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Nano-based approach to combat emerging viral (NIPAH virus) infection

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Abstract

Emergence of new virus and their heterogeneity are growing at an alarming rate. Sudden outburst of Nipah virus (NiV) has raised serious question about their instant management using conventional medication and diagnostic measures. A coherent strategy with versatility and comprehensive perspective to confront the rising distress could perhaps be effectuated by implementation of nanotechnology. But in concurrent to resourceful and precise execution of nano-based medication, there is an ultimate need of concrete understanding of the NIV pathogenesis. Moreover, to amplify the effectiveness of nano-based approach in a conquest against NiV, a list of developed nanosystem with antiviral activity is also a prerequisite. Therefore the present review provides a meticulous cognizance of cellular and molecular pathogenesis of NiV. Conventional as well several nano-based diagnosis experimentations against viruses have been discussed. Lastly, potential efficacy of different forms of nano-based systems as convenient means to shield mankind against NiV has also been introduced.

Key words: Nanomedicine; Diagnostics; Nipah virus; Antiviral; Virucide

In view of the adaptable nanotechnological achievements in the past decade, it is certain that, nanoscience is consistently intensifying its horizon across the globe in present and will be in centuries to come. Despite the expendability and plasticity in nanotechnological application, there is a wide gap in intrigue experimental biomedical application and their substantial commercialization. Moreover, their application in biomedical science is still lurking, and should be prioritized in order to bridge the gap. Additionally, the efficacy of conventional therapies is gradually fading away specifically in case of viral infections due to the development of resistance,[1] which could be certainly due to accelerated adaptation in peripheral protein sequence resulting in newfangled viral strain. Van Woensel et al for instance have stated that viruses are the ubiquitous causes of lower respiratory tract disease in babies and youngsters. Later a variation of coronavirus associated with severe acute respiratory syndrome and human metapneumovirus, lately recognized as a new respiratory pathogen over the entire age range has emerged.[2]

And presently Nipah virus (NiV) another respiratory tract infecting virus with an estimated case fatality rate ranging from 40% to 75% is causing serious issue through the world.[3] As indicated by WHO fact-sheet report, lower respiratory infection is ranked 1st and 6th leading cause of mortalities in low income countries and high income countries, respectively, and 4th leading cause of mortalities worldwide.[4] The BSL-4 virus with this high rate of morbidity and mortality, up to some extent has strangled the virologist since past 10 years or so for the exigency for a novel therapeutics.[5] Moreover, the conventional unidirectional serological diagnosis and therapeutics orchestrate numeral shortcomings such as cost deficit, sophisticated preparation procedures, efficient only on post-exposure prophylaxis and reduced amount of the product in consistent with human population and livestock to be vaccinated.[5,6] Majority of the therapeutics developed basically includes monoclonal antibodies targeting viral surface proteins such as F, G or M proteins.[7–9] Further a number of broad spectrum antiviral agents

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such as nucleoside analogues namely rebavirin, GS-441524, GS-5734 (remdesivir), R1479 (balapiravir) and most recent drug favipiravir (T-705; 6-flouro-3-hydroxy-2-pyrazinecarboxamine) which is an inhibitor of viral RNA-dependent RNA polymerase have shown certain degree of efficiency against this virus.[6] But lack of target specific action and probability of host cell toxicity are the major limitations of these synthetic drugs.[10,11] Taking into consideration, the severity of the infection and imperative necessity for a novel multidirectional, target specific and, non-toxic nature; the tunable nanotechnology based approaches seems to be a promising alternative. This technology harbors certain fascinating properties such as superparamagnetism, high surface plasmon resonance, luminescence, photon upconversion, bioavailability, biocompatibility, immunocompatibility / tolerability and biodegradability. The capacity to channelize through translucently breachable blood–brain barrier (BBB) and blood–air barrier (BAB), tunability and targeted control discharge are chief exclusive points which qualify them to be novel candidate for their utilization in biomedical therapy (antiviral).[1,12] The focal point of present review paper includes cellular molecular pathogenesis of NiV infection. Heterogeneous forms of nano-based approaches used as a means of therapy or diagnostic against other viruses, and finally, provised the future possibilities for nanotechnology in concern with the NiV detection and inhibition.

Cellular and molecular changes in NiV infection

In humans, severe acute respiratory sickness and/ or encephalitis can be provoked by a bat-borne zoonotic, paramyxoviral pathogen NiV.[13,14] This negative-sense single-stranded RNA virus belongs to the family *Paramyxoviridae*, genus *Henipavirus* and is closely related to Hendra viruses.[13,15] Like Hendra virus, NiV may also cause fatal pneumonia or an acute respiratory-distress-like syndrome.[13,16] It has been hypothesized that the respiratory disease transmission and pathogenesis are linked to infection of epithelial cells by the NiV at lower respiratory tract at the primary phase.[17] Recently Escaffre et al have described two types of infection in association to NiV, namely NiV-M and NiV-B of human respiratory tract based on differentiated epithelial models of trachea and small airways due to their close anatomical resemblance with epithelial cells of human lower respiratory tract.[13] According to the epidemiological reports NiV-M and NiV-B infections vary greatly in multiple aspects.[18] For instance the percentage of respiratory disease and case fatality rate of NiV-B infections is much higher than NiV-M infection,[19] whereas in NiV-M infection studies show that both human and hamster develop similar pathological changes such as presence of vasculitis, necrosis and inflammation. And certain neuronal changes such as antigen positive neurons, microvascular vasculitis and necrosis in hamster which in case of human progresses to encephalitis.[18,20]

An extracellular pleomorphic bilayer envelope spiked with two glycoproteins namely trimeric fusion protein (F) and tetrameric attachment protein (G) at the exterior surface and matrix proteins (M) at the interior surface, encapsulates NiV virion.[16,21,22] Further, the negative-sense single-stranded RNA, along with three other critically vital proteins namely nucleocapsid proteins (N), phosphoproteins (P) and large polymerase proteins (L) is contained within the virion made up of linear ribonucleoprotein (RNP).[21] Binding of viral G to the conserved receptors ephrin-B2 and ephrin-B3 marks the beginning of host cell and viral membrane fusion mediated by prior complex formation of viral G and F protein.[22]

From an evolutionary point of view it could be assumed that, during initial epidemic period of NiV, it has developed a specific mechanism to evade innate immune action of Pterous bat. The evolutionary conservation of this particular immune mechanism within all mammals has made NiV a broad spectrum virus against them.[23,24] The virus blocks the elicitation of innate and adaptive immune response by inhibiting synthesis of cytokines, interferon type I (IFN α/β).[25] The IFN α/β in case of viral infection, activate pathways within the viral infected cell which degrades viral mRNA and inhibits viral protein synthesis, hence hindering the rate of viral replication inside the infected cell and subsequently lowering viral load.[26,27] Song et al describe that IFN α/β can act as both autocrine and paracrine signaling molecule, where IFN α and IFN β are producers.[28] Therefore it could be said that inhibition of IFN α/β synthesis may severely affect both autocrine and paracrine activity, which may further lead to impaired immune response (Barth et al 2016).[29] The cellular and molecular changes during and post NiV infection starting right from NiV attachment and invasive pathogenesis leading to multiple organ failure have been explained in the Figures 1, 2, and 3. Understanding these changes will significantly improve present knowledge essential for developing and evaluating therapeutics against NiV.

Cellular changes in detail

NiV infection in the primary stage is restricted within the epithelial cells of host's upper and lower respiratory tract.[17] And NiV-F and G necessary for its fusion with the bipolar epithelial cell are at the epical side during initial infection period.[30] Here, G protein induced virus-cell fusion begins with the interaction between tetrameric G-protein head region and Ephrin B2/B3 on the epithelial cell. Simultaneously C-terminus region of G interacts with NiV-F protein, whose two hydrophobic N-terminal alpha helical heptad repeat domains (HR-1, HR-2) form a six-helical bundle structure that transverses through cell membrane of the host initiating pH independent class I type membrane fusion (Figure 2).[31–33] After the viral entrance through apical region, it replicates within the cell, sorting of proteins such as F and G on infected cell surface, is further destined for infection could also be regarded as markers.[32,33] Unlike G, precursor form of F protein, F_0 get lodged within the membrane and activated through endocytosis followed by cathepsin L mediated endosomal degradation to form mature $F_{1/2}$ (Cifuentes-Muñoz et al 2017).[34]

The local infection starts with the lateral spreading of virus occurred by basolaterally expressed protein (G, F) mediated cell–cell merging that gives rise to a consequential configuration of syncytia which are pathological hallmarks for NiV infection of epithelial cells. This has been seen at 14 h of post infection (p.i) which is the earliest time needed for protein detection in *in vivo* study.[30] The cell–cell fusion can be between epithelial cell and

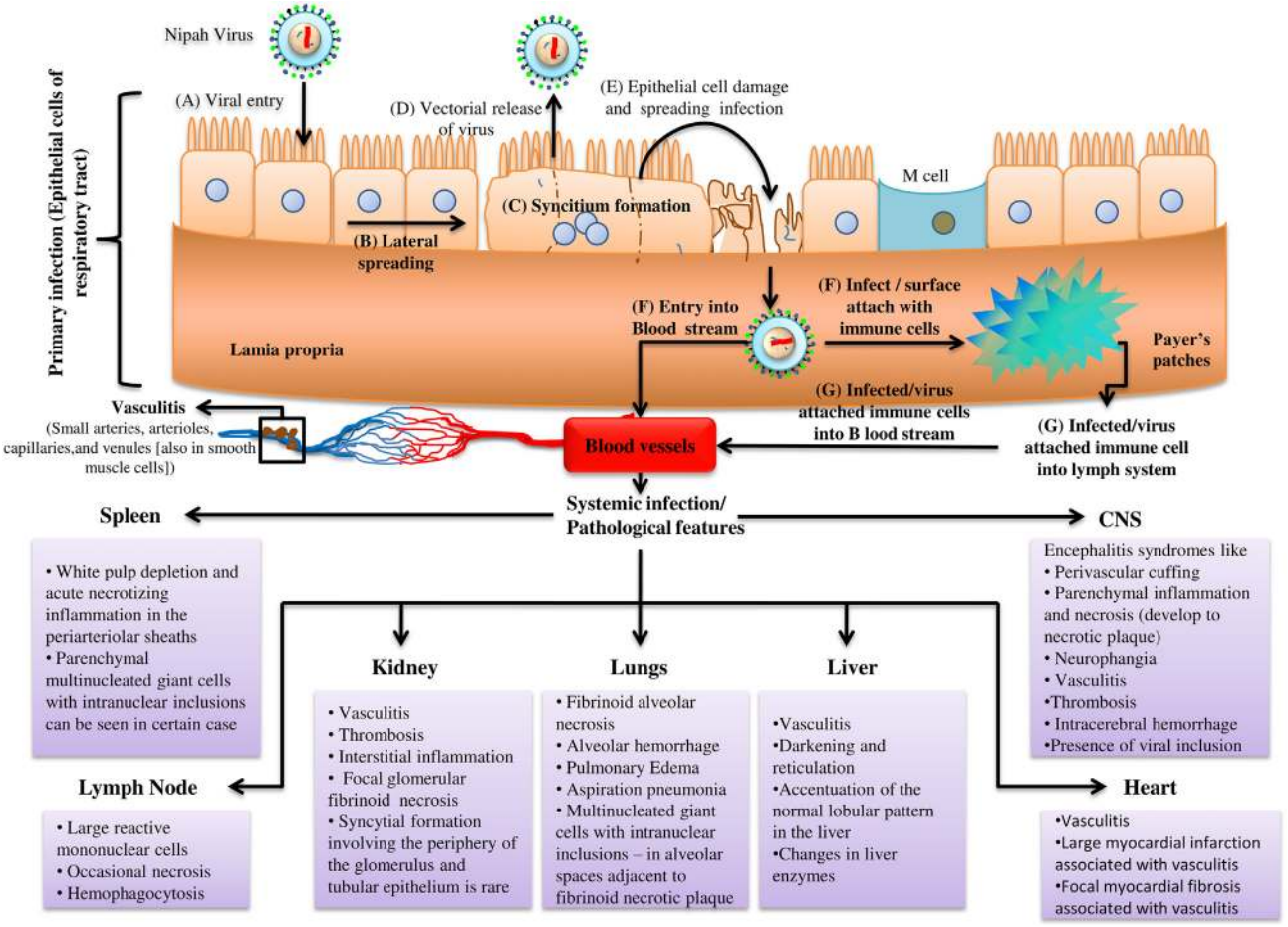

Figure 1. General representation of Nipah virus infection and pathological features.

stromal cell, heterologous fusion or between two epithelial cells, homologous fusion (Figure 2).[35] After disrupting monolayer epithelial cells the newly formed virus buds out from the apical side of the multinucleated epithelial cells. This vectorial release of virus is confirmed by the preferential localization of viral F, G and necessary for budding, M protein on the apical side (88%, 86%, 95% of total G, F and M respectively), which can be seen after 24 h p.i.[30] The released virus can either infect the immune cells of secondary lymphoid organs (Mucosal Associated Lymphoid Tissues [MALT], Gut Associated Lymphoid Tissues [GALT]) which are present just under the layer of mucosal epithelia cells. They might also contribute towards impairing antiviral activity by inhibiting synthesis of IFN α/β and reducing expression of cytokines involved in inflammatory process like CCL4, CCL5 and TNF-α. Again IFN induced antiviral genes such as MxA, ISG54 and repression of viral antigen presenting class-I MHC molecules might be another output (Figure 3, *D*).[36,37] The unconstrained virus could infiltrate the blood stream attaching to leukocytes such as macrophages, dendritic cells, $CD6^{+}CD8^{+}$ T cells, NK cells causing systemic infection and multiple organ failure in detailed brain, lungs, liver, heart, kidney and spleen ((Figure 1).[38] Histopathological lesions are necrosis and vasculitis in non-CNS organs. In case of CNS organs, perivascular cuffing, parenchymal inflammation and neurophangia are most common clinical signs, but are not exclusive for NiV infection and may also be detected in other acute viral encephalitis (Figure 1).[36,39]

Molecular changes in detail

With mortality rate of 40%-75% and an outrageous range of host, this atrocious human pathogen also infects neurons apart from endothelial cells.[40] In general, paramyxoviruses evade host immune system either by suppressing its detection through lowering the expression of pattern recognition receptors (PRRS) or by impeding the secretion of antiviral signaling molecules.[37] In case of NiV, viral P gene encoded post-transcriptionally modified phosphoproteins antagonize the secretion of IFN α/β and elicit antiviral activity at both cytoplasm and nucleolus.[37,41] The various proteins encoded by P genes are P, V, W and C with 407 amino acid length similarity at their N terminal end.[41] V and W mRNAs are frame shift mutates P mRNA at a particular conservation site, with insertion of one and two G nucleotide respectively whereas the C mRNA is nested within each P, V, W mRNA.[37,42]

The degree of immune response inhibition by each proteins P, V, W varies with P being less than V and W with highest inhibitory activity.[37,43] The elevated inhibition by W protein might be because of its nuclear localization ability.[41,47] This allows it to suppress expression of IFN α/β and antiviral gene at gene expression level

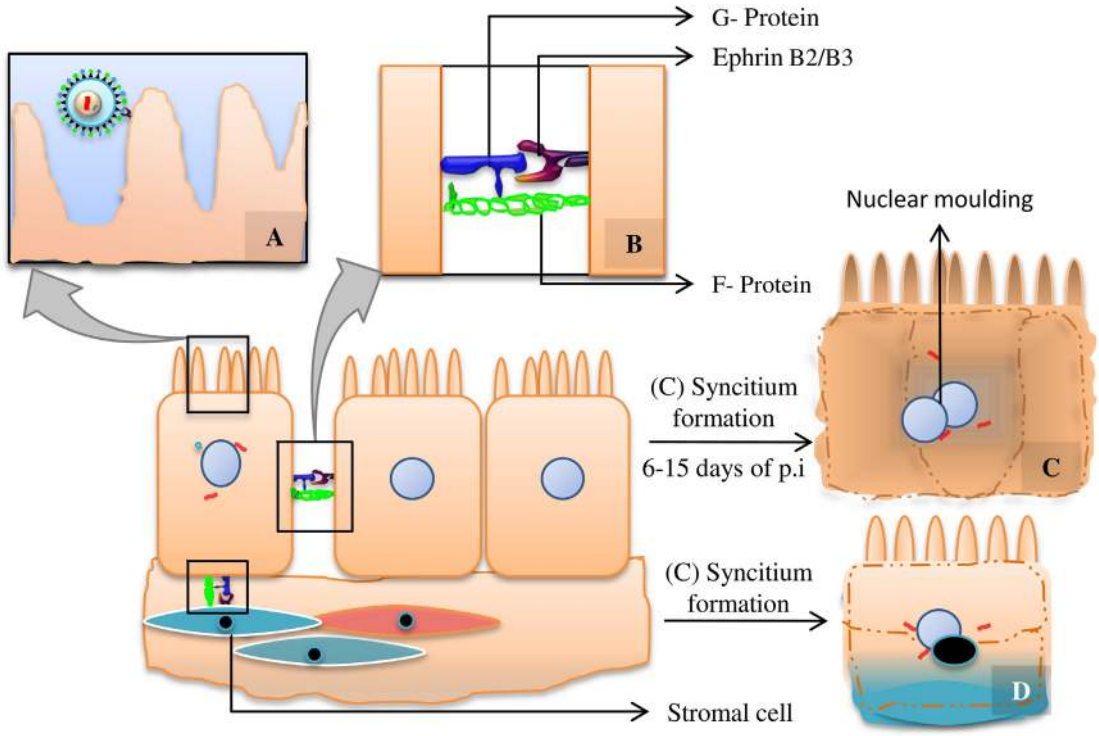

Figure 2. **(A)** Viral attachment *via* interaction between G protein and cell surface receptor Ephrin B2/B3, **(B)** Interaction between G protein with receptor Ephrin B2/B3 and F protein, **(C)** Multinucleated giant endothelial cells due to homologous fusion of epithelial cells, **(D)** Multinucleated giant cell formation due to heterologous fusion of infected epithelial cell and stromal cell. The concept was derived from Wynne et al (2016).[35]

and confirms lower probability of eliciting antiviral activity, than as happens in case of cytoplasmic inhibition by V proteins.[37,44,45] The cytoplasmic inhibitory activity of V proteins is achieved by its binding with dsRNA responding RLR receptor MAD5 hence down regulating the activation of TBK1 and IKKε which activates IFN α/β gene transcription factor IRF3 and IRF7 (Figure 3, *D.1*). This suppression of IFN β gene expression can be overcome by another TLR3 mediated alternative pathway by producing more amount of adaptor protein IRF1 which activates TBK1 (Figure 3, *B.1*).[37]

Further, attenuation of IFNs responded antiviral activity of an infected cell can be discussed considering the JACK/STAT signaling pathway necessary for transcriptional level activation of antiviral genes.[37,46,47] Responding to IFN α/β and γ, the interactions between phosphorylated STAT1 and STAT2 form their hetero or homodimer (by STAT1 only) respectively (Figure 3, *D.2*). These dimmers are precursor molecule of IFN α/β gene transcription factor.[48,49] Hence inhibitions of STAT1 and STAT2 interaction result in the absence of antiviral activity. Protein P, V and W interact with STAT1 with their amino terminal domain while only protein V can interact with STAT2.[37] Re-localization of non-phosphorylated STAT1 from its typically cytoplasmic location by protein W also makes its unavailability for STAT dimer formation and hence inhibition of IFN α/β gene transcription factor formation (Figure 3, *D.3*).[37] The viral C protein which is predominantly localized in cytoplasm and partly in nucleus is responsible for enveloped viral budding and release by recruiting host ESCRT pathway.[50,51] The C terminal domain of NiV-C, as it possesses homology in its sequence with host protein Vps28 could interact directly with TSG 101, an adaptor molecule between ESCRT I and ESCRT II. However, the reciprocal action among ESCRT I–NiV C and ESCRT II is not fully understood.[50] But it has been speculated that viral C protein interacts with M protein present in the inner leaflet of plasma membrane and thereby direct vectorial release of virus particles (Figure 3, *B.2*).[50,52]

Therapeutics against NiV

Guillaume et al developed a potent Vaccinia virus (VV) mediated VV-NiV-F and VV-NiV-G recombinant vaccines in a hamster model.[53] They found immunized organism shows complete immunity against NiV induced fatal encephalitis by producing neutralizing antibodies whereas it occurs within 7 to 10 days after intraperitoneal inoculation of NiV isolates. The low neutralizing ability of the produced antibodies as confirmed by the increasing level of serum antibodies gives an idea of studying effect of passive immunization against NiV. Intraperitoneal injection of polyclonal as well as monoclonal (mAb) anti-F and anti-G, separately shows that anti-F and anti-G mAb are more efficient in neutralizing NiV viral infection as compared to polyclonal Ab, with anti-F mAb having high degree of antiviral activity than anti-G mAb.[54] A recent hit on broad-spectrum small molecule antiviral purine analogue previously mentioned Favipiravir (T-705) which inhibits NIV and HeV replication *in vitro* with a minimal cytotoxic effect of highest concentration tested, having a CC_{50} value of >1000 μl (as observed in Hamster model) has provided a way to fight against the cytopathic effect of deadly NiV, HeV like paramyxoviruses.[6]

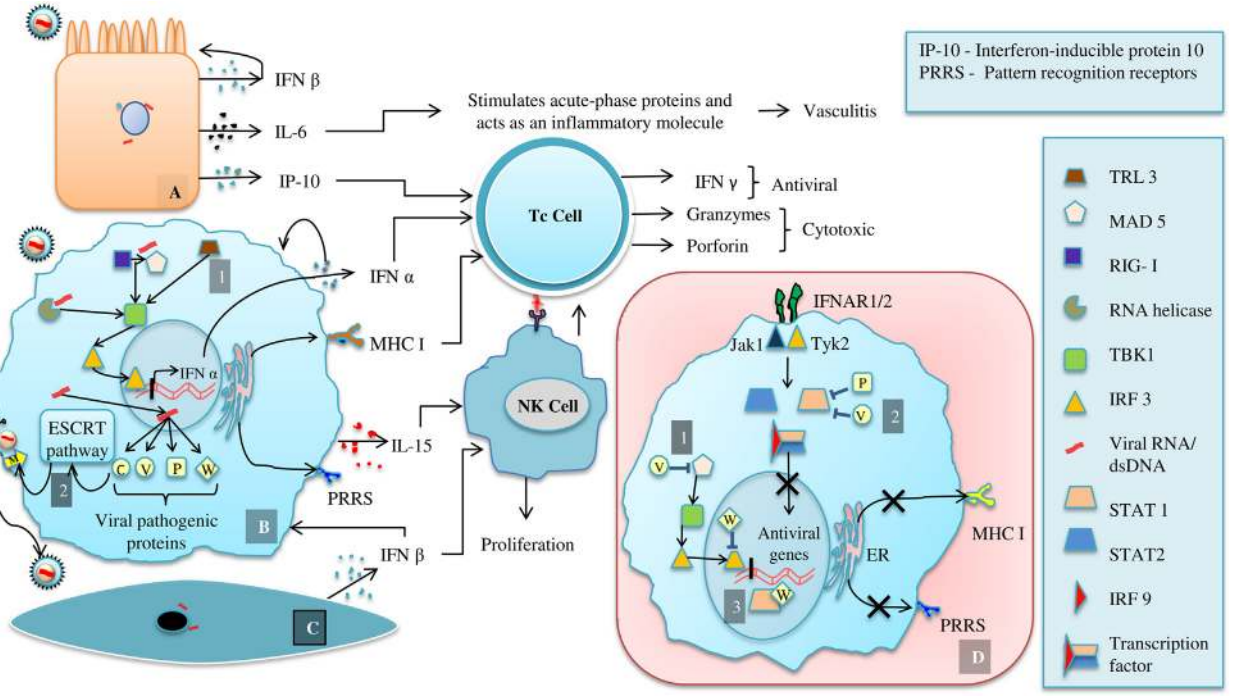

Figure 3. Immune response to viral infection **(A)** Infected endothelial cell, **(B)** Infected Macrophage, **(C)** Infected stromal cell, **(D)** Schematic representation of immune suppressing mechanism of NiV proteins. The concept was taken from Prescott et al (2012)[193]; de Weerd and Nguyen (2012)[194]; Welsh et al (2012)[195]; Au-Yeung et al (2013)[46]; Basler (2012)[37]; Tanguy et al (2017).[47]

It is not late when one day due to the consistent change in their genome these pathogens would get resistance to the conventional drugs which are unidirectional and have no specific targeted. These limitations could be ameliorated by finding a novel therapy with multiple pathways and biomarkers for the target oriented action. For example in NiV depletion of NiV-C recruited ESCRT pathway mechanism and deposition of other viral proteins (N, M, F, G and L) results in cytoplasmic budding and impaired release of virus from the infected cell.[50,51] There are numerous intermediate molecules associated with ESCRT pathway; targeting conserved intermediate molecules or their precursor might be a novel strategy to eliminate the virus. Further the ligands or receptors with a binding efficiency with viral intermediate molecules could be further enhanced by their amalgamation with nanotechnology.[1]

Nano-based antiviral therapy

The versatile mode of viral inhibition primarily depends on the type and form of NPs used. Therefore to understand the antiviral activity of NPs a general overview about different types and forms of NPs/ nano-based systems is a necessity. Nano-based antiviral agents extend from simple inorganic NPs to complex organic and hybrid nanosystems. Metallic NPs (MNPs) and NCs in the form of nanospheres, nanocapsule and nanocage could be categorized under inorganic NPs (INPs). Organic NPs (ONPs) include nanocapsule as in the form of NCs, primarily differentiated based on chemical composition. Hybrid nanosystems are standardized amalgamation of inorganic–organic, inorganic–inorganic (nanocomposites), and organic–organic nanoparticulated systems (lipid–polymer hybrid NPs) engineered based on specific requirement or use at targeted site.[55]

Inorganic nanoparticles

The other properties such as luminescence, tunable size, shape, composition and large surface-to volume ratio have invigorated the importance of INPs in biomedical field for multifarious application. Among these applications the ability of these INPs to expose their multiple surface binding sites as well as control their *in vivo* behavioral properties is widely explored.[12] This phenomenon of multiple interactions at a specific site with the targeted molecule further contributes towards the utilization of these NPs in active targeted imaging for diagnostics, hyperthermia therapy and medication.[56] The most common iNPs are MNPs such as silver (Ag), gold (Au), iron oxide (FeO) and NCs of silica, titanium, carbon *etc.*

Silver nanoparticles (AgNPs)

Silver nanoparticles (AgNPs) are most keenly researched nano-based approach to treat viral infection or their detection. Numerous evaluations of the NPs to develop a novel strategy to either annihilate or ameliorate the severity of infection had already been carried out. To date the efficiency of AgNPs as an antiviral has been checked in Human immunodeficiency virus (HIV)-1, Herpes simplex virus (HSV)-1, 2, 3, Feline Calicivirus, Poliovirus type-1, Peste des petits ruminants virus (PPRV), Murine norovirus-1, Avian

Table 1
Inorganic Nano-Based Approach for Viral Diagnosis and Inhibition.

Nanoparticles	Virus	Model Organism	Mechanism of Antiviral Action	Purpose	References
Silver (Ag)					
AgNPs	Human immunodeficiency virus (HIV)-1	HeLa-CD4-LTR-β-gal cells, MT-2 cells, human PBMC	Interaction with gp120 in order to prohibits CD4-based virion binding, blending, and pathogenesis	Viral entry inhibition and as virucidal agent	Lara et al (2010)[57]
	Coxsackie virus B3 Nancy strain	Vero cells	Fusion inhibition between virus and cells	Viral entry inhibition	Salem et al (2012)[138]
	Herpes Simplex Virus (HSV)-1, 2, 3	Vero cells	Binds with viral envelop or its protein	Viral entry inhibition and as virucidal agent	Gaikwad et al (2013)[139]
	HSV-2	Vero cells	Bonding with sulfhydryl groups on membrane glycoprotein of virus	Prevents viral internalization	Hu et al (2014)[59]
	Peste des petits ruminants (PPR) virus	Vero cells	Interaction with the virion surface as well with the virion core	Impaired viral replication during viral entry	Khandelwal et al (2014)[60]
	Avian influenza A virus, subtype H7N3	Vero cells	Blocking HA function and anomalous interaction viral replication pathway	Viral entry inhibition and possible deformation of viral replication	Fatima et al (2016)[140]
AgNPs immobilized on textile fabrics	Influenza A and Feline Calicivirus		Interaction with viral envelope	Impaired viral envelope resulting viral inhibition	Seino et al (2016)[141]
AgNPs	Poliovirus type-1	Human Rhabdomyosarcoma	Interaction with viral protein resulting in impaired interaction with the host cell	Inhibition of viral internalization	Huy et al (2017)[142]
	Murine norovirus-1	RAW 264.7 cells		Virucidal agent	Castro-Mayorgaa et al (2017)[143]
	Feline calicivirus	CRFK cells			
	Infectious Bursal Disease (IBD) virus	Embryonated chicken eggs	Interaction with viral envelope	Viral inhibition	Pangestika et al (2017)[144]
	S. cerevisiae dsRNA viruses	HeLa cells, NIH/3 T3 cells	Interaction with viral genome and inhibition of viral replication	Virucidal agent	Rónavári et al (2017)[61]
Titanium (Ti)					
Nanoparticles	**Biomolecule Loaded/ Conjugated**	**Virus**	**Model Organism**	**Mechanism of Antiviral action**	**Purpose**	**References**
TiO_2 NPs	-	MS2, PRD1, ΦX174, Fr	-	Interaction with viral capsid protein (alanine, glycine, and proline residues)	Photocatalytic inactivation of phages	Gerrity et al (2008)[74]
TiO_2 NPs	-	H3N2	-	Direct contact with virus	Virucidal agent	Mazurkova et al (2010)[75]
TiO_2 particles	-	MS2, ΦX174, PR772	-	Interaction with viral capsid/ surface proteins	Photocatalytic inactivation of phages	Misstear and Gill (2012)[145]
TiO2~DNA nanocomposites	DNA	H1N1, H5N1, and H3N2	MDCK cells	Targeted binding to conservative regions in the viral genome and inhibition of viral reproduction	Viral inhibition	Levina et al (2015)[146]
TiO_2 NPs	-	MS2	-	Interaction with viral surface proteins	Inactivation of phages	Syngouna and Chrysikopoulos (2017)[76]
Gold NPs						
Au NPs	-	HIV-1	HeLa-CD4-LTR-B-gal cell	Binding with viral gp120 and prevent CD4 attachment	Inhibition of viral entry	Vijayakumar and Ganesan (2012)[62]
Au NPs	-	Foot- and- mouth diseases	BHK-21	Arrests viral replication along	Virucidal agent	Hafashjani et al (2016)[63]

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Table 1 (*continued*)

Nanoparticles	Virus		Model Organism	Mechanism of Antiviral Action	Purpose	References
		virus (FMDV)		with transcription		
Au NPs	-	Influenza virus A (H1N1, H3N2)		Peroxidase-mimic enzymatic reaction	Viral detection	Ahmed et al (2016)[64]
Gold NPs (AuNPs)	Synthetic peptide resembling FMDV protein	FMDV	BALB/c mice	Antibody mediated immunity	Size dependent immunization	Chen et al (2010)[147]
AuNPs	DNAzyme (DDZ)	Dengue virus (DENV)	*Aedes albopictus* C6/36 cells	DDZ activation mediated salt-induced aggregation of AuNP	Viral detection	Carter et al (2013)[148]
AuNPs	Anti-A/Udorn/307/1972 antibody	H3N2	-	Nanodot deposition on the periphery of viral surface	Viral detection	Gopinath et al (2013)[149]
AuNPs	Small interfering RNA	DENV	Vero cells	Inhibiting viral replication and infectious virion release	Efficient delivery and viral inhibition	Paul et al (2014)[150]
AuNPs	Viral matrix 2 protein (M2e)	H1N1	BALB/c female mice	Antibody mediated CpG (cytosine-guanine rich oligonucleotide) immunity	Influenza vaccine	Tao et al (2014)[151]
AuNPs	Monoclonal anti-hemagglutinin antibody (mAb)	H3N2	-	Viral surface deposition of NPs- mAb	Colorimetric immunosensor viral detection	Liu et al (2015)[152]
AuNPs	Recombinant trimetric A/Aichi/2/68 (H3N2), Hemagglutinin (HA) and TLR5 agonist flagellin (FliC)	H3N2	Female BALB/c mice, HEK 293 T cells, JAWS II cells	Antigen-specific T cell-mediated immunity	Improved immunization	Wang et al (2017)[153]
Unmodified AuNPs	Charge-neutral peptide nucleic acids (PNA)	Bovine Viral Diarrhea virus (BVDV)	-	BVDV-RNA based PNA induced aggregation of the AuNPs	Colorimetric based viral detection assay	Askaravi et al (2017)[154]
AuNPs	Viral consensus matrix 2 peptide (M2e)	H1N1, H3N2, H5N1	BALB/c mice,	Strong humoral and cellular response	Universal influenza A vaccine	Tao et al (2017)[155]
AuNPs	Recombinant viral Hemagglutinin (HA) Toll- like receptor 5 (TLR5) agonist flagellin (FliC)	H3N2	BALB/c mice	Higher level of viral specific IgA and IgG, promotion of antigen-specific interferon-γ (IFN-γ)-secretion, $CD4^+$ cell proliferation and induced activation of strong effector $CD8^+$ T cell	Enhanced mucosal cellular immunity	Wang et al (2018)[156]
Iron (Fe)						
Fe_3O_4 NPs	Antibodies against viral HA protein, capped with methoxy-terminated ethylene glycol	H5N2	-	-	Rapid and specific viral detection	Chou et al (2011)[69]
Magnetic iron oxide NPs (γ-Fe2O3, α-FeOOH)	-	Bacteriophage MS2	-		Virus removal	Park et al (2014)[157]
Magnetic NPs	Aptamers specific for binding to the E1E2 glycoprotein of HCV	HCV	-	Aptamer targeted viral envelope protein binding	Efficient removal of viral particles	Delaviz et al (2015)[71]
Iron Oxide NPs	Anti-zika envelope protein (ZENV) antibody, AXL receptor, HSP70 receptor, TIM-1 receptor	Zika virus	-	AXL has the highest affinity for virus; HSP70, TIM-1, and phosphatidylserine might also play active roles in viral tropism	Timely and sensitive analysis of host pathogen interaction	Shelby et al (2017)[66]
Silica (Si) based NPs						
SiNPs	Biotin derivative dCTP bases	Human Papilloma Virus	-	Nucleic acid hybridization	Viral detection	Enrichi et al (2010)[85]
Hollow Mesoporous SiNPs	Porcine circovirus type 2-ORF2 protein	Porcine circovirus	BALB/c mice	Stimulate antibody and cell-mediated immune responses	Immunization against the virus	Guo et al (2012)[84]

SiNPs	Hepatitis B virus core (HBc) protein	Hepatitis B virus	BALB/c mice	Activates antibody and cell-mediated immune responses	Silica-adjuvant vaccines against the virus	Skrastina et al (2014)[158]
Mesoporous SiNPs	Glycosaminoglycans	HSV-1, 2	Vero cells	Inhibition of viral attachment to the host cell	Inhibition of viral entry	Lee et al (2016)[159]
Mesoporous SiNPs	Alkoxysilane (Hydrophobic, Hydrophilic)	GFP lentiviral vector harboring a vesicular stomatitis virus G glycoprotein, GFP lentivirus harboring an HIV-gp120 derived envelope	HEK293T cells	Attachment with the viral envelope protein	Immobilization of the virus resulting in inhibition of viral entry	de Souza et al (2016)[82]
Europium doped fluorescent SiNPs	Streptavidin	HIV (HIV-1 p24 antigen)	-	Binding to HIV-1 p24 antigen	Fluorescence based sandwich immunoassay detection of virus	Chunduri et al (2017)[83]
Carbon (C) based NPs						
Fullerenes						
Glycofullerenes	Carbohydrate moieties (Mannose)	Pseudotyped viral particles (Ebola virus)	Jurkat cells	Blocking the dendritic cell–specific intercellular adhesion molecule-3–grabbing non-integrin receptor (DC-SIGN)	Inhibition of viral attachment leading to inhibited viral entry	Luczkowiak et al (2013)[88]
Fullerenes	Maximin H5 peptide	Bacteriophage λ	-	Attachment with viral capsid or envelope and inhibiting viral entry / disruption of viral lipid layer lyses if of virion / inhibition of viral replication	Virucidal agent	Dostalova et al (2016)[90]
Fullerene derivatives 1, 2, 3 and 4		HIV-1 (Wild type)	SupT1 cells	Inhibition of Gag processing through a protease-independent mechanism	Blocks viral maturation	Martinez et al (2016)[160]
		HIV-1 (Resistant virus)	SupT1 cells	Impairing viral polyprotein processing through a protease-independent mechanism		
Globular multivalentglyco fullerenes (Tridecafullerene)	Carbohydrate moieties (Mannose)	Pseudotyped viral particles (Ebola virus)	Jurkat cells	Blocking of DC-SIGN	Inhibition of viral attachment leading to inhibited viral entry	Muñoz et al (2016)[161]
Glycodendrofullerenes	Carbohydrate moieties (Mannose, Galactose)	Pseudotyped viral particles (Ebola virus glycoprotein)	Jurkat cells	Blocking of DC-SIGN	Inhibition of viral attachment leading to inhibited viral entry	Muñoz et al (2017)[162]
Carbon nano-tubes						
Acid-functionalized multi-walled carbon nanotubes (MWNTs)	Protoporphyrin IX (PPIX)	H3N2	NCIH292	Photoactivated PPIX mediated interaction with viral envelope and its destabilization	Inactivates the virus	Banerjee et al (2012)[87]

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Table 1 (*continued*)

Nanoparticles	Virus		Model Organism	Mechanism of Antiviral Action	Purpose	References
Functionalized single-walled carbon nanotubes (SWCNTs)	Recombinant VP7 subunit vaccine	Grass carp reovirus (GCRV)	Grass carp	VP7 subunit vaccine mediated immunity against virus	Immunization	Zhu et al (2014)[89]
Ammonium-functionalized SWCNT	pEGFP-*vp5*vaccine	GCRV	Grass carp	Activation of pro-inflammatory factors (IL-1β, TNF-α) and DNA vaccine mediated immunity against virus	Immunization	Wang et al (2015)[163]
SWCNT	Ribavirin	GCRV	Grass carp	Affects viral transcription	Viral inhibition	Zhu et al (2015)[135]
SWCNT	pcDNA-*vp7*	GCRV	Grass carp	Activation of pro-inflammatory factors (IL-1β, TNF-α) and DNA vaccine mediated immunity against virus	Immunization	Zhu et al (2015)[165]
Carbon nanohorns						
Carbon nanohorns	T7 tag antibody	T7 bacteriophage		Attachment to the viral surface and photo-exothermic destruction	Viral elimination	Miyako et al (2008)[166]
Graphene						
Graphene oxide (GO)	Cationic polymer PDDA, nonionic PVP	Pseudorabies Virus, porcine epidemic diarrhea virus	Vero cells, PK-15 cells	Negatively charged GO interacts with viruses prior to viral entry resulting in virus damage due to its single-layer structure and sharp edge	Viral inhibition	Ye et al (2015)[167]
β-cyclodextrin (CD) functionalized-GO	Curcumin	Respiratory syncytial virus (RSV)	HEp-2 cells	The NP mimics heparin sulfate on the host cell surface and inhibits viral attachment	Viral inhibition	Yang et al (2017)[91]
Quantum dots						
Quantum dots	Streptavidin	RSV	HEp-2 cells	Streptavidin interact with G-protein in virus	Viral detection	Bentzen et al (2005)[168]
Carbon dots						
Carbon dots	-	Pseudorabies virus, porcine reproductive and respiratory syndrome virus	MARC-145 cells, PK-15 cells	Inhibits viral replication by inducing type I interferon production	Viral inhibition	Du et al (2016)[169]
Carbon dots	-	Human NoV GI.1 virus-like-particles (VLPs), GII.4 VLPs	-	Inhibits viral attachment to histo-blood group antigens (HBGA) receptors of host cell	Viral inhibition	Dong et al (2017)[170]

Table 2
Organic Nano-Based Approach for Viral Diagnosis and Inhibition.

Nanoparticles	Bioactive Compound	Virus	Model Organism	Mechanistic Mode of Action	Purpose	References
Polymeric NPs						
Poly (D,L-lactide-co-glycolide) NPs	Hemagglutinin (HA)	H1N1	-	Unaltered molecular weight and antigenicity	Future viral detection and immunization	Lemoine and Préat (1998)[100]
	p-HA	H1N1	Female Balb/c mice	Enhanced antigen particulate hydrophobicity	Immunization	Lemoine et al (1999)[171]
N-Trimethyl chitosan (TMC) NPs	Monovalent influenza (H3N2) subunit vaccine	H3N2	Female C57BL/6 (B6) mice	Enhanced systemic and local immune responses	Effective carrier for nasal delivery of influenza antigens	Amidi et al (2007)[172]
Polystyrene NPs	Mannose-specific lectin concanavalin A	HIV-1	-	Mannose-specific lectin concanavalin A and viral gp120 antigen binding	Mucosal vaccine	Wang et al (2007)[173]
Poly (ε- caprolactone) (PCL) NPs coated with poly(ethylene oxide) (PEO)	Dapivirine	HIV-1	CaSki, Caco-2, VK2/E6E7, TZM-bl cells, pig tissue models of vaginal and rectal mucosa	NPs differently modulated permeability and monolayer/tissue retention kinetics of dapivirine	Vaccine adjuvant	das Neves et al (2013)[102]
Chitosan-PEG NPs Poly (D,L-lactic-co-glycolic acid)-b-poly(ethylene glycol) NPs	Rabies whole attenuated viral antigen	Rabies virus	-	Effective and sustained elicitor of immune system with negligible toxicity	Immunization	Nivedh et al (2016)[101]
Methoxy-poly (ethylene glycol) 3000-poly (lactic acid) 34,000 (MePEG-PLA) NPs Maleimide-poly (ethylene glycol) 3400-poly (lactic acid) (Mal-PEG–PLA) NPs	Nonnucleoside reverse transcriptase inhibitor (NNRTI) DAAN-14f (14f), surface-conjugated with HIV-1 fusion inhibitor T1144	laboratory adapted HIV-1 strains, primary HIV-1 isolates, NNRTI resistant HIV-1 strains,T1144-resistant HIV-1strains	Sprague–Dawley rats	Viral entry inhibition by inhibition viral attachment, if compromised breach then inhibition of transcriptase	Viral inhibition	Li et al (2016)[174]
Poly(aniline-co-pyrrole) polymerized nanoregulators (PASomes)	-	Influenza A virus (H1N1, H3N2, and H9N2)	MDCK cells	ROS mediated viral replication inhibition and cell death	Antiviral agent	Kim et al (2017)[175]
Amide functionalised alginate NPs	Zidovudine	HIV	C6 glioma cells, neuro 2a cell lines	Inhibition of viral transcriptase	Effective antiviral delivery	Joshy et al (2017)[176]
Double-layered protein (Core Matrix protein 2 [M2e] coated with headless Hemagglutinin [HA]) NPs	-	Influenza A virus	BALB/c mice	Viral inhibition by antibody-dependent cell-mediated cytotoxicity or Antibody-dependent cellular phagocytosis and	Universal influenza vaccine with long lasting immunity	Deng et al (2018)[104]
Double-layered polypeptide (nucleoprotein epitopes at core coated with matrix protein 2 ectodomain epitopes) NPs	-	Influenza A virus	BALB/c strain	$CD8^+$ T cells involved protection against virus	NPs-vaccine	Deng et al (2018)[177]
Liposome						
Nano-liposomes	Acyclovir	-	-	-	Intravenous drug delivery and release	Mukherjee et al (2007)[178]
Solid lipid NPs	shRNA (Targeting internal	Hepatitis C virus	Huh-7 cells	Silencing of hepatitis C virus	Viral inhibition	Torrecilla et al

(continued on next page)

Table 2 (*continued*)

Nanoparticles	Bioactive Compound	Virus	Model Organism	Mechanistic Mode of Action	Purpose	References
	ribosome entry site [IRES])			replication		(2016)[137]
Solid lipid NPs	Ritonavir	Lentiviral-based pseudo-HIV-1 particles	Human 293T cells	Inhibition of viral protease	Efficient encapsulation, release and antiviral activity	Javan et al (2017)[179]
Solid lipid NPs modified with gelatin	Zidovudine (AZT)	HIV	MCF-7 and neuro 2a brain cells	Appreciable cellular internalization	Favorable loading, controlled discharge, hemocompatibility and nontoxicity	Joshy et al (2017)[103]
Polyvinylpyrrolidone (PVP)/stearic acid (SA)-polyethylene glycol (PEG) NPs	AZT	HIV	Murine neuro-2a and HeLa Cells	Appreciable cellular internalization	Favorable loading, sustained release, hemocompatibility and nontoxicity	Joshy et al (2018)[106]
Nanostructured nanolipid carriers	Podophyllotoxin (POD)	Human papillomavirus (HPV)	VK2/E6E7	Cell cycle arrest of virally infected cells at G2/M phase	Sustained release, hemocompatibility, nontoxic viral inhibition	Gao et al (2018)[107]
Dendrimer						
Peptide-derivatized dendrimers	Acyclovir (ACV)	HSV-1,2	Vero cells, HELFs cells,	Inhibition of viral entry by binding to glycosaminoglycan moiety of cell surface heparan sulfate proteoglycans, *in virto* viral replication	Antiviral activity	Luganini et al (2011)[110]
Dendrimer NPs	mRNA replicons (multiple antigen expressing replicons)	H1N1, Ebola virus	Wild-type female C57BL/6 and BALB/c mice	Activation of both $CD8^+$ T-cell and antibody responses	mRNA-vaccine	Chahal et al (2016)[111]
Modified dendrimer NPs	Venezuelan equine encephalitis virus (VEEV) replicon RNAs	Zika virus	C57BL/6 mice	Activation of both $CD8^+$ T-cell and viral E protein-specific IgG responses	mRNA-vaccine	Chahal et al (2017)[113]
Carbosilane dendrimer NA	16-mer oligoribonucleotide (RNA) decoy (genomic RNA of HIV)	HIV	HIV-infected MT4 lymphocytes	RNA decoy	Inhibition of HIV encapsidation	Parboosing et al (2017)[114]
Nonlinear globular G2 dendrimer	Citric acid and polyethylene glycol 600 (PEG-600)	Rabies virus	J774A.1 cell line and NMRI mice	-	Adjuvanticity efficacy	Asgary et al (2018)[112]
Niosome						
Nano-niosome	Acyclovir	-	-	-	Intravenous drug delivery and release	Mukherjee et al (2007)[178]
		HSV-1	HeLa cell line	-	Drug delivery and anti-viral activity	Monavari et al (2014)[119]
				-	Improved drug delivery, release, and anti-viral activity	Javad et al (2014)[118]
Nanomicelle						
Polymeric micelle	Efavirenz (EFV)	HIV	Male Wistar rats	-	Improved oral bioavailability	Chiappetta et al (2010)[121]
Nanomicelle	Curcumine	Hepatitis C Virus	APC49 Huh7.5 cells	Regulation of viral attachment and entry	Improved bioavailability and anti-viral activity	Naseri et al (2017)[122]
Polymeric nanomicelle	Biotinylated lipid prodrug of cyclic cidofovir (B-C12-cCDF)	-	D407, HCE-T cells	-	Efficient anti-viral drug delivery	Mandal et al (2017)[55]

influenza A virus subtype H7N3, Coxsackievirus B3, Infectious bursal disease virus and *S. cerevisiae* dsRNA viruses (Table 1). The AgNPs based mechanism for viral inhibition or virucidal activity varies virus to virus. For example Lara et al elucidated the antiviral efficacy of commercially available AgNPs against HIV-1 and some resistant strain such as IIIB, Eli, Beni, 96USSN20, Bal, BCF01, AZT_{RV}, $NNRTI_{RV}$, PI_{RV}, $3TC_{RV}$, and $Saquinavir_{RV}$ along with NP's mode of action.[57] Normally gp120 interaction with host receptor CD4 and associated co-receptor results in further conformational changes in virus, exposing gp41 which concordantly interacts and releases viral core into cytoplasm.[58] Their findings suggested that AgNPs impedes CD4-dependent virion binding, merging and pathogenesis by interacting with viral gp120 in both cell-free and cell-associated virus.[58] In case of HSV-2 the viral inhibition is portrayed by interacting with sulfhydryl group present on the membrane glycoproteins which prevent viral internalization. In Peste des petits ruminants' virus the NPs act by interacting with virion surface and core protein, impairing viral replication and entry.[59,60] Likewise in dsRNA viruses the AgNPs after interaction with viral genome, the NPs were found to inhibit viral replication.[61] The antiviral efficacies of AgNPs by these modes of viral entry or attachment inhibition or viral replication inhibition have also been evaluated in other viruses shown in Table 1.

Gold nanoparticles (AuNPs)

Unlike AgNPs though AuNPs could also be synthesized by green synthesis method but their direct use as an antiviral agent is scant. Except in some findings, that too when, AuNPs stabilized with certain biocompatible polymer could act as an effective antiviral agent against HIV-1, H1N1, H3N2, H5N1, dengue virus, bovine viral diarrhea virus and Foot-and-mouth disease virus (FMDB).[62–64] Vijayakumar and Ganesan et al had speculated that the mode of antiviral activity of polyethylene glycol encapsulated AuNPs against HIV-1, might be by blocking gp120 attachment with CD4, which results in inhibited viral entry.[62] Hafashjani et al in their finding later suggested that AuNPs arrested FMDV replication at post-entry stage, associated specifically with transcription within the host cell.[63] But the exact virucidal mechanism is unclear. The currently used AuNPs in combination with other nano-based formulation are applied for photothermal nanotherapy, bio-sensing, bio-imaging, catalytic activities.[65] The unique property of AuNPs contributing to these applications is different from its bulk form that is, Surface Enhanced Raman Scattering (SERS).[66] For example Ahmed et al described the capability of positively charged AuNPs for H1N1 and H3N2 detection by mimicking peroxidase enzymatic reaction assay. Likewise there are other examples where hybridized AuNPs demonstrated effective antiviral activity (Table 1).[64]

Magnetic nanoparticles (MNPs)

Iron oxide or superparamagnetic iron oxide in the form of either magnetite (Fe_3O_4) or maghemite (Fe_2O_3, γ-Fe_2O_3) NPs is the most imperative component of present day magneto responsive nanoparticulated systems.[67] These iron based nanoparticulated systems have created a tremendous impact in biomedical/ clinical diagnostics including magnetic resonance imaging, magnetic particle imaging, magnetic fluid hyperthermia and magnetic labeling and cell separation.[68] Therefore the direct application of MNPs as a therapeutic is limited. Presently the direct use of MNP as an antiviral agent has been evaluated against Bacteriophages such as MS2 and other highly infectious viruses like zika virus, HCV, H5N2 (Table 1).[69–72] There have been many other findings of exploiting MNPs but their application in hybridized form is much more appreciated, which is described later under *Hybrid nanoparticles* (Table 3).

Titanium nanoparticles (TiNPs)

Due to its brightness and high refractive index, titanium dioxide (TiO_2) a white pigmented molecule is widely used for a number of purposes. In various sectors of science and industries its nanoform that is TiO_2NPs is more abundantly produced and used specifically because of their high solubility, photocatalytic and anticorrosive properties.[73] Although their application in biomedical sector is marvels but still than their there is a large gap between classic and current research. Out of every possible implementation that could bridge this gap, antiviral application of TiO_2NPs is one of them. Present antiviral evaluation of TiNPs is only limited to influenza virus (H3N2) and certain bacteriophages such as MS2, PRD1, ϕX174, Fr and many others.[74–76] Moreover, the existing toxicity evaluations of the NPs though cannot completely eliminate health risks therefore, their biomedical application as an antiviral agent is questionable.[77] But considering beneficial role of TiNPs in biomedical sector, its antiviral activity however, needs to be perfectly conceptualized in animal models too.

Silica nanocarriers (SiNCs)

NPs based on silica due to their unique characteristics like tunable diameter, pore size, convenience in functionalization, biocompatibilities *etc.* are well appreciated for research all over the globe.[78,79] Apart from these, there are two other important properties, which display manipulative applicable properties including self- immobilization of ligands onto surface of SiNP and stimuli-responsive gatekeepers.[80] The practical application lies in their capability to control or accelerate release of the drug payloads simultaneously excluding premature release. Currently, exploiting these properties for photodynamic therapy by functionalizing SiNPs with photosensitizers, is one of the fastest emerging research.[79]

There are different forms of SiNPs, categorized as porous, mesoporous and non-porous and are utilized for diverse biomedical application.[78,81] Out of the multiple biomedical applications of SiNPs, the present review focuses on antiviral activity as the research in antiviral therapeutics or diagnostics, exploiting silica based NPs is limited.[82,83] Currently antiviral efficacy of SiNPs against some viruses like Human Papilloma Virus, Porcine circovirus, Hepatitis B virus, HSV-1, 2, HIV and recombinant viruses has been evaluated (Table 1). And the mode of antiviral activity is either mediated by immunization of the host against virus or by inhibiting viral entry.[82,84] Viral protein based fluorescent detection and nucleic acid hybridization are the two major methods of viral detection.[83,85] Despite the progress made in the therapeutics and diagnostics against viral infections, an achievement that cannot be questioned, the growing demand for a novel antiviral therapeutics or diagnostics can only be supplemented by further research and evaluations.

Carbon-based nanocarriers

Carbon-based nanocarriers are among the most frequently and widely evaluated nanoparticulated systems in biomedical application. The carbon-based materials such as fullerenes, carbon nanotubes, nanohorons, nanodots, grapheme and nanodiamonds *etc.* that also possess some of the above mentioned inimitable properties such as optical, electronic, mechanical and thermal properties have gained themselves much attention in the past decade. Among various beneficiary roles, biocompatibility, *in vivo* biodistribution, biodegradation and bio-corona formation *etc.* are few crucial properties that constantly impress the present scientific community till today.[86] Although carbon-based nanomaterials are supported by these spectacular advantageous properties, but still their utilization and evaluation in the field of virology are limited to some viruses (Table 1). Antiviral or virucidal activities of these carbon-based nanomaterials have been evaluated against some viruses such as Ebola virus (pseudotyped viral particles), Bacteriophage λ, HIV-1, H3N2, Grass carp reovirus (GCRV) and Respiratory syncytial virus (RSV).[87–91] Various modes of viral inhibition by carbon-based nanomaterials used as carriers are represented in Table 1. Advancement in the evaluation of carbon-based nanosystems against viral infection, though have developed immensely, but their commercialization is a rate-limiting phase and will be resolved with respect to time.[86,92]

Quantum dots

The nano-sized semiconductor crystals commonly known as quantum dots (QDs) with their exceptional electronic and optical properties are highly appreciated.[93,94] Specifically intensive fluorescence, high quantum yield, size-tunable light emission, appreciable chemical and photo-stability have revolutionized the concept of nano-based sensing or diagnostics. General elemental composition of QDs includes cadmium (Cd), lead (Pb), mercury (Hg) and zinc (Zn). But recently developed ternary I-III-VI QDs contain elements in different form, here "I" represents cupper (Cu) or silver (Ag), "III" represents gadolinium (Ga) or indium (In) and "VI" represents sulfur (S) or selenium (Se).[94] Owing to their extremely small size ranging from 2 to 10 nm QDs are well appreciated and used in biomedical sector as they could conveniently cross the BBB in conjugation with a therapeutic molecule.[94,95] Mahajan et al showed that fluorescent quantum rods (QRs) a form of QD in conjugation with transferring, a targeting molecule and HAAT (Highly Active Antiretroviral Therapy) drug Sequinavir could freely cross an *in vitro* model of BBB. They also showed that the nano-formulation showed promising antiviral activity against HIV-1.[96] Viral detection by QD based approaches is exceedingly escalating research of virology. Norouzi et al developed a cadmium–tellurium QD in association with a biotin acceptor and NH_2-receptor probes with target DNA for recognition of human T-lymphotropic virus-1 (HTLV-1) *in vitro*.[97] Likewise, there are many other evaluations where QDs have been utilized either as therapeutics or for *in vitro* diagnosis of viral pathogens.

Organic nanoparticles

If the size of therapeutic compound is very large, then INPs might not prove promising in carrying or delivering the desired compound. In those conditions Organic nanoparticles (ONPs) might prove beneficial in order to efficient carry or deliver the drug load.[98] Further the use of ONPs over INPs is well appreciated in biomedical sector specifically due to various safety issues.[99] Encapsulation of drugs favors avoiding off-target toxicity which results in enhanced augmentation at targeted site. Again, the mode of delivery of therapeutics could be modulated by selecting specific design features and chemical requirements for the synthesis purpose. Since, sustained release kinetics can directly influence therapeutic competence and toxicity of the nanosystem.[98] Multiple forms of ONPs are exploited in field of nanomedicine but only certain specific ONPs are presently being evaluated for their antiviral activity. These include polymeric NPs, lipid based NPs, dendrimers, neosomes and nanomicelles (Table 2).

Polymeric NPs

The exploitation of polymeric NPs for progress in the effectual antiviral treatment has been going on for more than a decade. Various forms of polymers (synthetic and natural) have immensely contributed towards meticulous understanding of definite properties such as biodistribution/ bioavailability, biocompatibility, immunocompatibility *etc.* in biomedical sector. But their uses either for development or for improvement of an antiviral have been investigated only for some pathogenic viruses like influenza, HIV and rabies virus (Table 2).[100–102] Their efficient self-assembly properties, nanosize, shape, and ability to be functionalized based on requirement to either carry the desired therapeutic agent in its core or conjugate the target molecule on its surface are simply magnificent. Recently, Joshy et al have demonstrated that amine functionalized polymeric gelatin NPs loaded with zidovudine against HIV. Simultaneously, they have also conducted hemolysis and aggregation studies to gain deeper understanding of other compatible properties of NPs. From their research they summarized that drug conjugated NPs showed promising biocompatibility and antiviral activity.[103] Deng et al on the other hand took a different approach by developing a universal influenza vaccine with double-layered protein NPs composed of tetramaric Matrix protein 2 (M2e) at its core and headless Hemagglutinin (HA) coating at its surface. The protein vaccine could induce substantial and prolonged immunity with complete protection of BALB/c mice against verity influenza A virus challenges.[104] With the contemporary improvement made in nanoscience it is certain that these impeccable polymeric NPs in near future will be soon used for the development of a novel antiviral against divergent array of infectious viruses like NiV.

Lipid based NPs

Currently developed solid-lipid NPs and nanostructured lipid nanocarriers have demonstrated their ability as an exceptional efficient biocompatible vehicle for therapeutics in the field of advanced medicine. Among the multiple possible applications of lipid based NPs, their exploitation to formulate a novel antiviral could be assumed primary concern of ongoing researches. Further their anomalous bio-absorbable and biocompatible properties have granted these nanosystems a unique prospective to be viewed at.[105] Despite past limitations, where it seemed difficult for a therapeutic to migrate across BBB, it seems promising now with the introduction of multifunctional lipid based nanocarriers. In a

Table 3
Hybrid Nano-Based Approach for Viral Diagnosis and Inhibition.

Nanoparticles	Bioactive Compound	Virus	Model Organism	Mechanistic Mode of Action	Purpose	References
Nano-based viral detection						
Silica (SiO_2) coated magnetic Fe_3O_4 NPs	-	Hepatitis B virus (HBV), Epstein–Barr virus (EBV)	-	-	Higher sensitivity in PCR-based viral detection	Quy et al (2013)[180]
Au_{102} (paramercaptobenzoic acid)$_{44}$ clusters	-	Enterovirus, Echovirus 1 and Coxsackie virus B3	-	Site-specific covalent Conjugation on viral surface protein	Viral targeting	Marjomäki et al (2014)[126]
Gold/Copper Sulfide Core/ Shell NPs	-	Human Norovirus Virus-Like Particles	-	Capsid protein degradation and capsid damage	Viral detection and inactivation	Broglie et al (2015)[124]
AuNPs-carbon nanotubes (CNTs) hybrid	Antibody	H3N2		Peroxidase-like activity of the nanohybrid	Colorimetric viral detection assay	Ahmed et al (2016)[127]
Chiral AuNPs-quantum dot nanocomposites	-	Avian influenza A (H4N6) virus, fowl adenovirus and coronavirus	-	Chiral plasmon–exciton systems	Viral detection	Ahmed et al (2017)[181]
Graphene-AuNPs nanohybrid	Anti-NoV antibody	Norovirus-like particles	-	Intrinsic peroxidase-like activity	Colorimetric immunoassays for viral detection	Ahmed et al (2017)[182]
Glycan-functionalized AuNPs (gAuNPs)	-	hRSV, vieH5N1, anhH5N1, guaH5N1, shaH5N1, guaH5N6, hebH5N8, wsnH1N1, shaH1N1, mosH3N2, aicH3N2, leeB, yamB, shaH7N9, anhH7N9	Vero cell	Aggregation of gAuNP probes on the viral surface	Viral detection and differentiation	Zheng et al (2017)[183]
Poly(DL-lactide-co-glycolide) (PLGA) encapsulated superparamagnetic iron oxide NPs	Clocking with RBC membrane vesicles with surface rich in sialic acids -	H1N1	-	Virus targeting and isolation *via* magnetic extraction	Enhanced viral detection	Chen et al (2017)[184]
Silica-shelled magnetic (Fe_3O_4) nanobeads (MagNBs) and AuNPs	-	H1N1, H3N2	-	MagNB mediated target separation and signal amplification by the enzyme-like activity of AuNZs	Ultra-sensitive colorimetric assay (magnetic nano(e)zyme - linked immunosorbent assay [MagLISA]) for viral detection	Oh et al (2018)[128]
Gold (Au)/iron-oxide magnetic NP-decorated Carbon nanotubes (CNTs)	Thiol-group-functionalized probe DNA	H1N1, norovirus	-	DNA hybridization	High sensitivity and selectivity detection of viral DNA	Lee et al (2018)[125]

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Table 3 (*continued*)

Nanoparticles	Bioactive Compound	Virus	Model Organism	Mechanistic Mode of Action	Purpose	References
(Au/MNP-CNT)						
Nano-based viral inhibition						
Silica doped TiO_2(P25) NPs	-	Bacteriophage MS2	-	Hydroxide radical mediated catalytic inactivation	Viral inactivation	Jafry et al (2011)[123]
Photocatalytic silver doped titanium dioxide (nAg/TiO2) NPs	-	Bacteriophage MS2		Hydroxide radical mediated catalytic inactivation	Viral inactivation	Liga et al (2011)[185]
Dextran-coated magnetic iron oxide NPs labeled with Cy5.5 fluorescence dye	DNAzyme, cell-penetrating peptide	Hepatitis C virus (HCV)	BALB/c mice, C57BL/6N mice	Silencing of HCV NS3 gene expression resulting in inhibited viral replication	Efficient delivery and viral inhibition	Ryoo et al (2012)[129]
Fullerene-liposome complex	-	H1N1	BALB/c mice	Reactive oxygen species regulation	Viral inhibition	Du et al (2012)[186]
Tannic acid modified AgNPs	-	HSV-2	C57BL6 mice	Direct inhibition of virus attachment, penetration and post-infection spread	Viral inhibition	Orlowski et al (2014)[130]
Aminopropyl-functionalized Fe_3O_4-SiO_2 core-shell magnetic hybrid colloid (MHC) decorated AgNPs	-	Bacteriophage ϕX174, Murine norovirus (MNV), Adenovirus serotype 2 (AdV2)	-	Damages viral coat proteins	Viral inhibition	Park et al (2014)[157]
Silver nanorods conjugated with sodium 2-mercaptoethane sulfonate (Ag-MES)	-	HIV, HSV-1	-	Inhibition of viral replication	Viral inhibition	Etemadzade et al (2016)[187]
Oseltamivir modified AgNPs (Ag@OTV)	-	H1N1	MDCK cells	Inhibits the activity of Neuraminidase (NA) and Hemagglutinin (HA) prevents viral attachment, inhibit the accumulation of reactive oxygen species (ROS) by virus, activates AKT and p53 phosphorylation	Viral inhibition	Li et al (2016)[188]
Titanium dioxide nanoparticles and polylysine (PL)-containing oligonucleotides (TiO2·PL-DNA) nanocomposite	Polylysine (PL)-containing oligonucleotides	H1N1, H5N1, H3N2	MDCK cells	Targeted binding to conservative regions in the viral genome and inhibition of viral reproduction	Viral inhibition	Levina et al (2016)[136]
Graphene oxide (GO) sheets	-	Feline Coronavirus (FCoV)	fcwf-4 cells, DF-1 cells	Association with viral lipid tails leading to aggregation and rupture of the envelop	Viral inhibition	Chen et al (2016)[131]
		Bursal Disease Virus (IBDV)		Inefficient in binding	Viral release	

GO sheets with silver particles (GO-Ag)	-	Feline coronavirus (FCoV)		Association with viral lipid tails leading to aggregation with attachment of AgNPs with –SH group of protein and rupture of the envelop	Viral inhibition	
		Infectious Bursal Disease Virus (IBDV)		AgNPs mediated interaction with -SH group of viral protein	Synergistic effect	
Polyethylenimine (PEI) encapsulated AgNPs	Small interfering RNA (siRNA),	Enterovirus 71 (EV71)	Vero cell	Block EV71 from infecting host cells and prevent DNA fragmentation, chromatin condensation and activation of caspase-3	Viral inhibition	Li et al (2017)[189]
OTV decoration of SeNPs (Se@OTV)		H1N1	MDCK cells	Inhibits the activity of Neuraminidase (NA) and Hemagglutinin (HA) prevents viral attachment, inhibit the accumulation of reactive oxygen species (ROS) by virus, activates AKT and p53 phosphorylation	Viral inhibition	Li et al (2017)[134]
Alginate (ALG) and stearic acid- poly ethylene glycol (SA-PEG) hybrid NPs	Zidovudine (AZT)	HIV	Glioma Neuro2a, HeLa cells	-	Efficient drug delivery	Joshy et al (2017)[176]
Mannosylated Niosomal system	AuNPs and Efavirenz (EFV)	HIV-1	HeLa cells	-	Viral inhibition	Malik et al (2017)[190]
AuNPs and AgNPs	Peptide FluPep	H1N1, H3N2, H5N1	MDCK cells	-	Efficient delivery and viral inhibition	Alghrair et al (2018)[191]
AuNPs Covered with SiO_2 and SiO_2 carrier conjugated with AuNPs	-	Human Adenovirus	MDCK cells	Interaction with viral surface protein leading to coagulation	Antiviral and virucidal action	Lysenko et al (2018)[192]
Surface decoration of selenium NPs by Amantadine (AM) (Se@AM)	-	H1N1	MDCK cells	Induces apoptosis, inhibits generation of ROS, and activates phosphorylation and AKT pathway	Viral inhibition	Li et al (2018)[132]

study Joshy et al again had developed zidovudine loaded polyvinylpyrrolidone (PVP)/ stearic acid (SA)-polyethylene glycol (PEG) NPs and have determined the *in vitro* drug loading, controlled discharge, hemocompatibility and non-toxicity in murine neuro-2a and HeLa cells under HIV challenge.[106] Similarly, Gao et al designed a nanostructured nanolipid carrier loaded with podophyllotoxin (POD) evaluated drug release parameters hemocompatibility and non-toxic viral inhibition in VK2/E6E7 cell lines challenged with Human papillomavirus (HPV).[107] Lipid based NPs in both of its form that is solid-lipid NPs and nanostructured lipid nanocarriers could serve as an exceptional addition to the group of vehicles needed for effective antiviral delivery. The current investigation of lipid-based NPs based antiviral against some viruses such as Hepatitis C virus, HIV and HPV has been documented (Table 2). But certainly in future this marvelous nanosystem could get even better through hybridization, so that it could be used in efficiency of therapy against NiV.

Dendrimers

Dendrimer an organic compound with well-organized, hyperbranched molecule is receiving much attention lately owing to their improving monodispersity, biocompatibility and biodegradability in the field of nanomedicine.[108] This molecule is also an extraordinary vehicle for gene, peptide or drugs (natural/ synthetic) delivery at the targeted site within the biological system.[109] They are widely used in biomedical science, but their application and utilization for evaluating an antiviral are limited. To date, dendrimers with antiviral activity in conjugation with therapeutic agents have already been documented against some viruses including influenza virus, ebola virus, zika virus, HSV-1, 2 and HIV (Table 2).[111–113] The antiviral efficiency of nanosystems was a result of viral entry inhibition, activation of $CD8^+$ T cell and/ or antibody mediated response and in some case RNA decoys.[111,113,114] Investigations regarding the efficacy of dendrimers as a nanoperticulated system for designing an antiviral therapy have been introduced by some of the pioneering researches, but their efficiency against NiV is yet to be evaluated.

Niosomes

The non-ionic surfactant-based vesicle in short niosomes structurally similar to liposome is slowly becoming the center of attraction of current investigators. Its physical and chemical properties such as stability, optical activity, biocompatibility, biodegradability, non-immunogenicity, and convenience in functionalization have greatly influenced the scientific community.[115,116] Additionally, efficiency to load both lipophilic and hydrophilic drug with superior bioavailability and guarded release at the intended site have granted niosome a unique prospective in the field of nanomedicine.[117] Despite their immense significance, the use of niosomes in biomedical sector specifically in formulation of antiviral agents is limited. For example till now antiviral activity against only HSV has been documented (Table 2). Javad et al and Monavari et al have evaluated the efficacy of acyclovir loaded nano-niosome against HSV-1. They found that the neosomes loaded with the drug showed promising antiviral activity with improved delivery and release kinetics.[118,119] Further *in vivo* evaluations are required to display the antiviral efficacy against other broad range of infectious viruses such as NiV.

Nanomicelles

Nanomicelles are supramolecular assembly of a surfactant molecule disseminated in a colloidal liquid giving rise to a globular micelle ranging in nano-size. Efficient encapsulation, biocompatibility, colloidal stability and prolonged circulation time *etc.* are some of the influential properties of polymeric micelles.[120] Moreover, a compound possessing these properties is of huge significance in nanomedicine and drug delivery system (Table 2).[121] Specifically to formulate an antiviral agent these polymeric nanomicelles is appreciated. For example Naseri et al formulated a nanomycelle encapsulating a bioactive phytocompound curcumin and verified bioavailability and antiviral activity *in vitro*. They documented that the nanoformulation displayed better bioavailability and satisfactory antiviral activity.[122] Present application of this marvelous compound is somewhat stagnant and needs more contribution from researchers all over the world.

Hybrid nanoparticles

Hybrid NPs are by far the most advanced form of NPs that could be thought of in the present century. INPs such as Ag, Au, magnetic NPs, TiO_2, SiO_2, CNT, fullerene and graphene oxide and ONPs such as polymeric NPs, lipid NPs and niosomes have been explored in their antiviral activity.[123–125] There are a number of viruses against which these NPs in their hybridized state have been evaluated; these include HIV, influenza virus, hepatitis virus, human adenovirus *etc.* (Table 3).

Hybridized NPs in virology may be categorized according to their utilization that is either diagnostic or therapy. Current investigations, where efforts have been made towards diagnosis or detection of the viruses have been documented by many investigators from different corners of the globe. Starting from the primary application that is detection, Marjomäki et al earlier had reported an accurate and precise enteroviruses labeling procedure and described it at the atomic level. Here they reported water-soluble thiol-stabilized gold cluster or chemically called Au_{102} (para-mercaptobenzoic acid)$_{44}$ cluster which by its metal core could covalently bind to cysteine molecule nearer to the surface of the virus. Through the above procedure enteroviruses echovirus 1 and coxsackievirus B3 viruses were precisely detected.[126] Ahmed et al have synthesized a multifunctional nanohybrid where AuNPs are first bonded with CNT surface, and then specific antibody (anti-influenza A virus HA H1 antibody) is conjugated to it. The nanohybrid displayed oxidative catalysis of 3, 3′, 5, 5′-tetramethyl-benzidine (TMB) by H_2O_2 gave rise to a deep blue color, the optical density of which depended on concentration of virus.[127] Lately, Oh et al developed an ultrasensitive magnetic nanozyme-linked immunosorbent assay for detection of H1N1 virus. The assay had two major components, the silica-shelled magnetic nanobeads (MagNBs) for binding and preliminary detection of the virus, and a gold nanozyme (AuNZ) an enzyme-like acting molecule for amplification of the preliminary detection signals. Together in combination the nanosystem could even detect virus concentration up to femtogram per milliliter.[128] There are a

number of examples where hybridized nano-based systems showed promising results in viral detection; some of them have been listed in Table 3.

Viral inhibition is foremost important after diagnosis which needs to be addressed immediately; thereafter the requirement of a novel antiviral to combat the viral infectivity has become the primary concern. Further, development of an antiviral within a stipulated time is actually a race against time. Under such case formulation of an antiviral that is biocompatible, non-immunogenic and non-toxic is of the critical requirement to which hybridized nanoparticulated systems are an appreciable option. It is because of the promising antiviral activity of these systems that has been portrayed by various scientific investigators. Ryoo et al had reported iron-oxide NP-based delivery of DNAzyme as a therapeutic for treating hepatitis C infection. Here, the magnetic NPs were linked to a cell-penetrating peptide (CPP) and functional DNAzyme which could induce knockdown of HVC gene *NS3* (non-structural protein 3) encoding viral helicase and protease.[129] Orlowski et al developed tannic acid functionalized AgNPs of specific size range that could reduce HSV-2 infectivity by blocking viral attachment, penetration as well as viral spread; provided a prior direct attachment of the nano-system with the virus is a basic requirement.[130] Chen et al compared the antiviral activity of both graphene oxide (GO) and GO conjugated AdNPs against both coronavirus (FCoV) and infectious bursal disease virus (IBDV). Their analyses showed GO in its non-conjugated and conjugated form had different effect on two different taken viruses. Overall they concluded that GO in its conjugated form that is GO-AgNPs could inhibit both the virus that is FCoV and IBDV effectively.[131] After diagnosis and therapy the next arising huddle is drug resistance that soon must be focused and acted accordingly. With this intention Li et al, after much evaluations and strategic understanding the drawbacks of conventional and nano-based antiviral, designed nanoparticulated system by decorating amantadine (AM) on surface of selenium NPs (SeNPs). Their designed Se-AM nanosystem could reverse the drug resistance induced by H1N1 virus.[132] Similarly, there are many other investigations which orchestrate the experimental efficiencies of hybrid nanoparticulated systems as antivirals listed in Table 3. Despite the heterogeneous research and investigations exploiting multiple ways and means to diagnose, inhibit the virus by a nano-based therapeutic agent or reverse the drug resistance, still there is hardly any sign of these applications concerning NiV.

Possible nano-based approach for NiV diagnosis

The elevated cost and in some case toxicity of conventionally available specific antiviral therapeutics have created an apparent requirement for specific and rapid viral diagnosis. Specific viral diagnosis may be helpful in discontinuation of broad spectrum antibiotic therapy and determination of prognosis, and it is also believed that rapid test result greatly influences case management. Prior to therapy, diagnosis therefore may be considered as an important aspect in viral infection treatment. There are multiple methods in the present era for laboratory based diagnosis of viral infection; these include serology, viral culture, antigen and nucleic acid detection.

The conventional technique of viral detection that is viral culture may be considered as the only technique through which viable isolate could be obtained for future characterization. Additionally, detection of a diverse array of viruses seems promising with this approach, which is also an advantage over antigen detection and nucleic acid detection. In order to preserve medically relevant viruses, maintenance of heterogeneous types of cultured cell is required as a support, which is a major limitation of this technique. Viral recovery through cell culture becomes difficult when the viral growth is slow; antigen detection in such cases is much useful. Rapidity and non-requirement of viral viability render immense plasticity in management and shifting of the specimens, which together may be considered as the major advantages of the technique. Fluorescent Antibody (FA) staining, Immunoperoxidase staining and Enzyme Immunoassay (EIA) *etc.* are crucial techniques involved in these methods. But viruses with antigenic heterogeneity and lack of cross-reacting antigens are tedious to be detected even through this technique. Drastic transformation in diagnosis has emerged with the development of analysis based on PCR. This transformation has allowed the detection of specific viral sequence with uttermost sensitivity. More specifically, viral RNA could be easily detected only by amalgamating reverse transcriptase with conventional PCR analysis. Real-Time PCR assay runs on highly sophisticated automated instruments; exploiting optical excitation systems and dyes labeled with fluorescent molecules has tremendously reduced time and probable contamination. The versatility of nucleic acid detection is growing day-by-day and will be in future with the progression of scientific innovation. Finally, the efficacy serology the traditional method viral diagnosis cannot be disregarded. The technique is exclusively promising for unambiguous antiviral immunity determination, but when speculated on clinical utility, assessment of acute and convalescent antibody titers, could be one of its limitations.[133] In case of NiV detection these mentioned detection techniques may be fruitful.

Upon considering the present encroachment in the field of nanoscience and virology, their intermediated research has initiated a new direction in rapid diagnosis of infectious viruses. Like Au/CuS core/shell NPs developed by Broglie et al for human norovirus-like particle detection and inactivation by capsid protein degradation and damage,[124] similarly a hybrid nanosystem could also be designed for binding with NiV virion two spiked glycoproteins F and G as well as RNA, and capsid proteins such as N, P, L contained within the virion (Figure 4).[21] A colorimetric viral detection assay exploiting peroxidase-like activity of AuNPs-CNT nanohybrid could also be developed for detection of NiV detection like Ahmed et al, who synthesized and examined the same nanohybrid for the detection of H3N2.[127] Likewise there are a number of versatile experimentation (Tables 1, 2, and 3) where diagnoses of a verity of viral infections have been summarized. Contemplating on these possibilities, the probabilities of developing a novel nano-based diagnosis technique for detecting NiV could be achieved.

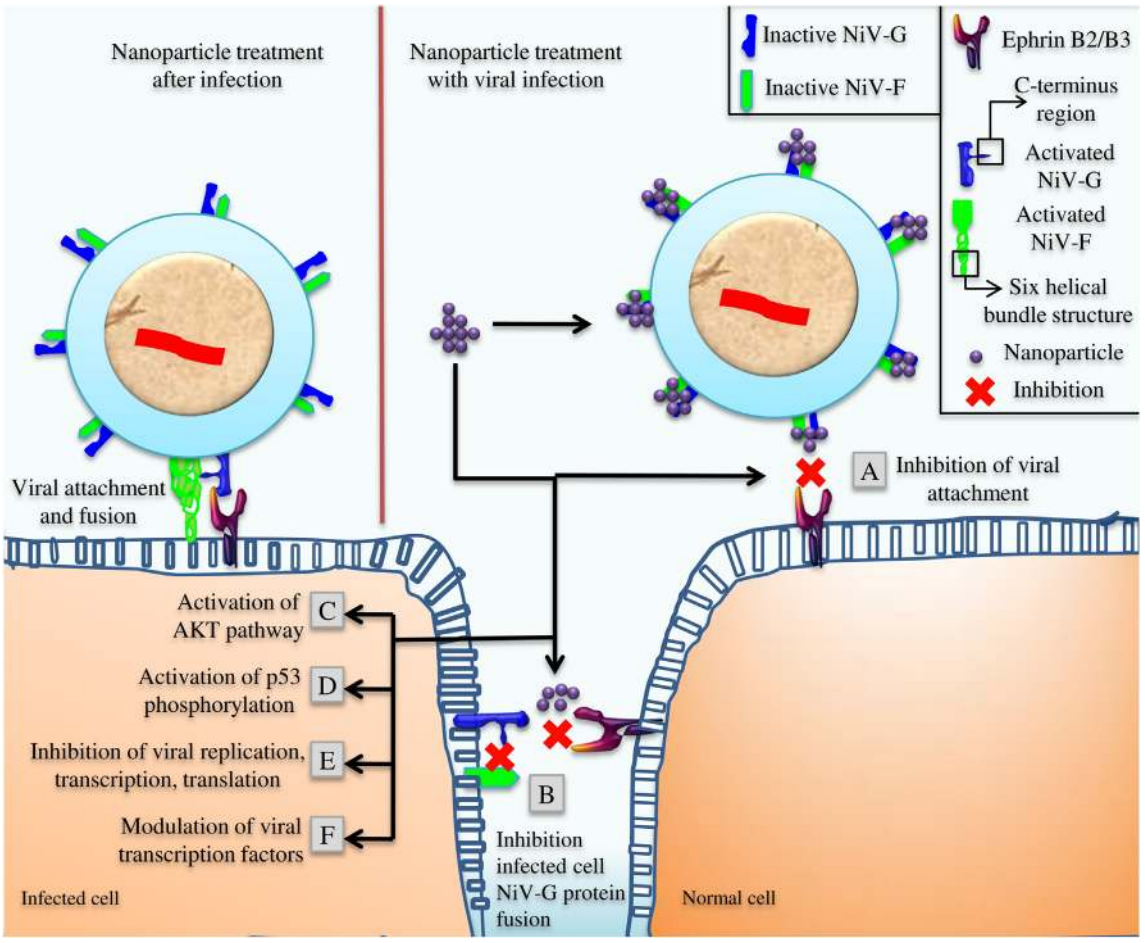

Figure 4. Speculated role of nanoparticles at different stages of NiV pathogenesis, **(A)** Inhibition of initial attachment and membrane fusion during viral entry, **(B)** Inhibition of infected cell NiV-G protein interaction with Ephrin B2/B3 of a healthy cell and activated NiV-G protein's C-terminus region mediated activation of NiV-F, **(C)** Activation of AKT, **(D)** Activation of p53 phosphorylation, **(E)** Inhibition of viral transcription, translation and replication, **(F)** Modulation of viral transcription.

Possible nano-based approach for NiV inhibition

If NiV detection could be possible, then elimination of the virus through nano-based system is not far or out of reach from the present investigators. The conventional means of viral inhibition or treatment / therapy have been documented under the topic "Therapeutics against NiV". The nano-based approaches like the use of acid functionalized multi-walled carbon nanotube (MWCTs) made of photoactivated molecules (Protoporphyrin IX) to inactivate H3N2 virus have been demonstrated by Banerjee et al.[87] The possible molecular mechanism involved is ROS-based inactivation through which oxidation of viral protein (neuraminidase [NA] and hemagglutinin [HA]) might have taken place; single stranded break in viral genome and protein-RNA crosslinking might have also been a possibility. Similar nano-based approach including pH or photothermal medium accompanied with ROS-based inactivation of NiV could also be evaluated *in vitro*. Inhibition of viral binding with the host cell surface receptor could also be achieved by preventing viral binding of gp120 and CD4 attachment. In a study, Vijayakumar and Ganesan have demonstrated this mode of inhibition of HIV-1 virus entry using AuNPs *in vitro*.[62] Similarly, NPs with the capacity to interact with NiV surface glycoproteins like G and F could prove to be promising candidates as viral entry inhibitors. Inhibition of virus mediated accumulation of ROS, activation of AKT, and p53 phosphorylation could also be a strategy for inhibiting the entry of infectious viruses. Li et al demonstrated this strategy of H1N1 viral inhibition using oseltamivir (OTV) decorated SeNPs (Se@OTV).[134] This strategy could be effectively evaluated *in vitro* in case of NiV inhibition. Likewise modulation of viral transcription using MWCTs- ribavirin by Zhu et al,[135] targeted binding on conservative regions on viral genome using TiO_2NPs and polylysine (PL)-containing oligonucleotides nanocomposite by Levina et al.[136] and silencing viral replication with the help of solid lipid NPs by Torrecilla et al[137] *etc.* all point in the same direction (Tables 1, 2, and 3). Though the efficiency of NPs as an antiviral agent against NiV is yet to be evaluated; still it could be roughly speculated that these investigations are direct representation of the possibility that NPs holds an enormous potential as an antiviral agent against NiV described in Figure 4.

Conclusion

Nanotechnology holds a tremendous opportunity for both viral disease diagnosis and their therapeutics. It is evidenced that NPs could be used as a measure to revert the antiviral resistance which is a slowly developing problem of conventional therapeutic available. Though it is possible that nano-based approaches are the next convenient strategy to deal with NiV, but still developing NPs is difficult if the NiV pathogenesis is not properly understood. Therefore the present review provides a brief knowledge about NiV pathogenesis at cellular and molecular level, where it would be easy to strategize a novel antiviral target using NPs. A brief introduction of various NPs in inorganic, organic and hybrid forms would be helpful in determining their suitability to be evaluated as diagnostics or therapeutics. Finally the overview of major antiviral approaches that have already been studied is represented in tabular format, which could help to strategize possible novel antiviral approach.

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