivery of chemotherapeutic agents	Tobacco Mosaic Virus	[11]
Gene Therapy	Delivery of siRNA/shRNA for gene silencing	Potato Virus X	[12]
Immunotherapy	Stimulation of immune response through antigen presentation	Cowpea Mosaic Virus	[13]
Imaging	Contrast enhancement for diagnostic imaging	Cowpea Chlorotic Mottle Virus	[14]
Combination Therapy	Integration with other therapies like chemotherapy and radiation	Brome Mosaic Virus	

Composition of plant virus nanoparticles

Plant viruses typically have two shapes for their nanoparticles: icosahedral (like Cowpea mosaic virus) and rod-shaped (like Tobacco mosaic virus (TMV) and Potato virus X (PVX). As nanoparticles in vivo, viruses with different shapes react in different ways. Without the need for its RNA genome to carry a drug payload on the surface or, to a lesser degree, within the internal channel of the nanoparticle, the tobacco mosaic virus may form into vectorless lipophile particles (VLPs). Potato virus X can only transport a payload on the exterior since it is unable to assemble itself without the presence of its RNA genome [16]. Without its RNA genome, the cowpea mosaic virus can be coaxed to self-assemble into empty virus-like particles, allowing it to transport a payload both inside and outside of its protein shell. The genetic material is enclosed in exterior protein shells that make up viruses. The term "capsid" refers to the group of numerous coat protein copies that make up a virus's outer shell. The capsid, which comes in a variety of sizes and forms, primarily serves to shield the genetic material from harm so that viruses can survive in harsh conditions [17]. Plant viruses are incredibly diverse in terms of their size and structure, which allows for customization for certain uses. Even when surface characteristics of viruses are changed through chemical and genetic manipulation, the structural integrity of the virus remains unaltered, giving imaging professionals control over which ligands, medications, and contrast agents to target. Plant viruses have been employed as virus-like particles and virus nanoparticles as epitope display systems to

produce vaccines. VLPs are a subgroup of VNPs that are not contagious because they do not have a nucleic acid genome. Plant virus-derived VNPs and VLPs are both biodegradable and non-pathogenic to humans. VNPs and VLPs are useful because they may be produced rapidly and function as incredibly adaptable molecular scaffolds. Tobacco mosaic virus (TMV) and cowpea mosaic virus (CPMV) are two examples of plant viruses that are used as vector lentiviral plaques. Potato virus X (PVX) is one instance of a plant virus used as a vector non-pathogen (VNP) [18].

Types of Plant Nanoparticles

Consisting of diverse types, each type of plant nanoparticle offers distinct advantages, from the structural uniformity and functional versatility of VNPs to the biocompatibility and eco-friendliness of phytonanoparticles and nanovesicles [19]. Their diverse properties enable them to cater to various biomedical applications, particularly in oncology, where precision and minimal toxicity are critical (**Table 2**). The most researched plant virus is tobacco mosaic virus (TMV), which was first identified in the 1800s. Because of its comparatively basic particle structure and genome organization, TMV is easily manufactured, purified, and genetically manipulable in large quantities. The 6.7 kb viral RNA genome within the rod-shaped virus particle, which has dimensions of 300 nm in length and 18 nm in diameter, is encased in 2,130 identical capsid protein particles arranged in a helical pattern [20].

Potato virus X (PVX) is a plant disease belonging to the Solanaceae family, notably affecting tobacco, tomatoes, and potatoes. Its positive-stranded RNA genome is 6.4 kb in size. The capsid is formed when several copies of CP group together around the genomic RNA. Because of its flexible and filamentous nature, PVX can carry heavy payloads, which opens up possibilities for imaging and medicinal applications. The PVX particle has dimensions of 515 × 14.5 nm and is made up of 1,270 CP subunits. Each CP subunit has an internal C-terminus and an exterior N-terminus that protrude to the completed particle, offering a favorable location for the modification. In contrast to other viruses that have been reported, the in vitro or in vivo assemblage of PVX CP subunits into filamentous VLP is not feasible in the absence of genomic RNA [17]. This illustrates the special relationship that virus RNA and CP have. One member of the Comovirus genus is the plant disease Cowpea mosaic virus (CPMV). The virus known as CPMV has an icosahedral form and a diameter of about 27 nm. It is made up of 60 copies of each of the large and small coat protein RNAs, RNA-1 and RNA-2, measuring 6 and 3.5 kb, respectively. For biomedical and nanotechnology applications, one of the most developed VNPs is CPMV because it can target particular tissues and functions well as a drug delivery system. Additionally, it is said to be well-suited for different molecules to attach themselves to the coat protein. The CPMV coat protein's five reactive lysine residues offer locations for chemical coupling to a variety of substances, including fluorescent dyes [21].

Table 2

Plant Virus Nanoparticles: A Review of their types, nature, formation, functions, mechanisms of action, and possible therapeutic strategies

Type of Plant Virus	Nature	Formation	Functions	Mechanism of Cancer Development	Mechanism of Cancer Treatment	Reference
Tobacco Mosaic Virus (TMV)	Rod-shaped	Self-assembly of capsid proteins	Structural protein, antigen delivery	Induce autoimmune responses	Deliver antigenic epitopes to APCs, stimulate immune response	[22]
Cowpea Mosaic Virus (CPMV)	Spherical	Self-assembly of capsid proteins	Structural protein, antigen delivery	Induce autoimmune responses	Deliver antigenic epitopes to APCs, stimulate immune response	[22]
Potato Y Virus (PYV)	Filamentous	Self-assembly of capsid proteins	Structural protein, antigen delivery	Induce autoimmune responses	Deliver antigenic epitopes to APCs, stimulate immune response	[23]
Tomato Bushy Stunt Virus (TBSV)	Spherical	Self-assembly of capsid proteins	Structural protein, antigen delivery	Induce autoimmune responses	Deliver antigenic epitopes to APCs, stimulate immune response	[15]
Cowpea Chlorotic Mottle Virus (CCMV)	Spherical	Self-assembly of capsid proteins	Structural protein, antigen delivery	Induce autoimmune responses	Deliver antigenic epitopes to APCs, stimulate immune response	[24]

Functions in Cancer Therapy

Because VLPs mimic native virus conformations and harness their inherent immunogenicity without sacrificing safety, they can be effective vaccine candidates. Because VLPs are easily absorbed by antigen-presenting cells (APCs) and provide the best

platforms for the processing of antigen and epitope display to immune cells, they effectively elicit immunological responses. The capsid (coat) proteins, which make up VLPs, are duplicates that, when put together, resemble repeating, multivalent molecular scaffolds. Consequently, the coat protein's numerous copies may make it easier for antigens fused to their surface to display multivalently [25]. Consequently, when it comes to immunogenicity, VLP vaccines are superior to antigens in their soluble forms. Furthermore, the natural adjuvant qualities of plant viral VLPs and VNPs eliminate the need for further adjuvants to elicit potent immune responses.

A polio vaccine is one example of how TMV VLPs have been used as epitope display systems in a variety of contexts. Subsequently, TMV was employed as an epitope displaying vehicle for a vaccine against malaria as well as other viruses such as the human immunodeficiency virus, hepatitis B virus, norovirus, foot and mouth disease virus, and human papillomavirus [26]. Theranostic applications can benefit greatly from the multifunctionality and multivalency of plant nanoparticle platforms. Accurate cancer diagnosis and treatment can be achieved through the exact molecular imaging that plant nanoparticles can provide [27]. The delivery of imaging probes via nanostructures might increase the likelihood of diagnosing cancer in its early stages by utilizing a variety of modalities to improve resolution, sensitivity, penetration, time, cost, and most importantly, clinical relevance when compared to single technologies. Depending on the type of tumor, drug-conjugated nanoparticles injected intravenously target it through an increased permeability and retention (EPR) effect [28].

A new area of biomedicine called molecular imaging makes it easier to see how molecules function in vivo. Imaging technologies allow for the examination of molecular and cellular functions in both healthy and sick situations in human beings. Examples of these techniques are optical imaging, computed tomography (CT), positron emission tomography (PET), and magnetic resonance imaging (MRI). Because they have no negative consequences and have a brief duration in the system compared to manufactured nanoparticles, plant VLPs may be more advantageous for molecular imaging technologies [29]. Additionally, because plant VLPs may be altered by incorporating antibodies, peptides, and aptamers to improve targeting to particular cell types and tissues, they are readily prepared and incorporate a broad variety of contrast molecules and fluorescent tags. MRI is a potential diagnostic tool because of its rich contrasts and excellent image quality; yet, virus-based nanoparticles are being utilised to boost susceptibility. Fluorescent dyes enable biosensing and bioimaging, as well as high payloads of MRI contrast imaging agents, which are capable of being delivered to sick tissue types by TMV. Because of its multivalency and biological reliability, TMV is an appropriate transporter for in vivo agents for imaging. For instance, TMV rods were coupled to "BF3," a fluorophore that absorbs multiple photons, enabling long-term mice brain imaging while not requiring passage through the blood-brain barrier [30]. As previously indicated, genetic modification was used to create the tiny fluorescent iLOV protein on the outermost layer of PVX, which functioned as a fluorescent probe with potential applications in vivo imaging. Interestingly, fluorescent PVX was found to be effective for monitoring particles in vivo in an HT-29 murine model, imaging HT-29 cells in vitro, and detecting infectious viruses in plants. Additionally, CPMV can be tailored for enhanced transparency alongside a retention response which fosters tumour penetration, and in addition to intravital imaging, which allows it for the imaging of cells that operate inside of multicellular organisms. CPMV-based VNPs have been effectively intended for targeting particular tissues for in vivo tumour imaging. Additionally, such tumor-targeting VNPs offer biocompatible bases for intravital imaging and treatments for cancer [31].

Plant virus vector-like particles are suitable for the precise administration of drug compounds due to several appealing characteristics. Using VNPs and VLPs, the cancer-preventing medication doxorubicin (DOX) has already been administered with success. DOX delivery has been accomplished with effectiveness using VLPs and VNPs produced from TMV and PVX. In this connection, substantial aspect ratio helical VNPs like TMV and PVX have shown to be particularly useful for efficient medication delivery [32]. With the discovery that the straightforward adsorption of DOX on the exterior of VNPs can effectively inhibit tumour progression, the virus has shown significant promise. Its cargo RNA serves as a measurement tool to determine the length of the viral particles. Peptides with diagnostic or targeted efficacy contrary to different malignancies can be delivered by TMV [33]. Corresponding to this, a method of administration known as PhenPt-TMV, which loads the cancer-fighting drug phenanthriplatin into a hollow TMV transporter, is an illustration of a stimuli-responsive mechanism since it causes the medicine to flow out when it is placed in an acidic condition. TMV's external appearance coupled with the Transacting Activation Transduction (TAT) peptide enhanced internalisation and the protein's capacity to leave the endo/lysosomal compartments. The majority of such VLPS demonstrated strong immunogenicity and were taken up by macrophages and dendritic cells. Therefore, during chemotherapy for cancer, therapeutic nucleic acids are able to be conveniently administered to immune cells [34].

Directed delivery of platinum-based cancer treatments has been accomplished through the use of VNPs. It is significant because such platinum-derived medications are used in 50% of chemotherapeutic regimens. It has already been shown that TMV effectively delivers the platinum-based medications cisplatin and phenanthriplatin. Steady covalent compounds or charge-driven couplings were employed to carry the medicines within the TMV VNP cavities [20]. Using HepG2 and MCF-7 lines of cancer cells, an in vitro methodology was used to demonstrate the better, more targeted cytotoxicity and enhanced rapid incorporation by cancerous cells which made possible by this type of TMV-based system for delivering drugs. It was successfully demonstrated that TMV encapsulates mitoxanthrone (MTO), another cancer-preventing medication that is a topoisomerase II inhibitor. In mice cancer models, VNPs demonstrated better tumour shrinkage yet prevented the serious cardiovascular consequences which could occasionally result from immediate MTO delivery [35]. To increase their immunological efficiency, helical plant virus nanoparticles, or VLPs, were additionally used along with therapy. In comparison to mice administered with either PVX or DOX by itself, the PVX-DOX (doxorubicin) mixture was demonstrated to be significantly successful in promoting cytokine/chemokine concentrations and extending the longevity of mice in melanoma models [36].

By PVX's affinity for attaching to cancerous B cells, a novel and effective medication along the way of administration for non-Hodgkin's B cell lymphomas (NHL) was disclosed. In a mouse model, PVX supplemented alongside monomethyl auristatin (MMAE) and given to tissues containing cancerous B cells that inhibit NHL development. In a mice B-cell lymphoma model, researchers found that conjugating PVX to an idiotypic (Id) tumor-associated antigen (TAA) recombinant via a biotin/streptavidin linkage evoked a 7-fold greater anti-Id IgG response than Id itself [37]. Such mice's cytokines profile showed that TLR7 needed to occur for the identification of viral RNA, in addition to the production of IFN-α and IL-12 [38]. The protein vimentin, which is present on the outermost layer of the majority of cells, might attach to CPMV nanoparticles. Since vitetin is elevated when tumours advance, cancer treatment finds this protein to be a compelling target. The capacity of CPMV to identify tumour cells that invade was significantly proved by the reality that the exterior vimentin expression in these studies coincided with CPMV incorporation [39].

Because the tumour microenvironment is immune-suppressive and promotes tumour immunity escape by inhibiting tumour fighting T-cells, it presents a significant obstacle to immune clearances. In mouse models of lung melanomas, ovarian, colon, and breast tumours, it has been demonstrated that CPMV VLP nanoparticles inhibit tumour development. In terms of mechanics, it was successfully demonstrated that CPMV reprogrammes the tumour microenvironment by attracting natural neutrophils and killer cells and facilitating the change from M2 to M1 tumour fighting macrophages [40]. The resulting group of innate immune cells then fights the tumour, causing cell destruction. Currently, researchers determined that the TLRs are in charge of these characteristics. Through the use of enzyme-mediated binding, chemical-based conjugation, and genomic fusion, CPMV VLPs are linked to TAAs (tumour associated antigens). For instance, the icosahedral CPMV has been effectively used to conjugate the human epidermal growth factor receptor 2 (HER2) epitope, enabling improved lymphatic system delivery and APC stimulation that increased the anti-HER2 immune system reaction [41]. In mice experiments, the CPMV HER2 candidate vaccination prolonged life by slowing tumour growth and metastasis. Significantly, in mouse experiments, CPMV-HER2 elicited a mostly Th1 immune response, whereas Sesbania Mosaic Virus-HER2 and CCMV-HER2 primarily produced a Th2 response. These findings demonstrated how an epitope carrier's nature is a crucial factor in controlling the Th1/Th2 biases. This might be the result of variations in epitope presentation on the capsid and VNPs' surfaces [20].

Cancer vaccinations targeting tumor-associated carbohydrate antigens (TACAs) may help slow the growth of tumours. Plant viruses that carry carbohydrates, however, have low immunogenicity, which means that they may strengthen the body's defence against TACAs. In models of animals, it was shown that CPMV-TACA conjugates that target the Tn antigen (GalNAc-α-O-Ser/Thr) elicit higher IgG titers, indicating increased T-cell-based defence and antibody isotype conversion [42]. In trials involving mouse sera that had been introduced to breast cancer cell lines, IgG interaction with the Tn antigens was identified. While combined with CPMV VNPs, the chemotherapy drug cyclophosphamide significantly increased TAA identification and antigen expression in mice tumour models, released extracellular TAAs, and stimulated immunity cell invasion. Additionally, CPMV VNPs were given in conjunction with CD47-blocking antibodies, which have been shown to work to inhibit the development of tumours in murine ovarian tumour models by activating phagocytes and triggering the adaptive immune reaction. Whenever CPMV VNPs are administered alongside the anti-programmed cell death-1 checkpoint inhibitory agents, similarly beneficial outcomes are seen. Moreover, CPMV can be effectively utilised in conjunction with treatment with radiation to enhance tumor-fighting effects [43]. Eighty particles of

the anticancer medication doxorubicin (DOX), directly attached to carboxylates at the CPMV nanoparticle's exterior, were used to create the CPMV-DOX conjugate. When utilised in small amounts, the drug delivery carrier has been demonstrated to be significantly more cytotoxic than unbound DOX; although at larger doses, the cytotoxicity of CPMV-DOX is time-delayed. Cancerous cells can withstand immune therapies because tumours are immune-suppressive [44].

Challenges

Although the plant virus nanoparticle has several promising aspects, there are some challenges to implementing this nanoparticle in targeted drug delivery for cancer cells. Firstly, the limited availability of research on the direct application of VNPs in cancer therapy requires careful synthesis of related studies in nanomedicine, plant virology, and oncology to provide a comprehensive overview. Additionally, the interdisciplinary nature of the topic demands balancing foundational knowledge with advanced insights, making it accessible to readers from diverse scientific backgrounds [45]. Inconsistencies in data, particularly regarding efficacy and toxicity, pose another hurdle, requiring critical analysis and comparison to highlight trends and limitations. Moreover, addressing scalability and production challenges is crucial, as the feasibility of large-scale manufacturing of VNPs often remains unexplored [46]. The lack of clinical studies further complicates the discussion, as most research is confined to preclinical stages, emphasizing the need to outline pathways to clinical applications. Lastly, differentiating VNPs from other nanoparticle systems and identifying knowledge gaps are essential to underscore their unique advantages and future potential. A well-structured approach can effectively address these challenges and contribute valuable insights to the field [45].

CONCLUSION

Particularly contrasted to naked pharmaceuticals, the utilisation of VNPs as a means of delivering drugs for the cure of persistent and infectious illnesses, like cancer, is favourable. Locally existing plant viruses are currently used to create the greatest potential nanoparticle platforms. Since plant viruses are harmless, inert, and nontoxic to mankind, this makes them perfect for medicine administration. Plant-virus-based nanoparticles may recognise and attack the unique antigens on the exterior of cancerous cells, thus enabling clinical implementation of cancer detection and treatment. Locally existing plant viruses including Potato virus X, Cowpea mosaic virus, Tobacco mosaic virus, and numerous others are being used to create the greatest potential nano-scale technologies. Such novel approaches are primarily being used in small-scale manufacturing at the moment. There will be a wide range of potential uses in the domains of biomedical engineering and medical sciences when these methods are developed progressively. Plant virus nanoparticles will require development shortly for high-throughput capabilities generation. Units which can use multiple thousands of plants to create several grammes of plant virus nanoparticles will need to dedicate themselves to this task. Plant molecular farming now has manufacturing infrastructure, and modifications are being made for nanoparticles. To expedite the procedure, further research into the process of regulation will be necessary. There needs further investigation to be done on the effects of plant virus nanoparticles on the immune system. Ultimately, new therapy routes, like microneedle patches, and plant virus chimaeras or semi-synthetic plant virus nanoparticles with novel features need to be investigated.

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