REVIEW PAPER

Trends in nano-platforms for the treatment of viral infectious diseases

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Abstract−Viral diseases have always been a major health issue, from the currently eradicated poliovirus to the still unresolved human immunodeficiency virus, and have since become a recent global threat brought about by the COVID-19 pandemic. Pathogenic viruses easily spread through various means such as contaminated food and water intake, exchange of bodily fluids, or even inhalation of airborne particles mainly due to their miniscule size. Furthermore, viral coats contain virulent proteins which trigger assimilation into target cells on contact through either direct penetration or induction of endocytosis. In some viruses their outer envelope contains masking ligands that create a means of escape from detection of immune cells. To deal with the nanometer size range and biomolecular-based invasion mechanism, nanoparticles are highly suitable for the treatment. The review highlights the progress in nanoparticle technology, particularly viral therapeutics, including therapeutic strategies and existing clinical applications.

Keywords; Viral Diseases, Nanotechnology, Viral Treatment, Nanoparticle Treatment

INTRODUCTION

Viruses are infectious particles that replicate inside host cells and scarcely have the characteristics of living organisms, because they cannot function by themselves; however, following their entry into the host cell, viruses can rapidly assume control of the cell's biological mechanisms [1]. Typically, following host entry, viruses exponentially increase the number of viral particles inside the host within a short period, and this bolsters the high rate of infection as well as the infamously rapid mutation rate in viral diseases [2]. As more virus particles are created for each individual host cell, several generations can be produced within a short time span and this, together with the special replication mechanisms, allows the virus to evade host immunity and subsequently replicate exponentially [3]. Infection routes vary depending on the host, although the nanometer size of viral particles facilitates spread via any medium. The simplest form of a virus is a small segment of either DNA or RNA that comprises a protein coat (capsid) which protects the virus, as viruses rely on the host cell for most of their life cycle and contain only the bare necessities required for replication. Viruses that contain this basic form are called naked viruses, such as adenoviruses and most bacteriophages. Other viruses have lipid membranes around the capsid that usually contain proteins that enable the infection of the host cell. Coronaviruses (CoV), which include influenza and severe acute respiratory syndrome (SARS) viruses, as well as the human immunodeficiency virus (HIV), demonstrate the lipid-enveloped capsid morphology. The viral capsid itself is composed of several protein subunits that can assemble into various shapes (e.g., helical, icosahedral, etc.) or other complex structures. The components of the capsid are self-assembling, and thus each subunit has surfaces that are capable of intermolecular interactions, such as amphiphilicity [4]. Based on the composition of their genetic material, viruses can be divided into two types: RNA and DNA viruses. Examples of DNA viruses include adenoviruses, pox viruses, and the herpes simplex virus, whereas RNA viruses include coronaviruses, such as the influenza virus and SARS-CoV-19. This method of propagation is uniform for all viruses, and encompasses the four stages of their life cycle (lytic cycle): viral invasion, genome incorporation, viral component replication, and viral assembly and release. The first stage of host invasion occurs following contact with the plasma membrane and, depending on the morphology of the viral coat, can progress differently. Non-enveloped viruses, which lack a lipid membrane, invade the host cell by either direct disruption of the plasma membrane or through cell endocytosis [5]. Enveloped viruses, in contrast, mimic naturally occurring vesicles, and their lipid membrane is derived from the previous host cell wherein they were produced [6]. Following successful invasion, the next phase involves the incorporation of the viral genome into the host machinery. Based on the nucleotide that is used, the viral genome may enter the nucleus or other cell organelles, particularly the endoplasmic reticulum. Viral DNA can then merge with the host DNA and produce messenger RNAs for prolific production of viral components. RNA viruses may require reverse-transcription before they can reach this stage; however, others can function directly as mRNAs and jump-start viral protein translation. The endoplasmic reticulum is a hotspot for protein synthesis and, as such, is the primary site of viral particle production and assembly. The viral mRNAs either emerge directly

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from the invading RNA virus or from the hijacked host genome and are delivered to the cell organelle for translation. After hundreds of copies of the virus have been produced and assembled, the process proceeds to the final phase of viral release. Host-cell lysis occurs and is either triggered directly by the massive wave of viral particles exiting the cell or through the initiation of apoptosis. These viral particles are then able to infect the adjacent cells or even distant tissues after they reach the bloodstream, and thus complete their life cycle. Few viruses enter a quiescent phase whereby they remain within the host genome without triggering lysis (lysogenic cycle), and this phenomenon enables the virus to create a reservoir after the initial explosive replication and plays an important role in highly evasive viral diseases, such as acquired immune deficiency syndrome (AIDS), where total recovery is difficult to achieve due to the existence of such viral stores.

HUMAN VIRAL DISEASES

Viral infections are one of the most difficult-to-treat diseases, mostly because of the high infection rate. Viruses currently hold the record for having caused the greatest number of pandemics, most of which have been devastating with regard to the scale of infection spread and the mortality rate [7]. Such pathogenic feats are possible due to the special features of the viral structure as well as their unique life cycle, and gaining further insights into viruses may be key to identifying better therapeutic strategies for viral diseases.

1. Viral Pathogens

Three widely known virus-related diseases have plagued humanity for years: AIDS, herpes simplex virus (HSV) infections, and SARS. One of the long-running infamously incurable human diseases to date is caused by the human immunodeficiency virus (HIV), which causes AIDS, and is composed of single-stranded RNA [8] that is surrounded by a conical capsid and which is further covered by a lipid membrane [9]. The virus spreads through the exchange of bodily fluids, usually by sexual contact; however, in rare cases, maternofetal vertical transmission or spread via blood transfusion may occur. AIDS is characterized by a steady decline in the number of immune cells, which gradually increases the patient's vulnerability to opportunistic pathogens that are normally restrained by the immune system.

Another well-known viral pathogen is HSV, and although it is rarely fatal in adults it can cause severe neonatal diseases [10]. HSV has a double-stranded DNA (~150 kilobase pairs long) that is encased in an icosapentahedral capsid, which is further surrounded by several tegument proteins before finally being packaged in a lipid envelope [11]. The virus spreads via contact with mucosal surfaces and wound entry and, similar to HIV, has the ability to integrate with and remain dormant in the host cell. Although relatively harmless, HSV can induce complications on infecting neuronal cells. In such a case, HSV remains dormant in neuronal cells, and sudden HSV reactivation in these cells could inflict irreparable brain damage. HSV-1 mainly infects the oral region, whereas HSV-2 mainly affects the genital area.

Among all pathogenic diseases, viral airborne diseases have always been the most contagious. This includes the influenza virus and the recently discovered SARS-CoV-2, both of which have reached pandemic proportions historically [12]. The coronaviruses are a family of enveloped viruses that include many pathogenic strains. such as the Middle East Respiratory Syndrome MERS-CoV and SARS-CoV-2. Coronaviruses are roughly spherical enveloped RNA viruses [13] with a genome size of 20-30 kilobase pairs [14]. The single-stranded RNA genome of coronaviruses is encased in a helical capsid with multiple nucleocapsid (N) protein subunits, that is enveloped by a lipid membrane that contains multiple membrane (M), envelope (E), and spike (S) glycoproteins on the surface [15]. The influenza virus is a roughly spherical enveloped RNA virus that has a similar morphology except for one notable difference: genome segmentation. The influenza genome consists of eight negative-sense ssRNAs that encode for the spike proteins as well as the viral polymerase subunits [16]. This unique genome structure permits swapping of genome segments between subtypes that have infected the same cell. The antigenic shift thus facilitated enables the influenza virus to produce completely novel antigenic proteins, which is the main reason why the mutation rate of the influenza virus is considerably higher than that of other viruses. Similar to SARS-CoV, the influenza virus comprises the hemagglutinin (HA) protein that binds to the host receptor and initiates endocytosis [17]. The HA protein's ligands include sialic acid residues that are ubiquitous in glycosylated surface proteins of many cell types, such as those which constitute the human respiratory epithelium. The neuraminidase (NA) protein is responsible for initiating the budding of new viral particles out of the cell. Influenza-related symptoms include fever and nasopharyngeal irritation and are mostly non-lethal. During the H1N1 strain pandemic, however, the abrupt antigenic shift caused a sudden total absence of immunity in a vast population. The SARS-CoV strains trigger an extremely strong immune response during infection wherein most patients experience the acute respiratory distress syndrome (ARDS), which induces breakdown of blood vessel walls and subsequent extravasation into the alveoli.

2. Acute and Chronic Infections

Viruses can have a diverse morphology and host cell type; however, the course of the infection can be categorized into two phases: short bursts of acute infections or long-lasting chronic infections. Acute infections have a rapid onset and usually resolve quickly based on the innate immune system [18]. As the viral load is unusually high, the corresponding inflammatory response that is generated against the pathogen can be excessive. Thus, acute infections have two possible outcomes: rapid clearance of the virus associated with the development of long-term immunity against the virus, or death of the host due to either overwhelming tissue damage or lethal levels of circulating cytokines from the elevated inflammation (cytokine storm). In the case of neuronal infections, acute infections are benign, and result in minor localized tissue damage [19]. Treatment of acute infections is focused on either alleviating the inflammation or developing prior immunity through vaccination. Chronic infections, on the other hand, comprise an equilibrium state that is maintained by both the virus and the host immune system, as it could be advantageous for the virus to prolong the infection because more particles can be produced and spread in the long term. As the virus tries to maintain low circulating particle concentrations to prevent an elevated immune response that could lead to infection clearance, the host system has to adjust to the persistent pres-

ence of the virus and prevent immune exhaustion [20]. Chronic infections are actually heterogeneous and can either develop through continuous replication or involve an initial latency followed by a subsequent reactivation. Most viral treatment strategies are designed around chronic infections, and either destroy the circulating viral particles and lessen the viral load enough for the immune system to completely clear the infection, or target the replication cycle and terminate the continuous production of viruses.

TREATMENT OF VIRAL INFECTION

Information on both viral morphology and life cycle has been crucial for developing treatment strategies [21]. For example, different stages of viral infection can be targeted, and each has respective advantages and disadvantages (Fig. 1). The pre-infection phase is theoretically simple because only the destruction of the viral capsid before cell entry is necessary. The viral capsid is a protein shell that encases the genetic material of viral pathogens and is of great interest as a drug target material because it plays an essential role in protecting and delivering the viral genome. The viral envelope is another key factor of cell entry. The enveloped viruses interact with the host cell receptors via glycoproteins on its envelope. After receptor recognition, virus particles can internalize into the host cell and start infection. The problem that emerges is the effective capture of viral particles, which could be coated in complex substances, such as mucus, which need to be removed first, or that the number of particles present could be too high for conventional treatment to work. Viral capsid proteins are known for mutating at an incredible rate such that drugs targeting the capsid of one genera-

tion may not be able to bind to the capsid of the next-generation viruses. Thus, another therapeutic strategy involves the disruption of how the virus replicates inside the host cell. This includes disruption of the viral mRNAs, coat protein translation, or viral assembly. Inhibition at any of these points in the viral cycle could prevent the production and spread of new viruses and simultaneously minimize the tissue damage caused by viral release.

1. Virus Particle Targeting

The viral envelope is key to both the penetration of the host cell as well as the integrity of the virus in general. The envelope components have the potential to become good targets for drug treatment [22]. Different classes of viruses present different druggable targets: non-enveloped viruses have coat proteins that surround the capsid, whereas in enveloped viruses, both the protein and lipid components could potentially be disrupted. The membrane of enveloped viruses is actually of similar composition as their host cell, which makes it susceptible to lipid disruption and opsonization. The surface proteins that are originally obtained from the host cell and have been incorporated into this envelope can be exploited for drug targeting. In addition to structural integrity, the outer layer of viruses is responsible for cell entry, and this is mainly due to the key ligand proteins that are present either on the capsid or on the envelope surface [23]. These proteins play a very important role in host contact and subsequent initiation of either endocytosis or membrane penetration [24]. In HIV-1, for example, the glycoprotein gp120 is responsible for initiating binding of helper T cells to the CD4 receptors. Studies have shown that impairment of this protein could lead to non-infective HIV particles [25]. Thus, targeting these virulence factors is another way of neutralizing the virus, to render
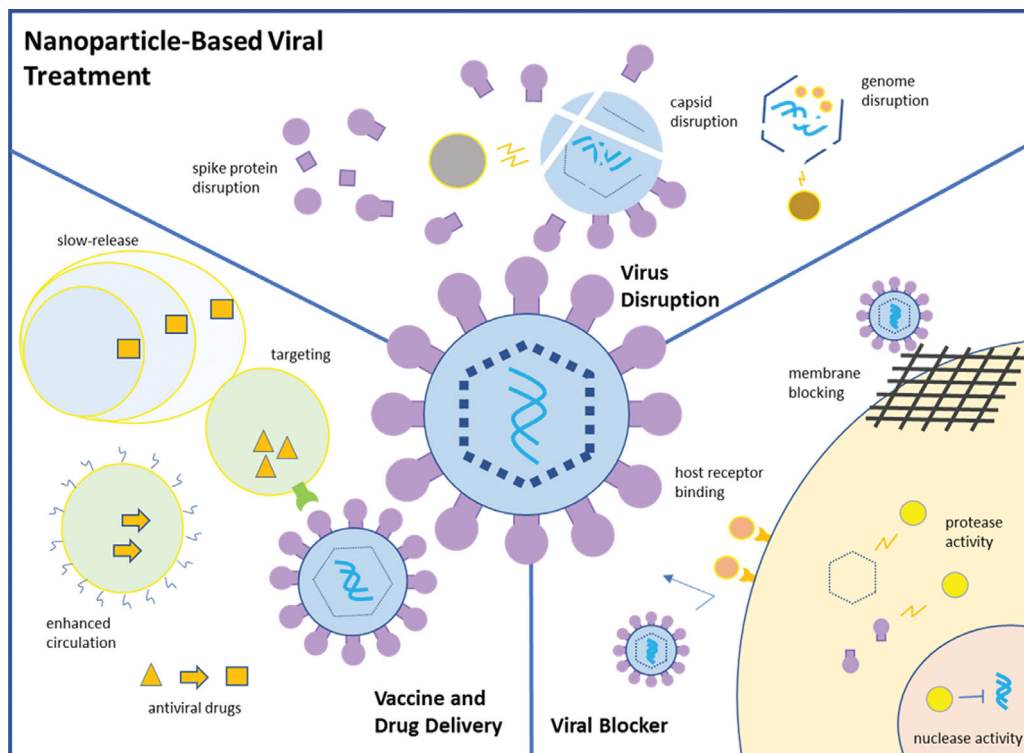

Fig. 1. Nanoparticle-based strategies for viral treatment.

the virus incapable of infection.

2. Inhibition of the Viral Mechanism

A different way to resolve viral infections is to target the biological processes that are related to viral replication. If the therapy fails to break down the free-floating virus particle, each phase of viral infection can be targeted to disrupt the spread to other tissues. The first stage of a virus' life cycle is cell invasion, and the mechanism of viral binding can be inhibited in multiple ways. Thus, blocking the receptors in the host cell can prevent viral particles from initiating cell entry, and this can be undertaken using antibodies. Antibodies are naturally produced by the immune system to bind very specific parts or epitopes of the potential pathogen, and this has been widely used in therapeutics due to their combined specificity and strong affinity [26]. Monoclonal antibodies that are specific to the target receptor are relatively easy to create and mass-produce, and can be delivered to target tissues to cover potential viral binding sites [27]. A typical antibody can only bind 1 epitope at a time, which can constitute a problem for viruses that either have multiple receptor affinities or are able to directly disrupt the plasma membrane without a need for the receptor. This is especially true for enveloped viruses, whose viral envelope is derived from the host cell membrane, and the similarity in composition between the two membranes will enable the virus to merge with the cell despite receptor blocking [28]. This phenomenon can be resolved through artificial antibodies that have multiple affinities. By linking together the binding domains of multiple antibodies to create a multispecific antibody, all possible entry sites for the virus can be covered. After entering the cell, the viral genome starts to recruit the host machinery to either start producing the other viral components or to transport the virus into the nucleus for integration into the host genome. The production of protein subunits for viral assembly is a crucial step for the virus to be able to replicate, and this presents an opportunity for targeted drug therapy [29]. Protease inhibitors are effective at this stage in that they disrupt the concise cleavage of viral subunits and thus hamper their assembly. Furthermore, transcription inhibitors can be used to prevent the viral genome from replicating as well as producing the necessary messenger RNAs to start viral protein production. The last step of a viral infection is the establishment of a stable pool of viral particles, preferably within the host. In some viruses, this means integrating into the host DNA and becoming quiescent, whereby the infected cell can become virtually indistinguishable from a normal cell. These reservoir cells replicate the viral genome whenever they undergo mitosis and, at any time in the patient's lifespan, can trigger the production of new viral particles to cause a resurgence. This phenomenon remains a current roadblock; however, attempts to either identify these cells or to instigate a resurgence early in the infection phase are being studied to identify a suitable therapeutic strategy to solve this issue.

3. Viral Vaccines

Although not exactly a form of treatment, vaccination is one of the most impactful means of dealing with viral diseases [30]. The development of the vaccine was historically associated with viruses [31], and for centuries since then several diseases have been virtually eradicated thanks to this technology [32]. The effectiveness of vaccines stems from the fact that the immune system can remember p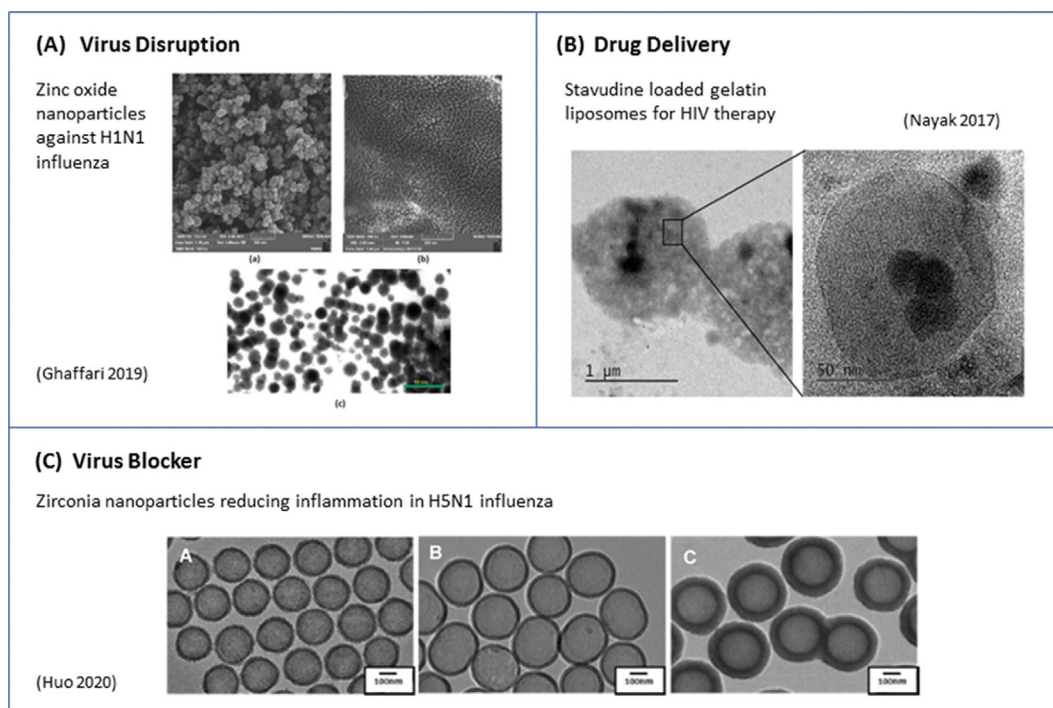athogens after initial exposure, through the memory T-cells produced by this prerogative immune response. The fast-paced and overwhelming nature of viral infections (particularly acute ones) is the main factor that contributes to their fatality: viral load increases exponentially that the immune response tries to but fails to keep up with, ultimately leading to extreme inflammatory symptoms and immune exhaustion. To address this, vaccination introduces sterilized fragments of the virus along with the adjuvant to imitate the infection. The adjuvant along with key recognizable virus components initiates a strong enough inflammatory response that triggers the creation of memory cells. Since no actual viral propagation occurs, the immune response is temporary and non-lethal. The existence of memory cells enables the immune system to recognize the virus at low concentrations, which prevents it from building up and triggering the cytokine storm. The main hurdle for vaccine development is the identification of key viral components that would enable recognition, factoring the fact that new unidentifiable strains can quickly show up over time.

4. Nanoparticle Treatment

Nanotechnology as a treatment option has slowly gained popularity over the recent years, and in the case of antiviral drug discovery it has become a useful tool for both improvement and innovation [33]. Existing antiviral drugs can be very effective in combating viral spread, although they may face difficulty in reaching the target tissue or in sustaining its release. Through drug delivery, nanoparticles are able to add targeting capabilities to otherwise nonspecific drugs. In fact, potential drug candidates which exhibit antiviral properties but are highly toxic to cells can be packaged in nanoparticles to increase their biocompatibility and enable their use in viral treatment. Moreover, nanoparticle carriers enable insoluble or hydrophobic drugs to arrive at the target tissue location and penetrate the target cell while improving circulation time [34]. By attaching ligands onto the nanoparticle, bioactive properties can be added like stimuli-response mechanisms, viral load sensing, and biological substrate interaction. These modified nanocarriers are able to remain in circulation for longer periods of time while seeking infected tissues that have high concentrations of the virus. The responsive nanocarrier would then release the drug as a response to this stimulus, and since it is a localized release the effectivity of the drug is substantially improved [35]. Also, in the case of viruses that undergo lysogenesis, it is crucial to have sustained drug release in order to suppress the spread of viruses from the quiescent reservoirs. Several nanomaterials have a slow-release mechanism that can supply the required dose of the antiviral drug over the course of the infection [36]. This prevents resurgence of new viral particles after the initial clearance. Since nanoparticles are highly adaptable and modifiable, they can become antiviral drugs themselves. Their comparable size with viral particles provides better opportunities for the nanoparticle to interact directly with the virus. Furthermore, this means that the particles can enter the cell as easily as the virions themselves. Certain metals for example that have been proven to be bactericidal through disruption of the plasma membrane can also be virucidal, and thus turning them into nanoparticles would enable their use on antiviral therapy [37]. Simply put, the application of nanoparticle technology on antiviral treatment is a good way of putting the advantages of nanoparticles against the difficulties in treating viral infectious diseases (Table 1 and Fig. 2).

Table 1. Summary of various nanoparticle strategies for viral treatment

Treatment strategy	Advantages	Limitations	Nanoparticle type	Viral disease	Reference
Virucidal nanoparticle	Simple and direct method, easy to test, most effective treatment when it works	High dosage need, possible cytotoxicity	AgNP, AuNP	HSV-1, NDV	[41-43]
			ZnO-PEG	H1N1	[38]
			CuO NP	HSV	[39]
			Graphene oxide	PEDV	[44]
Drug delivery	Able to target affected cells, biocompatible	Not therapeutic by itself, fast clearance	Gelatin NP	HIV-1	[21]
			Lecithin NP	HIV-1	[25]
			Selenium NP	H1N1	[60]
Viral blocker	Effective for chronic viral pathogens, currently comprises most of the viral drug treatments available	Needs frequent, high dosages delivery necessary	AgNP	HIV-1, Influenza, SARS-CoV-2	[46-48]
			AuNP	HIV-1	[50]
			ZnO-PEG NP	HSV	[45]
			FeO NP	H1N1	[52]
			Graphene oxide-AgNP composite	PEDV, PRRSV	[51]
			PLGA NP	HIV-1	[54]

Fig. 2. Nanoparticles used for viral treatment.

NANOPARTICLE VIRAL TREATMENT

1. Virucidal Nanoparticles

Attacking the viral particle is the most direct way of treating the infection, and nanoparticles have been tailored to attack these nano-meter-sized pathogens. Metal nanoparticles have been found to be virucidal with the same effectiveness as their bactericidal properties. Zinc oxide nanoparticles have been shown to exhibit virucidal properties against H1N1 influenza, and although zinc oxide alone showed cytotoxicity at 200 μg/mL concentrations conjugation with

PEG significantly reduced its cytotoxic effect [38]. Copper oxide nanoparticles have also been confirmed to be effective against HSV-1 infection [39]. In addition to their virucidal properties, copper oxide NPs can disrupt capsid formation and viral DNA packaging. The main disadvantage of metal nanoparticles, however, is that they are highly cytotoxic in their pure form, which necessitates additional processing steps to increase their biocompatibility. It has been shown that biogenic synthesis of metal nanoparticles can alleviate the issue. This form of synthesis makes use of the fact that certain plants and species of algae are able to sequester normally toxic levels of metal ions and form these more biocompatible nanoparticles that they either secrete out or use as a sort of chemical defense mechanism [40]. Thus, combining the metal ions and plant or algal extracts would reduce their cytotoxicity and increase their biocompatibility, making them suitable for antiviral treatment. Silver and gold nanoparticles from blue-green algae *Oscillatoria* and *Spirulina* were found to have antiviral activity against herpes simplex HSV-1 [41]. The algae were grown in the presence of high silver and gold concentrations after which they were harvested for nanoparticle extraction. These nanoparticles were both present intracellularly as well as secreted by the algae, which necessitated mechanical disruption of the algae biomass followed by magnetic separation. Silver nanoparticles that are biosynthesized with the clove (*Syzygium aromaticum*) flower bud extract were shown to be effective against the Newcastle Disease Virus (NDV) [42]. Although this disease is a major threat only for poultry, direct contact can cause conjunctivitis in humans. There have also been rare cases of the more popular avian influenza affecting individuals in the vicinity, and this study could pave the way to preventing its transmission. In another study biosynthesis of silver nanoparticles with powdered plant extracts from the family Aizoaceae - specifically from *Lampranthus coccineus* and *Malephora lutea* - showed antiviral activity against the enteroviruses coxsackievirus CoxB4 and hepatitis A HAV-1, as well as HSV-1 [43]. Furthermore, graphene oxide has been shown to destroy viral capsids on contact. Carbon-based nanoparticles have been found to both have antiviral properties as well nanocarrier potential, mostly due to their propensity for surface functionalization. One study created carbon dots (CD) loaded with the curcumin and tested its antiviral property against porcine epidemic diarrhea virus PEDV [44]. The successful inhibition of viral replication proved that the nanoparticles were able to penetrate the cells.

2. Virus Replication Blockers Using Nanoparticles

Metal nanoparticles in general have been shown to have antiviral properties as they are able to bind and inhibit viral envelopes and capsids alike. Zinc oxide nanoparticles with PEG coating were found to inhibit HSV by trapping virus particles and preventing cell contact [45]. Silver nanoparticles with various biomaterial coatings were found to inhibit several viral pathogens, ranging from influenza to HIV [46,47]. In HIV, silver nanoparticles are able to bind to the glycoprotein gp120 of HIV-1 which prevents it from interacting with helper T cell receptors. Polyvinylpyrrolidone (PVP)-coated silver nanoparticles were shown to confer long-lasting virucidal properties against HIV-1 in a cervical explant model [48]. The nanoparticles were able to inhibit viral entry as well as block viral replication even after successful intracellular HIV infection. PVP-Ag nanoparticles were also shown to work against Respira-

tory Synctial Virus (RSV), which is an etiological infection in children [49]. In addition to viral replication inhibition, AgNPs were shown to exhibit immunomodulatory effects, inducing a state of neutrophilia in mice after inoculation. Gold nanoparticles worked in a similar way, and were shown to bind the gp120 protein in vitro [50]. Composite nanoparticles can provide the necessary modification needed to enhance bioactivity, and in one study silver nanoparticles were modified with graphene oxide to produce a composite that has better biocompatibility than silver alone [51]. The nanocomposite was able to block viral entry of both PEDV and porcine reproductive and respiratory syndrome virus (PRRSV) as well as inhibiting expression of viral proteins in the culture. These viruses come from different families (PRRS from Arterivirus while PEDV is a Coronavirus), and although both share the enveloped RNA virus morphology, it is suspected that the treatment has a broad spectrum and can be applicable to more viral pathogen types. Iron oxide has also been shown to inhibit viral RNA transcription of the H1N1 influenza virus [52]. In another study, the avian strain of influenza H5N1 was shown to be susceptible to zirconia nanoparticle inhibition [53]. More specifically, ZrO_2 nanoparticles were able to inhibit viral replication, while at the same time regulate the immune response of mice under viral challenge, suppressing the inflammatory response that makes influenza dangerous. Another strategy that can be employed is to mimic the host surface receptors in order to bind and neutralize virus particles. In one study, poly(lactic-co-glycolic acid) PLGA nanoparticles coated with a T-cell membrane were tested for its antiviral property against HIV-1 in vitro [54]. To disrupt the gp120-mediated process during the infection phase, carbohydrate-coated gold nanoparticles that mimic the mannose glycan of gp-120 were used [55]. It was able to inhibit HIV-1 DC-SIGN-mediated trans-infection of T cells even at low treatment concentrations.

3. Nanoparticle Drug and Viral Vaccine Delivery

Nanoparticles have been one of the leading materials used for drug delivery, and in the context of viral diseases several NP-based treatments are being studied. Liposomes are one of the most prominent NPs that have become the standard carriers for drug delivery and vaccines. Their biocompatibility and efficient diffusion rate make them ideal vessels for the otherwise insoluble or potentially cytotoxic drug compound. Liposome-based delivery in general has also been successful due to its versatility, since the surface of liposome is amenable to many modifications. One of these is a "stealth" formulation that was used to deliver small interfering RNAs (siRNAs) against SARS-CoV-2 [56]. The unique composition of the liposome contains 50% 1,2-dioleoyl-3-trimethylammonium-Propane (DOTAP), which gives the liposome surface a positive charge. Lecithin-liposome coated gelatin nanoparticles have been used for loading the antiviral nucleoside analog stavudine for HIV-1 treatment [21]. Stavudine can inhibit viral DNA replication, which is crucial for HIV lysogenesis, but its short lifespan coupled with severe side-effects such as development of patient acidosis and neuropathy lowers its effectiveness. As such, gelatin nanoparticles were used to act as slow-release carriers for the drug to stop HIV reservoirs from forming while preventing patient side-effects and the liposome coat ensures increased circulation as well as cell uptake by immune cells. Soy-lecithin nanoparticles (SLN) have been used to load ritonavir,

an HIV protease inhibitor that causes HIV to lose its infectivity [25]. Ritonavir is usually pumped out by efflux transporters and thus has low bioavailability, but loading it in the SLN enabled not only increased uptake but also enabled sustained release of the drug. Poly(lactide-co-glycolide) (PLGA) was used for loading bictegravir (BIC), a type of integrase strand transfer inhibitor (INSTI) [57]. HIV makes an enzyme called integrase in the host cell, and performs the process of merging with the host cell's gene. By using inhibitors of the integrase required for replication of HIV, shortening of lifespan and inhibition of replication of HIV can be achieved. Encapsulation of the hydrophobic BIC resulted in the mitigation of cytotoxicity and prolongation of intracellular drug uptake and intracellular retention, enabling sustained defense from HIV. Alginate NPs have been used for delivery of the nucleoside reverse transcriptase inhibitor (NRTI) zidovudine for retroviral therapy [58]. Zidovudine has a short half-life and dose-dependent anemia has been reported. The zidovudine enabled sustained-release drug release and overcame low bioavailability through non-toxic and easily removable alginate NPs. In addition, the low serum binding properties of alginate NPs can improve the circulation time of nanoparticles and maintain drug release. Chitosan NPs conjugated with PCS peptide antigen (PSC5) performed antigen delivery for improved immune response [59]. PCS is a highly conserved region of the HIV-1 virus and mutations do not reduce the activity of the vaccine produced by PSCs. The conjugation of PCS5 with chitosan NPs was very stable at physiological pH, but the release of PCS5 was triggered in the presence of GSH. This means that peptides are only released inside cells where GSH is present in high concentrations, and can enhance the immune response by preventing antigen release until processed by immune cells such as APCs. An interesting study was done on selenium nanoparticles as a delivery system for the influenza drug ribavirin [60]. In this case an actual broad spectrum virucidal metal nanoparticle was used as a carrier for the drug, which enhanced its effect against H1N1 influenza virus. Interestingly, metal NPs have also been used as carriers of viral particles for vaccine purposes. Ferritin nanoparticles were conjugated to a hepatitis C soluble fragment and were able to confer immunity comparable to inactivated whole virions [61].

CONCLUSIONS AND FUTURE DIRECTIONS

The relevance of antiviral treatment has peaked due to the recent pandemic, which brought the spotlight onto nanoparticle technology, an area increasingly popularized in biomedical treatment. The high compatibility of these two fields of research could only mean more studies in the future, and more nanoparticle-based antiviral drugs would be discovered in the process. Hopefully, such trends can uncover the solution to the current COVID-19 epidemic as well as for other viral diseases that are yet incurable (most notably AIDS).

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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