Role of Viruses in Nanoparticles Synthesis

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Abstract

Nanotechnology has revolutionized with lots of applications in the medicinal field to prevent, detect and treat several biological problems including disease and infections. The plant virus nanoparticles (VNPs) and virus-like nanoparticles (VLPs) obtained through viral nanotechnology have become a versatile platform in several fields such as in obtaining high selectivity and specificity, optics and biosensing, drug delivery and targeting, nanocatalysis, next-generation nanoelectronics. The capsid proteins in plant viruses aid in the production of novel nanomaterials, also they can self-assemble and form well-organized icosahedral viruses with altered coat protein subunits, interior and exterior size properties. The virus interior is particularly used to protect the sensitive compounds and encapsulate them, while their exterior can be utilized to coat small molecules in a précised manner. These properties of viruses including their biocompatibility nature have led to the development of VNPs/VLPs to achieve targeted drug delivery. Plant viruses are natural immunogenic and thus they are altered to use as vaccines against various pathogens. In this chapter, we discuss their applications and role in nanoparticle synthesis to create an effective and alternate way related to both medicine and nanotechnology disciplines.

Keywords

Nanotechnology · Nanoparticles · Biosensing · Nanocatalysis · Immunogenic

Abbreviations

BMV	Brome Mosaic Virus
CarMV	Carnation Mottle Virus
CCMV	Cowpea Chlorotic Mottle Virus
CP	Capsid protein
CPMV	Cowpea Mosaic Virus
CPs	Capsid proteins
DNA	Deoxyribonucleic acid
DOX	Doxorubicin
EGF	Epidermal growth factor

HCRSV	Hibiscus Chlorotic Ringspot Virus
MP	Movement protein
MPs	Movement proteins
MRFV	Maize Rayado Fino Virus
PAA	Polyacrylic acid
PC	Polyacid
PEG	Polyethylene glycol
PSA	Polystyrenesulfonic acid
PSD	Particle size distribution
RCNMV	Red Clover Necrotic Mottle Virus
RNA	Ribonucleic acid
SeMV	Sesbania Mosaic Virus
ssRNA	Single-stranded RNA
TYMV	Turnip Yellow Mosaic Virus
VLPs	Virus-like particles
VNPs	Virus-based nanoparticles

6.1 Introduction

Since ancient times, humans have widely used natural products against several diseases and infections. Nearly 25% of modern medicines are derived from natural resources. Drug discovery based on natural products has been gaining a lot of interest in designing lead molecules (Swamy and Sinniah 2016). The chemically diverse natural products are being screened to treat various diseases and infections including inflammations, diabetes, cancer, cardiovascular and microbial diseases as it exhibits extraordinary biological and chemical properties with several unique advantages, such as fewer side effects and toxicity, low-price, good therapeutic potentials and macromolecular specificity (Siddiqui et al. 2014). The usage of large-sized compounds/materials as drugs poses major complications including poor bioavailability, poor absorption, poor solubility, in vivo instability, issues related to target specific delivery and adverse effects of drugs (Thilakarathna and Rupasinghe 2013; Bonifácio et al. 2014). Hence, now there is a need for a new drug delivery system that could help in solving this crisis and can also help in targeting the specific body parts (Jahangirian et al. 2017). In such a situation, nanotechnology plays a major significant role in drug formulations by controlling the drug release and its delivery with immense success (Ansari et al. 2019, 2021; Balasamy et al. 2019; Khan et al. 2019; Rajakumar et al. 2020; Murali et al. 2021). Nanoscience applies nanophases and nanostructures in various fields of sciences especially in the field of nano-based nanomedicine and drug delivery systems and thus is found to connect the barriers of physical and biological sciences (Patra et al. 2018; Anandan et al. 2019; Kavya et al. 2020).

Viruses are nanosized which can deliver their genetic material and can infect the host cells. Viruses infect all living organisms including animals, algae, plants, bacteria and fungi. The host-specific viruses are classified into mycophages,

zoophages, cyanophages, phytophages and bacteriophages (Beijerinck 1898). In vitro self-assembling of viral components can be done under proper conditions due to the presence of self-assembled capsid proteins (CPs) with encapsulated DNA or RNA genetic material. Virus parasites require a host cell for their assembly and replication (Heise and Virgin 2013). They are described to be non-enveloped or enveloped based on the absence or presence of lipid bilayer, this envelope aids the infection process through host cell entry (Singh et al. 2006). Due to their bioconjugation potential, size property, stabilities, mutagenesis, the non-enveloped viruses are used as bionanomaterial such as nanocontainers or nanocarriers in the field of nanobiotechnology.

6.2 Nanoscience and Nanotechnology

Nanoscience is the phenomena involving manipulation of materials at atomic, molecular and macromolecular levels; and nanotechnology involves the design, characterization, production and application of systems and devices of nanometer scale (Yang et al. 2008). Both nanoscience and nanotechnology are the growing fields that have transformed various industries such as cosmetics, biotechnology, food sciences, electronics and pharmaceutics (Devalapally et al. 2007). Particularly the application of nanotechnology in the field of pharmaceutical research has led to the development of nanomedicines that operate at the nanometer scale range that provides a wide range of medical benefits in treating various infections and diseases (Onoue et al. 2014). The nanomaterials used to carry out such applications are well defined with sizes ranged from 1 to 100 nm and are usually nanospheres. Nanotechnology develops the nanomedicines by employing curative agents at the nanoscale level and hence can move freely inside the human body when compared to large-sized materials (Rudramurthy et al. 2016).

6.2.1 Nanomaterial

Nanomaterial refers to the manufactured, natural or incidental material which comprises particles either in aggregate or in the unbound state. Structures such as carbon nanotubes, graphene flakes and fullerenes have their dimensions below 1 nm and are considered to be nanomaterial; also the materials with surface area by volume ratio are included in this category (Oh and Han 2020). These nanomaterials are very promising in the medicinal field as they act as drug carriers. According to the European Union, three factors help us in identifying the nanomaterial which is size, particle size distribution (PSD) and surface area (Soares et al. 2018).

6.2.1.1 Size

Size is the most important feature as it applies to several materials with a size range of 1–100 nm. The particular size for a particle to be treated/considered as a nanomaterial is 100 nm including other properties. Nanomaterial manufacturing

includes two different approaches: top-down and bottom down. The top-down approach involves the breakdown of heavy material into smaller simpler pieces by chemical or mechanical energy. On the other hand, bottom down approach utilizes the molecular or atomic approach that helps the precursor particles to combine and increase their size through a chemical reaction (Luther 2004).

6.2.1.2 Particle Size Distribution

The widely used parameter for the identification of nanomaterial is PSD. The setting up of PSD is important as the nanomaterial is polydisperse which means it is composed of particles of different sizes (Bleeker et al. 2013).

6.2.1.3 Surface Area

The material falls into the definition of nanomaterial if its surface area by volume ratio is 60 m^2/cm^3 including its size and PSD characteristics (Soares et al. 2018).

6.3 Application of Nanotechnology

Over a few years, nanotechnology has become a daily routine in everybody's life. This revolutionized technology has been implied in various fields of science. Nowadays there are increased applications and product development of new medicines that usually contain nanomaterials belonging to the field of biomedical and pharmaceutical research (Bleeker et al. 2013). A number of nanoparticles have been synthesized by different routes that show excellent antimicrobial and anticancer potentialities (Jalal et al. 2016; Ali et al. 2020; Almatroudi et al. 2020; Ansari et al. 2020a, b; Farouk et al. 2020; Prasad et al. 2020; Sumanth et al. 2020; Rehman et al. 2020; Ansari and Asiri 2021; Alomary and Ansari 2021). Further, various nanotechnology applications have been approved using viruses as vaccines, including biomaterials, molecular electronic materials and chemical tolls (Singh et al. 2017).

6.4 Viruses as Nanomaterials

Viruses have become an ideal example for nanoscale fabrication/ nanomaterials because of their well-characterized geometries with surface and size uniformity (Brumfield et al. 2004; Klem et al. 2003). They replicate and produce in living cells/host cells and allow the assembly of millions of nanoparticles. Viruses are ubiquitous as they infect plants, mammals and bacteria; these have been used in the manufacturing of virus-based nanoparticles (VNPs). Viruses have naturally evolved with the capacity to deliver nucleic acids and are therefore ideally used to deliver molecules like drugs and other reagents (Koudelka et al. 2015).

VNPs are well known for their biodegradability, efficient delivery of drugs to target cells, biocompatibility and ability to cross biological barriers as they are primarily composed of proteins (Guenther et al. 2014). The nucleic acids which code for viral proteins of VNPs can be modified before synthesis (Wirth et al. 2013).

Viruses can specifically interact with proteins, with the ability to hijack intracellular machinery and nucleic acid delivery, due to such properties of viruses it has led to the development of VNPs but ruling out the pathogenic effects caused by host–virus interactions is difficult (Ylä-Herttuala 2012). On the other hand, VLPs (virus-like particles) are the subclass of VNPs that are non-infectious naturally occurring bio-nanoparticles which are biocompatible, replication-deficient and biodegradable with genome free viral protein cages. They also differ in terms of size, self-assembly, morphology and structural organization (Yan et al. 2015). Icosahedral (roughly spherical in appearance) viruses are the most commonly used tool to produce viral protein cages by offering several properties such as high tolerance to pH, chemical modifications, organic solvent mixtures and temperature (Loo et al. 2007). The fully functional plant and bacteriophage-based VNPs cannot infect humans and thus are regarded to be safe (Yildiz et al. 2011).

Nucleic acids are enclosed tightly in a capsid of plant and bacteriophage viruses comprising multiple copies of coat proteins. The capsids are usually icosahedral in nature with flexible filaments or stiff tubes (Sapsford et al. 2013). Both plant and bacteriophage viruses are not usually enveloped with lipid membrane as they must withstand harsh environmental conditions to infect the host cell (Manchester and Singh 2006). For such reasons, icosahedral plant VNPs and VLPs have become a potential platform used for developing bionanoparticles in the fields of nanomedicines, nanobiotechnology and nanoelectronics (Narayanan and Han 2017a, b) (Fig. 6.1).

6.5 Different Types of VNPs/VLPs and their Roles

6.5.1 Plant Viruses

Plant viruses are obligate parasites on hosts and compared to other organisms, viruses are non-cellular. They are non-hazardous to human beings because it is non-infectious and attacks only the plants. Morphologically these plant viruses are either icosahedral or helical (flexuous filaments or rigid rod) (Narayanan and Han 2017a, b) and using the host machinery three proteins are produced such as structural proteins, replication proteins and movement proteins (MPs) to enable the movement through plasmodesmata in the host (Pogue et al. 2002). Viruses rely on insects or dissemination through the environment to infect the host as they are immobilized outside the infected host. The viruses possess single-stranded, positive-sense, linear RNA (ssRNA) as genetic material in Cauliflower mosaic virus, Geminivirus and Dahlia mosaic virus (Narayanan and Han 2017a, b).

6.5.2 Icosahedral Plant VNPs and VLPs

Icosahedral plant VNPs and VLPs are very common structures among viruses predicted by Crick and Watson in 1956 (Caspar 1956). On the surface of the sphere

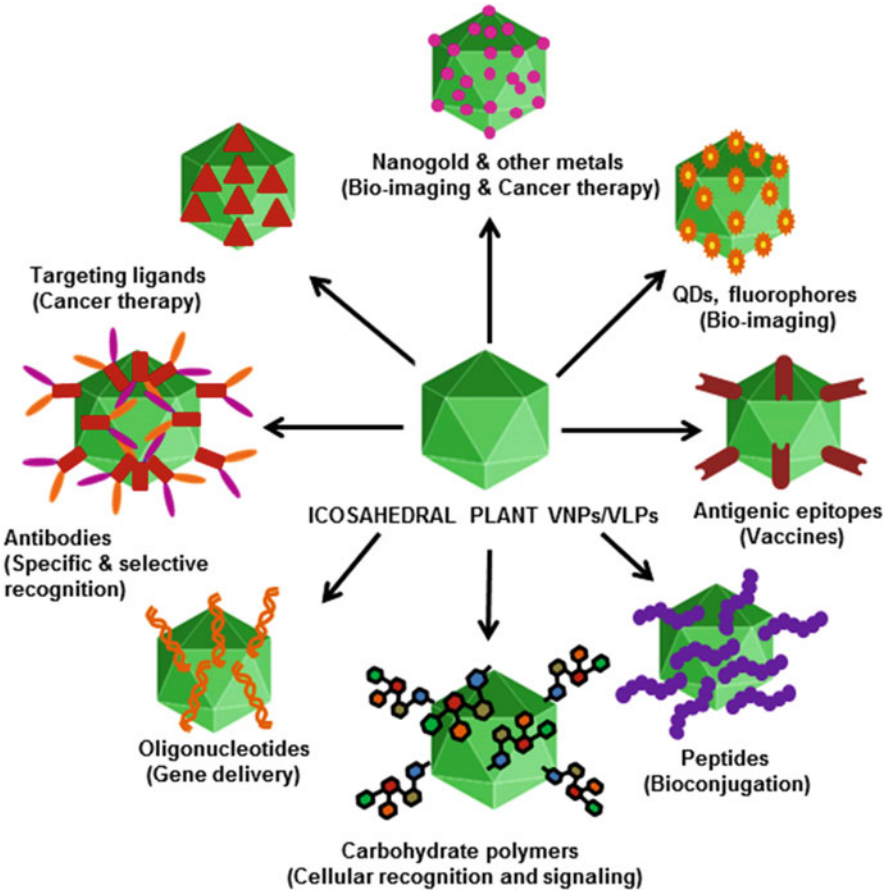

Fig. 6.1 Icosahedral plant VNPs/VLPs nanoparticles (Narayanan and Han 2017a, b)

60 identical subunits are arranged that display two-fold, three-fold, five-fold and icosahedral symmetries as represented in Fig. 6.2 (Finch and Klug 1959). In recent studies, icosahedral plant VNPs and VLPs such as *Carnation mottle virus* (CarMV), *Cowpea mosaic virus* (CPMV), *Maize rayado fino virus* (MRFV), *Sesbania mosaic virus* (SeMV), *Brome mosaic virus* (BMV), *Cowpea chlorotic mottle virus* (CCMV), *Hibiscus chlorotic ringspot virus* (HCRSV), *Red clover necrotic mottle virus* (RCNMV) and *Turnip yellow mosaic virus* (TYMV) have gained a lot of importance in the field of nanotechnology (Caspar and Klug 1962) (Fig. 6.3).

6.5.2.1 Carnation Mottle Virus (CarMV)

It is a pathogenic virus belonging to *Tombusviridae* family, consisting of 4.0 kb genome with positive-strand ssRNA and is of 30 nm (Morris and Carrington 1988). The capsid of CarMV is composed of protein subunits of 37.79 kDa with crown-like hexamers and pentamers on its surface (Forrest 1997). CarMV can be used as VLPs

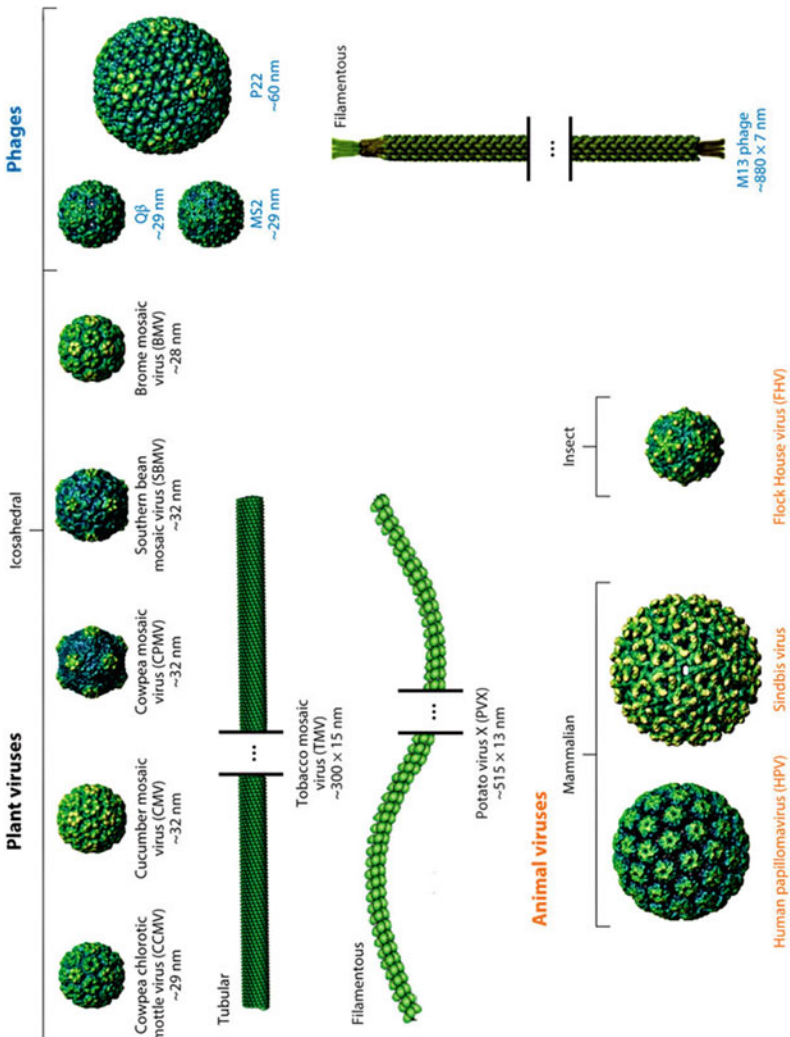

Fig. 6.2 Different plant and animal viruses used as virus-based nanoparticles (Koudelka et al. 2015)

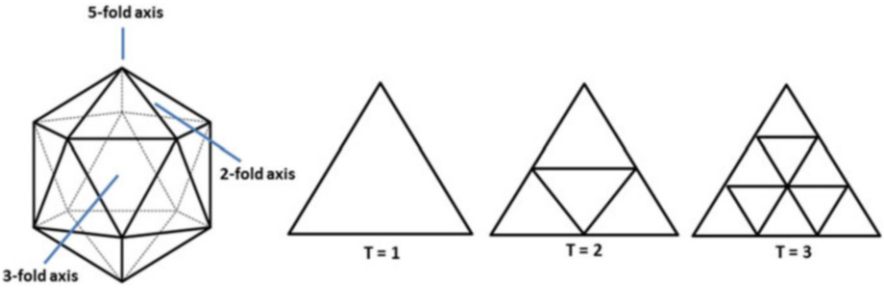

Fig. 6.3 The regular geometry of icosahedron VNPs (Narayanan and Han 2017a, b)

synthesized using heterologous expression to produce organic/inorganic nanostructures (Lvov et al. 1994).

6.5.2.2 Cowpea Mosaic Virus (CPMV)

CPMV is a plant virus that belongs to *Comoviridae* family (Lin and Johnson 2003). It is widely used as nano building blocks to synthesize materials which are 30 nm sizes consisting of non-enveloped, positive-strand ssRNA (Wang et al. 2002). CPMV VNPs do not dissociate and remain stable during purification and diagnostic techniques such as electroelution, ultracentrifugation, agarose electrophoresis and chromatography (Soto et al. 2004).

6.5.2.3 Maize Rayado Fino Virus (MRFV)

It belongs to the maize rayado fino virus group that causes small chlorotic stripes and fine dots along the leaf veins of infected maize (Gamez 1980). It consists of 20–25 nm isometric protein with positive-sense ssRNA containing 180 subunits of protein clustered into 12 pentamers and 20 hexamers (Gamez 1969). MRFV is an excellent nanomaterial candidate with well-defined geometry. The wild-type MRFV-VLPs were mutated to produce Cys-MRFV-VLPs to provide anchors for functional groups (Gamez and Leon 1988). Hence, the MRFV-VLPs can be used in novel bionanomaterial platforms for therapeutic applications (Koenig et al. Koenig 1988).

6.5.2.4 Sesbania Mosaic Virus (SeMV)

Sesbania mosaic virus belonging to *Sobemovirus* genus infects both mono and dicotyledonous plants (Natilla and Hammond 2011). The SeMV forms VLPs ~30 nm by self-assembling of coat proteins (Bhuvaneshwari et al. 1995). These VLPs help in entering mammalian cells to deliver monoclonal antibodies like Herclon (anti-HER2 receptor), D6F10 (anti-abrin) and anti-α-tubulin DM1A by crossing cell membrane (Govind et al. 2012). Thus, SeMV VLPs have become a universal nanocarrier which can be used in delivering antibodies.

6.5.2.5 Brome Mosaic Virus (BMV)

BMV belongs to the group of Bromovirus family with separately encapsulated positive-strand ssRNA (Abraham et al. 2016). It causes white or yellow spots and streaks on leaves by infecting both monocots and dicots (Lane 1981). This RNA icosahedral plant virus coats protein around the functional gold nanoparticles to form VLPs and their properties being similar to the native BMV virus (Noueiry and Ahlquist 2003). These VLPs create functional and optical probes for bioimaging and biosensing applications (Larson et al. 2005).

6.5.2.6 Cowpea Chlorotic Mottle Virus (CCMV)

CCMV is a multi-component plant virus that belongs to Bromoviridae group of family with tripartite genome encapsidated inside the capsid of inner cavity diameter ~ 18 nm and an outer diameter of ~28 nm (Chen et al. 2005). CCMV comprises 180 subunits of coat protein that contains 190 amino acids (Ma et al. 2012). The CCMV VLPs are a multifunctional nano platform used in the effective diagnosis and treatment for several viral and bacterial infections (Tang et al. 2006).

6.5.2.7 Hibiscus Chlorotic Ringspot Virus (HCRSV)

HCRSV is a non-enveloped and monopartite plant virus with a positive-strand ssRNA genome and is a member of *Carmovirus* genus (Brumfield et al. 2004). It mostly infects flowering plants like *Malvaceae*. Certain studies have demonstrated that VLPs derived from HCRSV are used as a transport vehicle for polyacid (PC) drug molecules with a molecular mass of ~13 kDa like polyacrylic acid (PAA) and polystyrene sulfonic acid (PSA) (Ke et al. 2004).

6.5.2.8 Red Clover Necrotic Mottle Virus (RCNMV)

RCNMV is an icosahedral soil-transmitted plant virus which belongs to *Tombusviridae* family *Dianthovirus* genus (Cheng et al. 2009). It is made up of 180 protein subunits with ~17 nm wide inner cavity (Basnayake et al. 2006). This virus consists of two ssRNA encoding capsid protein (CP), virus movement protein (MP) and viral polymerase (Loo et al. 2006). The RCNMV nanoparticles loaded with doxorubicin (DOX) in conjugation with CD46 is used as next-generation imaging and therapeutic delivery agents to HeLa cells (Lockney et al. 2011).

6.5.2.9 Turnip Yellow Mosaic Virus (TYMV)

TYMV is the first isolated, purified and crystallized spherical virus belonging to *Tymoviridae* family and *Tymovirus* genus with 28–30 nm diameter containing coat protein subunits of 20.13 kDa and ssRNA (Gibbs 1999). Because of its empty capsids, it is the most widely used plant virus isolated from host plants (Canady et al. 1996). This bionanoparticle is used for constructing nanomaterials by employing their protein scaffold (Barnhill et al. 2007) (Fig. 6.4).

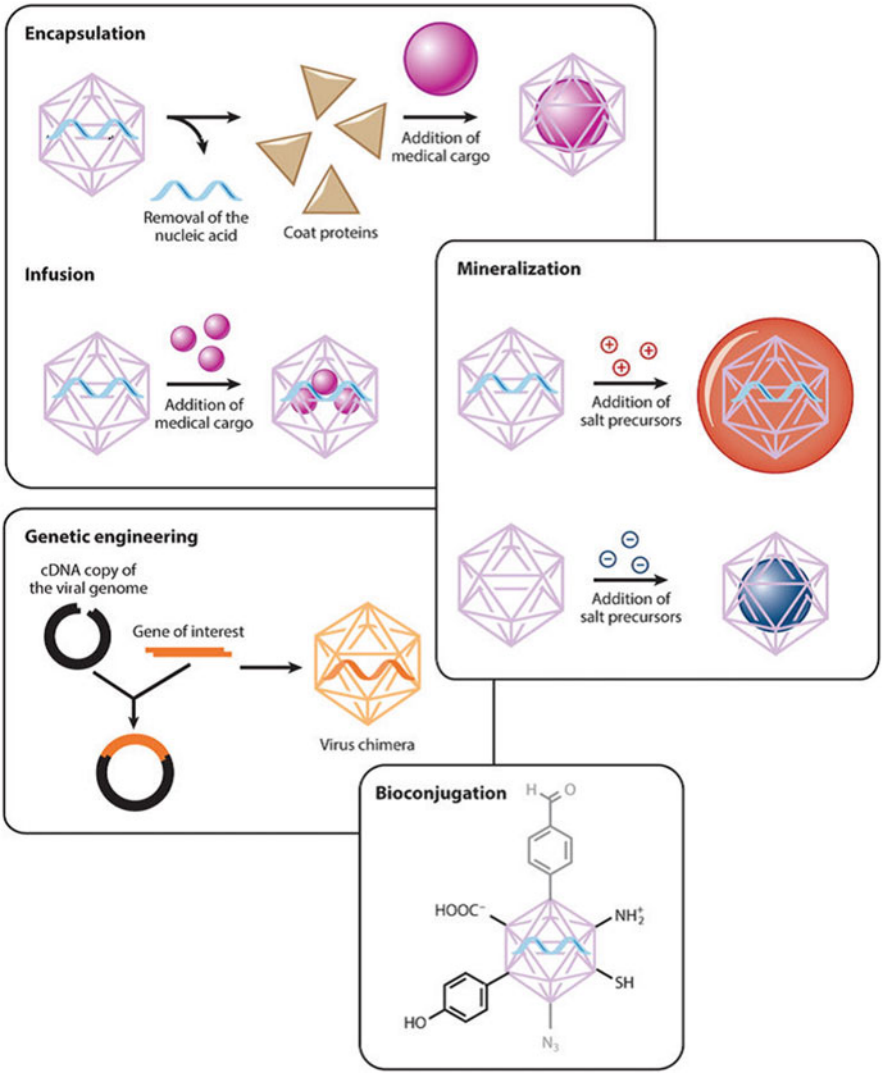

Fig. 6.4 The general modification strategies made while developing functional VNPs (Koudelka et al. 2015)

6.6 Role of VNPs in Therapeutic Interventions

The VNPs can be utilized to target specific cells such as cancer cells and immune system cells. Also, they can be used as vaccines to present antigens in the immune system (Cao et al. 2014). The targeting of VNPs can be achieved through genetic variations or by the chemical addition of molecules which is designed to bind to

specific receptors (Choi et al. 2012). These small molecules can be assigned as ligands that are attached/added to the ends of PEG chains or displayed on the surface of the capsid. For example, EGF, folic acid, RGD peptides and transferrin are used as ligands attached to VNPs (Azizgolshani et al. 2013).

6.7 Role of VNPs as Drug Delivery Agents

VNPs are widely used for delivering conventional drugs, therapeutic agents, genes, photoactive molecules, even viral genomes involved in gene therapy or short interfering RNAs to a particular cell or receptor present on the cell surface (Zeng et al. 2013). The hybrid VNPs carrying metal nanoparticles have been investigated for photothermal therapy (Galaway and Stockley 2013).

6.8 Role of VNPs Against Infectious Diseases

VNPs have achieved great success against various bacterial, fungal and viral infections. The virus–antigen complex given in a single dose induced to act against several viruses has produced a protective immune response (Huang et al. 2011). The VLP vaccine combinations administered into lungs have been demonstrated as a powerful strategy in immunotherapy and vaccine development (Hovlid et al. 2012).

6.9 Conclusion with Future Perspective

The icosahedral plant viruses used to design VNPs and VLPs offer a versatile platform in manipulating the viruses' genome or coat proteins to target the specific sites for therapeutic applications. Icosahedral plant viruses have been used to develop new bionanomaterials to improve their functions in drug delivery to the target, catalysis, biomineralization, cell imaging and other purposes. Also, the development of fabricated nanomaterials has been evaluated only on a few in vivo and in vitro tissue culture systems. VNPs and VLPs have generated great immune responses due to the presence of diverse functions and properties (bioconjugation potentials, capsid sizes and stabilities). However, the use of viruses in nanotechnology as delivery is relatively less explored and more of in vitro evaluations and studies are must for a better understanding of side effects and physiological changes/functions to ensure a safe virus-based therapeutics against various infections/diseases.

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