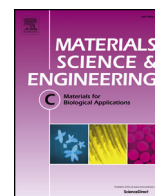




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## Review

## An overview of functional nanoparticles as novel emerging antiviral therapeutic agents

Lu Chen, Jiangong Liang\*

State Key Laboratory of Agricultural Microbiology, College of Science, Huazhong Agricultural University, Wuhan 430070, PR China

## ARTICLE INFO

## Keywords:

Functional nanoparticles  
Antiviral  
Viricidal activity  
Disease treatment

## ABSTRACT

Research on highly effective antiviral drugs is essential for preventing the spread of infections and reducing losses. Recently, many functional nanoparticles have been shown to possess remarkable antiviral ability, such as quantum dots, gold and silver nanoparticles, nanoclusters, carbon dots, graphene oxide, silicon materials, polymers and dendrimers. Despite their difference in antiviral mechanism and inhibition efficacy, these functional nanoparticles-based structures have unique features as potential antiviral candidates. In this topical review, we highlight the antiviral efficacy and mechanism of these nanoparticles. Specifically, we introduce various methods for analyzing the viricidal activity of functional nanoparticles and the latest advances in antiviral functional nanoparticles. Furthermore, we systematically describe the advantages and disadvantages of these functional nanoparticles in viricidal applications. Finally, we discuss the challenges and prospects of antiviral nanostructures. This topic review covers 132 papers and will enrich our knowledge about the antiviral efficacy and mechanism of various functional nanoparticles.

Viruses are infectious pathogens that can destroy cells, tissues and organs, with most of them causing disease and even death in humans and mammals [1,2]. Viruses have been reported to cause 2,000,000 human deaths annually world-wide [3]. To date, the optimal approach to prevent viral infections is vaccination. Unfortunately, there are not enough effective vaccines against various viruses and their variations at present, suggesting the emergency to develop highly effective drugs to prevent viruses from entering host cells for replication. Currently, several chemical drugs are available for the clinical treatment of some virus diseases. For example, acyclovir is established as a popular antiviral drug in clinical practice to treat diseases such as HBV and HCV [4]. Another commonly used antiviral drug is ganciclovir, which is effective for treating varicella and other infections in children [5]. However, research on the efficacy of these chemical drugs has revealed their unavoidable side effects on normal human cells and tissues, especially for children [6], thus limiting their wide application in clinical treatments and suggesting the imperative need to develop new effective and safe antiviral drugs. Among various antiviral strategies, nanotechnology has shown a powerful ability to address this issue, and emerging nanoparticles have been reported to exhibit extraordinary efficacy against virus infection and replication [7–9].

Nanotechnology has penetrated all aspects of virus research [10–15]. Firstly, nanotechnology-based probes have been widely used

in virus detection, leading to the production of various biosensors and bioelectronics based on novel functional nanoparticles [16–18]. Secondly, many nanomaterials have been prepared by using various virions and virus-like particles as templates [19–21], making biocompatibility and biosynthesis methodology a focus in recent biochemical research. Thirdly, intensive endeavors have been devoted to the development of fluorescent nanoprobe and their applications in research of the molecular mechanism of virus-infected cells [22–24]. Finally, more and more functionalized nanoparticles have been reported as highly potent inhibitors of viral proliferation [25]. Since the first three research areas have been summarized and reported, this paper focuses on the inhibitory effect of functional nanoparticles on viruses and the related mechanisms.

### 1. Classification and infection mechanism of viruses

Currently, viruses can be divided into eight categories according to the International Committee on Taxonomy of Viruses (ICTV) [26]. The first category consists of the double stranded DNA and single stranded DNA chimeric virus like *haloarcula hispanica* pleomorphic virus 1; the second one, the double stranded DNA viruses, such as poxviruses, herpesviruses, and adenoviruses; the third one, the single stranded DNA virus such as parvoviruses; the fourth one, the double stranded RNA

\* Corresponding author.

E-mail address: [liangjg@mail.hzau.edu.cn](mailto:liangjg@mail.hzau.edu.cn) (J. Liang).<https://doi.org/10.1016/j.msec.2020.110924>

Received 10 January 2019; Received in revised form 23 March 2020; Accepted 31 March 2020

Available online 06 April 2020

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virus like reoviruses; the fifth one, viruses with positive-sense single-stranded RNA genomes, such as the current outbreak severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), enteroviruses, hepatitis A virus, poliovirus, rhinoviruses, hand-foot-and-mouth (HFMD) virus, SARS virus, yellow fever virus, hepatitis C virus (HCV), and rubella virus; the sixth one, viruses with negative-sense single-stranded RNA genomes, including the deadly Marburg viruses and Ebola as well-known members of this group, as well as measles, influenza virus and mumps; the seventh one, viruses with single-stranded RNA viruses that replicate through a DNA intermediate, such as human immunodeficiency virus (HIV); the eighth one, viruses with double-stranded DNA genomes and replication via reverse transcriptase, such as the hepatitis B virus (HBV).

Viruses must use their host cells for self-reproduction, and viral infection involves mainly six steps: attachment, penetration, uncoating, replication, assembly, and release [27]. Specifically, viruses attach to a specific receptor site on the host cell membrane using the attachment proteins in the capsid or the glycoproteins embedded in the viral envelope, and this interaction specificity determines the host cells that can be infected by a particular kind of virus. Basically, only the nucleic acid of bacteriophages enters the host cell, while the capsid remains outside the cell. The viruses of animals and some plants can enter cells through endocytosis, with the entire virus being surrounded and engulfed by cell membranes. When the viral envelope fuses directly with the cell membranes, the enveloped viruses will enter their host cells. Once inside the host cells, the viral capsid is degraded, leading to the release of the viral nucleic acid, which then becomes available for replication and transcription. The replication mechanism depends on the viral genome. DNA viruses usually use the enzymes and proteins of host cells to produce additional DNA, which is transcribed to messenger RNA (mRNA), and then used for direct protein synthesis. RNA viruses usually use the RNA core as a template for synthesis of viral genomic RNA as well as mRNA. The last stage of viral replication is the release of the new virions produced in the host cells, allowing the infection of adjacent cells and repetition of self-replication cycles. The viral replication cycle can produce dramatic structural and biochemical changes in host cells and cause damage to them [28].

## 2. Antiviral assay methods for functional nanoparticles

### 2.1. Plaque assay

Plaque assay, a method usually used for virion adsorption test, can directly determine the effect of functional nanoparticles on virion [29]. As the infectivity of a virus can be calculated by plaque assay, the antiviral ability of functional nanoparticles can also be estimated by plaque assay results. In a typical plaque assay, a virus stock is 10-fold diluted, and 0.1 mL aliquot of the dilution is inoculated onto the monolayers of susceptible cells. After an incubation period, the virus is allowed to attach to the cells, and the monolayers are covered with a nutrient medium agar. After a period of further incubation, the original infected cells release the virus progeny, and the presence of the gel restricts the spread to neighboring cells, leading to the formation of a zone of infected cells called a plaque, which becomes large enough and visible to the naked eye under room temperature conditions. The titer of a virus stock can be calculated in plaque-forming units per milliliter (PFU/mL), which is the exact value of the viral infectivity. The viricidal ability of nanoparticles can be precisely determined by calculating the PFU value of the virus before and after binding with antiviral functional nanoparticles.

### 2.2. TCID<sub>50</sub> assay

The tissue culture infectious dose (TCID<sub>50</sub>) assay is a typical virus quantification assay for determining the infectious titer of any virus which can cause cytopathic effects in tissue culture for about five to

twenty days while cells remain in viable conditions. In a typical assay, dilution steps are required to determine the amount of the virus for killing 50% of infected host cells or causing a cytopathic effect in 50% of inoculated tissue culture cells. This assay is a commonly used in clinical research for quantitation of a lethal dose of viruses. When used in tissue culturing, host cells are plated, and serial virus dilutions are added. After incubation, the percentage of cell death is calculated and recorded for each virus dilution, and results are collected as a TCID<sub>50</sub> result [30].

### 2.3. Confocal imaging assay

Confocal virion adsorption assay is used to observe the changes in host cells when infected by viruses [31]. The confocal microscopy, a powerful technique for illustrating the course of viral infection in host cells, is widely used in antiviral assay of functional nanoparticles. Likewise, indirect immunofluorescence experiment can be also performed by confocal microscopy imaging to show changes in the structure of viral proteins before and after treatment by functional nanoparticles. The confocal imaging is a visualization technique to display the antiviral results of functional nanoparticles.

### 2.4. $\beta$ -Galactosidase assay

$\beta$ -Galactosidase entry assay is another protocol developed by the US Food and Drug Administration (FDA) to measure host symptoms after vaccination, which is now modified to be specific for detecting virus entry [32].  $\beta$ -Galactosidase is an exoglycosidase that can hydrolyze the  $\beta$ -glycosidic bond formed between a galactose and its organic moiety and may also cleave fucosides and arabinosides, but with much lower efficiency.  $\beta$ -Galactosidase is vital to organisms as a key provider of energy and a carbon source via the breakdown of lactose into galactose and glucose. The  $\beta$ -galactosidase assay can be used in genetics, molecular biology, and life sciences. In antiviral characterization of functional nanoparticles, it is commonly used as a reporter gene to monitor the expression levels in host cells, providing indirect evidence for the ability of functional nanoparticles to treat viral infections by showing the physiological state of infected host cells.

### 2.5. Transmission electron microscopy

Transmission electron microscopy (TEM), a major analytical technique in physical, chemical and biological sciences, can capture fine details even as small as a single column of atoms, which is thousands of times smaller than a resolvable object seen in a light microscope. Therefore, TEM can be used as an effective way to show the viricidal conditions with clear images about the binding between viruses and functional nanoparticles [33]. The TEM results can provide visual image about the infected cells and demonstrate the viricidal ability of functional nanoparticles. Another important TEM technology is transmission electron cryo-microscopy, usually known as Cryo-TEM, which can observe unstained or unfixed specimens and display them in their natural environment. In 2017, the Nobel Prize in Chemistry was awarded jointly to Richard Henderson, Jacques Dubochet, and Joachim Frank for their development of the cryo-electron microscopy for determination of high-resolution structure of biomolecules in solutions. In antiviral research, it can be used for characterization of the effects of functional nanoparticles on virus-infected cells.

### 2.6. Western blot assay

Western blot assay, a method extensively used in biochemistry for qualitative detection of individual proteins and protein modifications, can identify the protein degradation of the virus treated with functional nanoparticles [34]. In a typical experiment, the sample undergoes protein denaturation, followed by gel electrophoresis characterization

and creation of a primary antibody via a synthetic or animal-derived route for recognizing and binding to a specific target. Next, the electrophoresis membrane is washed twice in a solution containing the primary antibody before excess antibody is washed off, followed by adding a secondary antibody to recognize and bind to the primary antibody. The secondary antibody can be visualized by various methods, such as staining, radioactivity and immunofluorescence, allowing indirect detection of a specific target protein. In antiviral characterization of functional nanoparticles, the Western blot assay can show the variations in the protein structures of viruses after interaction with functional nanoparticles.

### 2.7. Real-time polymerase chain reaction

Real-time polymerase chain reaction (RT-PCR), also known as quantitative polymerase chain reaction (qRT-PCR), a molecular biology laboratory technology based on polymerase chain reaction (PCR), is mainly used to monitor the amplification of a targeted DNA during the PCR procedure. This technology can also be used to detect the virus DNA after its interaction with functional nanoparticles [35]. For instance, it can detect the gene expression of host cells as an indicator of viral infectivity, and PCR results can clearly show the growth and metabolism status of host cells after virus infection and treatment with functional nanoparticles. Therefore, the PCR technique provides indirect evidence for the antiviral ability of functional nanoparticles.

### 2.8. Flow cytometry assay

Flow cytometry, a technique for detecting the physical and chemical characteristics of a population of cells or particles, can be used to sort different cells and count large numbers of cells as well as determine their characteristics and functions. In flow cytometry analysis, large amounts of cells can be quickly examined, with data being gathered and processed by a computer. Therefore, flow cytometry can be used to count the virus-infected cells and determine the killing efficiency of functional nanoparticles [36].

### 2.9. In vivo analysis

In vivo research refers to the test of the effects of various biological facts on whole living cells or organisms, including animals, humans, and plants. This analysis is aimed to discover the effects of chemicals or drugs on biological systems. In antiviral research, it aims to protect lives through vaccines and chemicals, thus it focuses on the safety of vaccines and chemical drugs for plants, animals and humans. For instance, Pardi and Hogan group has developed a single low-dose intradermal immunization with lipid-nanoparticle-encapsulated nucleoside modified mRNA (mRNA-LNP) encoding the pre-membrane and envelope glycoproteins of a strain from the Zika virus [37]. By vaccination in live mice, a single dose of 50 µg was found to be enough for protecting non-human primates against a challenge at five weeks after vaccination. The work shows that nucleoside-modified mRNA-LNP could be a potential candidate as an anti-Zika virus vaccine. These in vivo mouse data demonstrate that animal vaccine assay is a necessary and useful method for analyzing the antiviral performance of functional nanoparticles.

### 2.10. Computer simulation

Computer simulation refers to the reproduction of a chemical or biological behavior by using a computer to simulate the outcomes of a mathematical model associated with an order system. Computer simulations have become a useful tool for mathematical modeling of many natural systems in biochemistry. In antiviral research, computer simulation is an auxiliary means to calculate variations in a specific DNA and protein site during interactions between a virus and functional

nanoparticles, providing necessary indirect evidence for predicting the changes in viruses and host cells after the intervention of functional nanoparticles [38].

## 3. Recent progress of antiviral functional nanoparticles

### 3.1. Quantum dots

Quantum dots (QDs), semiconductor nanocrystals with peculiar size-dependent optical and electronic properties [39], have been widely used for virus and cell labeling, detection and image tracking, due to their distinguished luminescent properties, such as broad excitation spectroscopy, narrow and bright emission spectroscopy, long fluorescence lifetime, and size-dependent emission wavelengths [40–42]. However, whether traditional QDs have antiviral ability is largely unknown, and our group has done some research on this issue. For instance, Du et al. have investigated the antiviral effect of glutathione (GSH) capped CdTe QDs by using pseudorabies virus (PRV) as a testing model [43]. After systematical investigation by one-step growth curve, MTT assay, and fluorescence colocalization analysis, CdTe QDs were shown to alter the structure of the viral surface proteins and inhibit the PRV from entering host cells. Meanwhile, the release of Cd<sup>2+</sup> from CdTe QDs was also found to decrease the virus number that infected the host cells. Both the surface charge and size of QDs were identified to have significant anti-PRV effect, with higher inhibitory efficacy for positively charged QDs than negatively charged QDs. Additionally, the bigger the QD size, the higher the antiviral ability. For the toxicity of QDs, our group further explored the antiviral effect of lower toxic QDs, such as Ag<sub>2</sub>S NCs and carbon dots. Du et al. have demonstrated that Ag<sub>2</sub>S NCs had excellent viral inhibitory ability with a different mechanism from other functional nanoparticles [44] (Fig. 1). The viral inhibitory mechanism can be divided into two main categories based on viral infection, which starts from virion adhesion or binding to the surface receptors of host cells, followed by penetration and viral replication. Accordingly, effective blocking of viral attachment and entry can produce a remarkable prophylactic effect against viral infectious diseases, and the other strategy is focused on inhibition of viral replication and budding. Previous experimental results have shown that Ag<sub>2</sub>S NCs treatment can not only inhibit the synthesis of viral negative-strand RNA and viral budding, but also positively regulate the generation of IFN-stimulated genes and the expression of proinflammation cytokines, which might prevent the infection of porcine epidemic diarrhea virus (PEDV). Moreover, the Ag<sub>2</sub>S NCs were also shown to have comparable virus inhibitory effect on other RNA viruses, such as porcine reproductive and respiratory syndrome virus (PRRSV). Consistent with the result for PEDV, Ag<sub>2</sub>S NCs displayed inhibitory effects on the viral protein expression level of PRRSV. Therefore, Ag<sub>2</sub>S NCs have been identified to have broad-spectrum antiviral properties against RNA viruses.

To explore the antiviral ability of lower toxic QDs, our group investigated the viral inhibitory effect of carbon dots step by step. The viricidal capacity of carbon dots was found to be closely related with their carbon precursors and synthesis conditions, implying the necessity of systematic investigations of the antiviral activities of different carbon dots. Our group has developed a facile and cost-effective method to prepare uniform and stable carbon dots (CDs) with antiviral properties [45] (Fig. 2), and investigated their effects on viral reproduction by using PRV and PRRSV as the test models of DNA virus and RNA virus, respectively. Experimental results showed that CDs can significantly inhibit the multiplication of both PRV and PRRSV. The treatment of CDs can also dramatically induce the production of endogenous interferon and the expression of interferon-stimulating genes (ISGs), both of which can inhibit virus replication. Additionally, we prepared a kind of blue and cyan fluorescent CDs, which could strongly inhibit PRV, and the antiviral mechanism was demonstrated by RNA exaction and RT-qPCR assays. The CDs were shown to greatly influence the innate immune

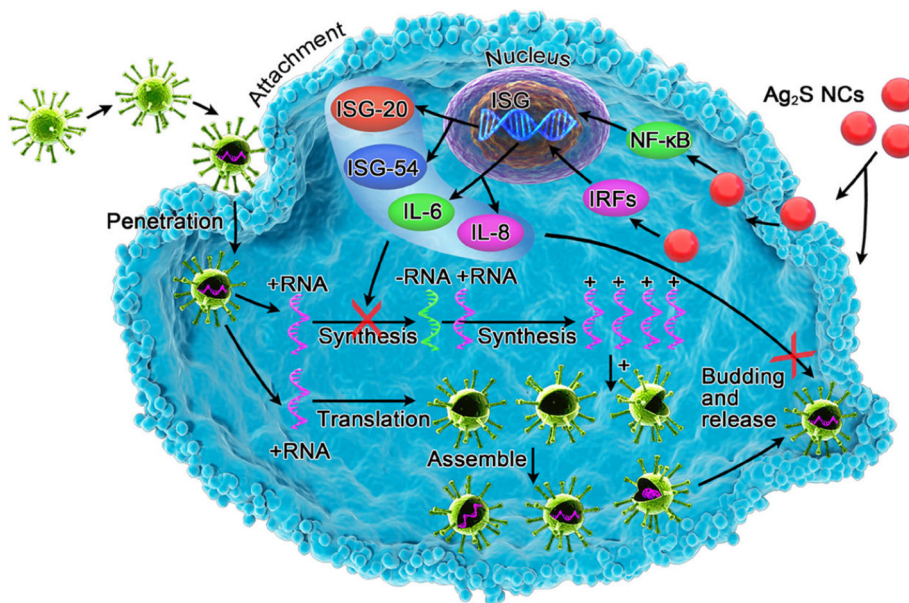


Fig. 1. The potential mechanism for the antiviral activity of Ag<sub>2</sub>S NCs (Reprinted with permission from Ref. 44 Copyright 2018 ACS).

response of host cells by stimulating them to produce more interferons (IFNs), which play a significant role in defense against viruses. Furthermore, the CDs were also found to enhance the expression of many ISGs, which is vital to the CDs-based antiviral mechanism [46]. Additionally, Huang et al. have fabricated benzoxazine monomer derived carbon dots (BZM-CDs) and demonstrated their infection-blocking ability against flaviviruses and non-enveloped viruses, such as porcine parvovirus and adenovirus-associated virus [47]. BZM-CDs were shown to directly bind to the surface of virions, and inhibit the first step of virus and host cell interaction, providing direct evidence for the viricidal ability of functional CDs.

Previous studies have suggested that the antiviral activity of functional CDs can be apparently improved by proper surface chemical modification. For instance, Szunerits et al. reported that the carbon nanodots (C-dots) surface-functionalized with boronic acid or amine can be used to combat herpes simplex virus type 1 (HSV-1) by simply inhibiting the virus from entering host cells [48]. The inhibition mechanism is found to be involved in their ability to bind to HSV-1 and

change the virus coat proteins, and the carbon dots were shown to interfere with HSV-1 infection in a concentration-dependent manner with EC<sub>50</sub> = 80 ng mL<sup>-1</sup>. The same group has also found that carbon quantum dots (CQDs) with different ligand modifications vary in their inhibitory activities against human coronavirus. CQDs derived from ethylenediamine/citric acid were found to show almost no virus inactivation effect, in contrast to excellent virus inhibitory effect with an EC<sub>50</sub> lowered to 5.2 ± 0.7 µg/mL for CQDs prepared by surface modification with 4-aminophenylboronic acid [49].

In recent years, scholars have paid more attention to the use of traditional Chinese medicine for combating viruses. Du et al. have developed a one-step method by using curcumin to prepare uniform and stable cationic carbon dots (CCM-CDs) with antiviral properties [50]. The inhibitory performance of CCM-CDs on viral replication is studied by using porcine epidemic diarrhea virus (PEDV) as a coronavirus model, and CCM-CDs were found to inhibit the proliferation of PEDV with much higher efficiency than non-curcumin modified carbon dots. The treatment of CCM-CDs was shown to change the viral surface

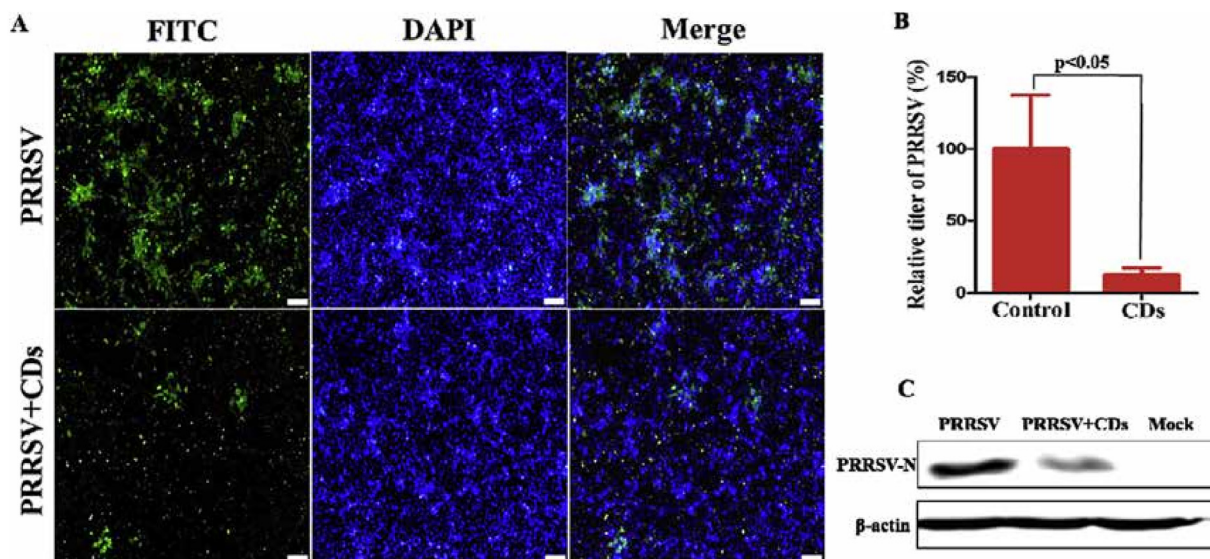
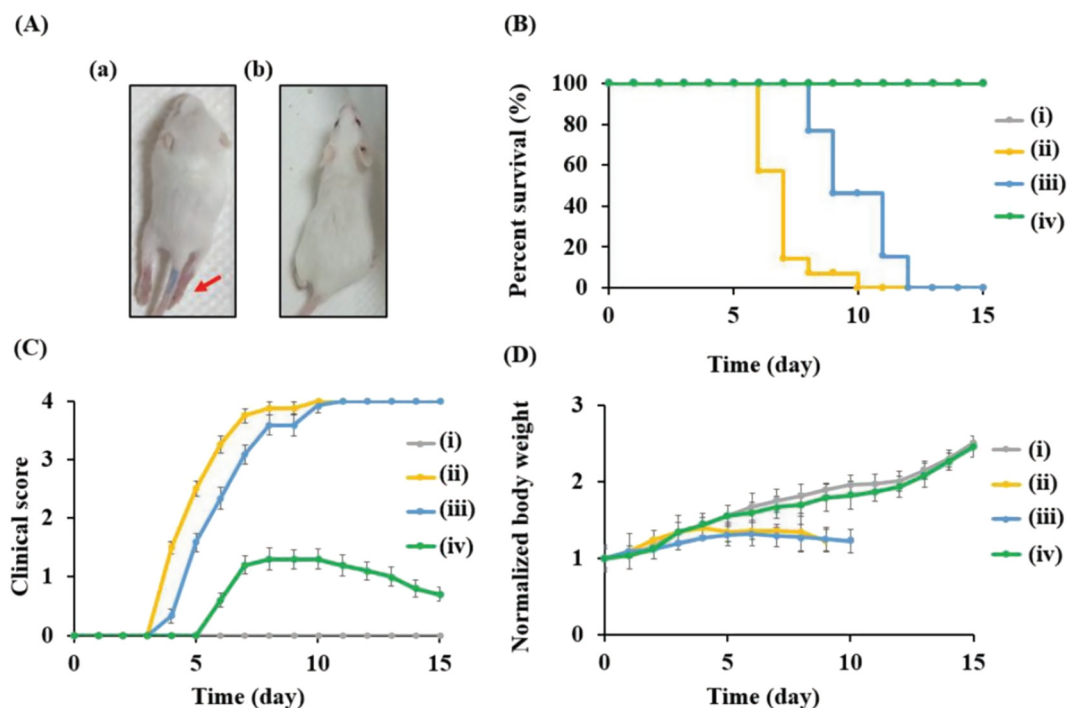


Fig. 2. The antiviral results of carbon dots on PRRSV (Reprinted with permission from ref. 45 Copyright 2016 Elsevier).

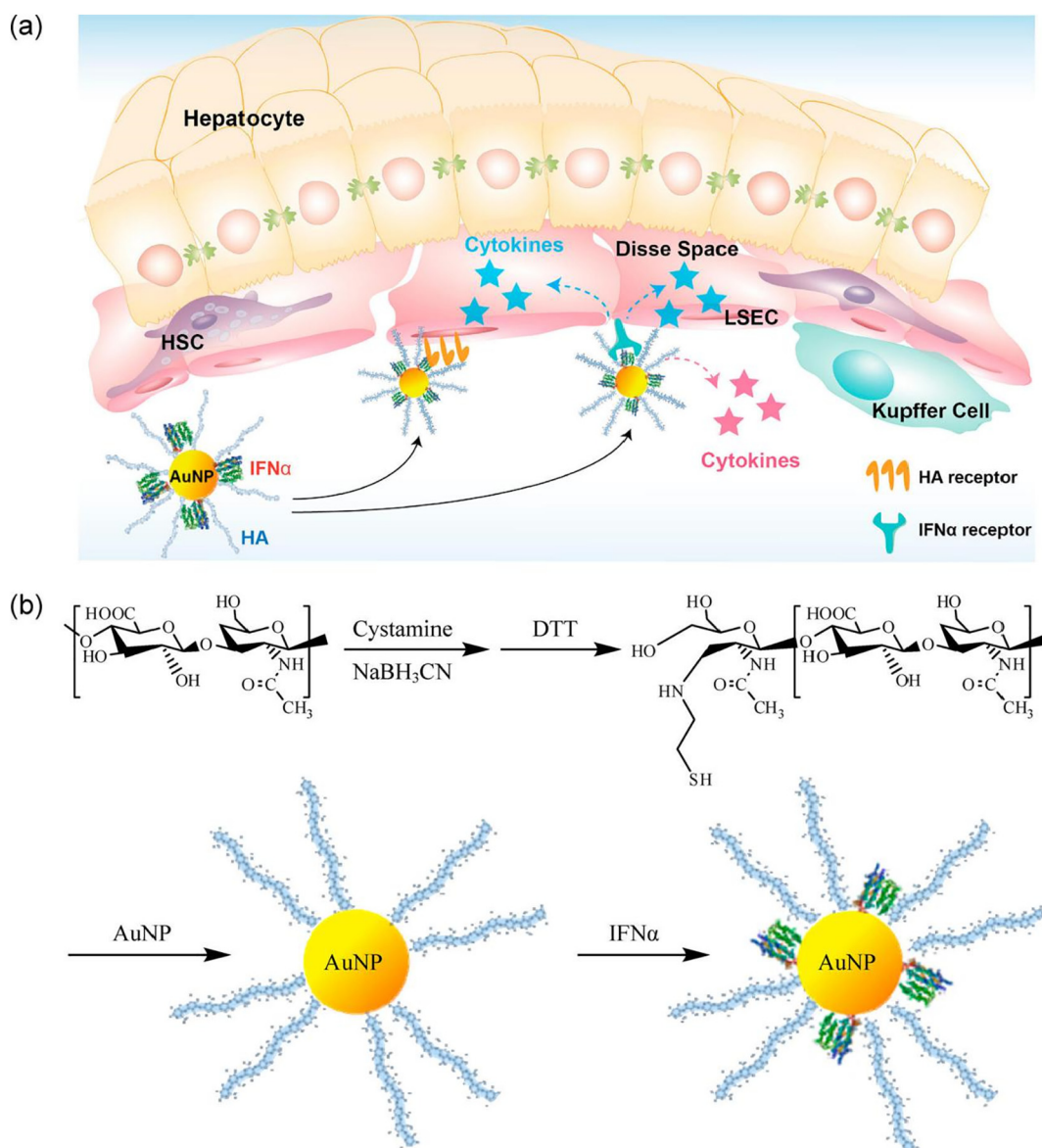


**Fig. 3.** (A) Representative photographs on day 7 post-infection (a) without and (b) with treatment of Cur-CQDs-180 (25 mg kg<sup>-1</sup>). The red arrow indicates apparent limb paralysis in the untreated infected mice. (B) Survival rates, (C) clinical scores, and (D) body weights of (i) newborn mice without infection and (ii – iv) newborn mice intraperitoneally injected with (ii) PBS, (iii) curcumin (25 mg kg<sup>-1</sup>), or (iv) Cur-CQDs-180 (25 mg kg<sup>-1</sup>) followed by intraperitoneal injection of EV71 at the dose of  $2 \times 10^6$  PFU. A group of uninfected mice treated with sterile PBS was used as an uninfected control. The curcumin or Cur-CQDs-180 treatment was performed every 12 h daily for seven consecutive days. The mice were monitored for 15 d. (Reprinted with permission from Ref. 51 Copyright 2019 Wiley). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

protein structure, and then inhibit the viral entry. This treatment can also suppress the synthesis of virus negative-strand RNA, virus budding, and the accumulation of reactive oxygen species for PEDV. Moreover, the intervention of CCM-CDs is also found to suppress viral replication by stimulating the production of ISGs and proinflammatory cytokines. Interestingly, when curcumin was used to synthesize carbon dots against enterovirus 71 (EV71) in vivo with new-born mice as test models [51], the carbon quantum dots derived from curcumin (Cur-CQDs) through one-step dry heating were demonstrated to have superior EV71 inhibitory characteristics. The most valuable contribution of this work is the identification of direct effects of heating temperature during preparation on the antiviral activity of Cur-CQDs by mouse test (Fig. 3). As shown in the results, one-step heating of curcumin at 180 °C preserves many of the moieties of polymeric curcumin on the surfaces of the as-synthesized Cur-CQDs, resulting in superior antiviral characteristics. Later, our group has developed a new type of highly biocompatible carbon quantum dots (Gly-CDs) with glycyrrhizic acid (an active ingredient of Chinese herbal medicine) using a hydrothermal method, and the as-prepared Gly-CDs were shown to inhibit the proliferation of PRRSV by up to 5 orders of viral titers [52]. Further investigations reveal that Gly-CDs can inhibit PRRSV invasion and replication, stimulate antiviral innate immune responses, and suppress the accumulation of intracellular reactive oxygen species (ROS) caused by PRRSV infection. The Gly-CDs were also observed to have a broad antiviral capacity against PRV and PEDV. These results have demonstrated the high bactericidal activity of CDs modified by traditional Chinese medicine and suggest the necessity for the development of more traditional Chinese medicines in the near future to prepare CQDs for antiviral research to facilitate their wide applications in clinical trials and the treatment of viral infectious diseases with high efficiency and low cost.

### 3.2. Silver nanoparticles

Silver nanoparticles (AgNPs) have been employed as chemical drugs thanks to their unique physiochemical and chemical properties as well as biological features, such as anti-inflammatory, anti-angiogenesis, antiplatelet, antifungal, anti-cancer and antibacterial activities [53–56]. Currently, AgNPs have attracted increasing attention in biological and medical applications due to their easy synthesis process. For instance, AgNPs have been reported as biomedical therapeutic agents, such as wound dressings and long-term burn care products [57], and anti-bacterial lotions containing silver nanoparticles are now commercially available. However, silver nanoparticle-based antiviral agents are still in the infancy stage, and very few reports have been published about their viricidal activity [58,59]. The latest reports have shown that silver nanoparticles exhibit antiviral activities against influenza A virus, hepatitis B virus, human parainfluenza virus, herpes simplex virus, and human immunodeficiency virus [60]. Sreekanth et al. have developed a simple and green ultra-sonication synthesis route for preparing quasi spherical silver nanoparticles with an aqueous extract from *Panax ginseng* roots, and the as-prepared silver nanoparticles were found to be viricidal against influenza A virus with excellent performance [61]. While AgNPs exhibit concentration-dependent cytotoxicity, their antiviral ability is not affected by the relatively low cytotoxicity. Interestingly, AgNPs have been shown to produce enhanced inhibitory effect on influenza A virus. Chen and Zhu et al. have prepared an anti-influenza A virus drug zanamivir loaded by silver nanoparticles (Ag@ZNV) to inhibit H1N1 influenza virus [62]. They systematically investigated the viral suppression mechanism and found both AgNPs and zanamivir had relatively high antiviral efficacy, but with synergistic virus inactivation effects observed for the Ag@ZNV nanostructure, which not only exhibited remarkable thermodynamics and kinetics stability, but also obvious inactivation effect on influenza virus. By resisting the production of excess ROS, the Ag@ZNV nanostructure can easily regulate the



**Fig. 4.** (a) Strategic illustration of HA-AuNP/IFN $\alpha$  complex for the target specific systemic treatment of HCV infection. (b) Schematic representations for the preparation of thiol end-modified HA and HA-AuNP/IFN $\alpha$  complex (Reprinted with permission from Ref. 72 Copyright 2012 ACS).

neuraminidase activity, a key domain for assessing the effect of influenza viruses on infected cells. Furthermore, they found that p38 and p53 signaling pathways were related with the down-regulation of ROS-mediated apoptosis induced by Ag@ZNV in MDCK cells after H1N1 virus infection. Collectively, the Ag@ZNV has great potential in controlling influenza virus infection and can be used in clinic treatment.

As mentioned above, most silver nanoparticle-based antiviral agents are prepared in a liquid atmosphere, which greatly limits their wide applications in virus control. To tackle this problem, many efforts have been made recently. One of the effective solutions is hydrogel, a semi-solid preparation that can broaden the application field of silver nanoparticle-based reagents. For instance, Szymańska et al. have developed a multifunctional tannic acid-modified silver nanoparticle-based mucoadhesive hydrogel for improving the local treatment of herpes simplex virus (HSV) infections [63]. The silver nanoparticles modified with tannic acid (TA-AgNPs) were shown to effectively reduce the HSV-2 infectivity at the vaginal mucosal surface, suggesting the potential use of functional nanoparticles as microbicides in HSV prevention. In order to further improve the antiviral efficiency of TA-AgNPs, they fabricated a three-dimensional cross-linked polymer matrix to encapsulate the TA-

AgNPs and form a hydrogel, and the hydrogel made from mucoadhesive polymers provided closer contact between the drug carrier and the mucosal tissue, thus improving the activity of TA-AgNPs. The combination of AgNPs and tannic acid (a plant metabolite) was demonstrated as a promising approach to treat HSV-2 infection. Notably, hydrogel not only serves as a carrier of antiviral agents in virus suppression, but also has a wide spectrum antiviral ability. For instance, Walid Azab's group has produced a nanogel that has been shown to have broad-spectrum antiviral properties [64]. Polymeric nanogels, the cross-linked hydrogel particles with a 3D network consisting of water-soluble and swellable polymers, represent a better and promising choice for the design of virus entry inhibitors, due to the reason that they can be degraded to smaller sized fragments and removed by renal clearance. This broad-spectrum antiviral universality lies in the virus inhibitory mechanism, which prevents the virus from attaching to the heparan sulfate proteoglycan on the host cell surface, and then causes a series of events to prevent the entry of the virus. As many human viruses attach to their host cells via heparan sulfate moieties, these flexible nanogels have the potential of robust inhibitors against these virus infections.

### 3.3. Gold nanoparticles

Gold nanoparticles, one of the earliest synthesized nanomaterials with superior electric, optical and mechanical properties [65,66], have attracted attention in nanodiagnostic and nanomedical applications due to their exquisite quantum size effect, surface effect, and macroscopic quantum tunneling effect. Thus far, various methods for the preparation of gold nanoparticles have been reported and reviewed [67–69], and many small molecule, DNA sequence, protein, bacterial, and virus detection methods have been developed based on gold nanoparticles. For example, Mirkin and his coworkers are the first team dedicated to the preparation and application of gold nanoparticles in biology and medicine, and they systematically reviewed the synthesis, modification and application of gold nanoparticles [70]. Apart from considerable contributions in biochemistry, gold nanoparticles also possess the display effect on pathogens, fungi and viruses. For instance, Chattopadhyay et al. have prepared highly mono-dispersed quasi spherical gold-nanoparticles and used them to inhibit herpes simplex viruses [71]. Using an ultrasonic strategy, gallic acid was modified onto the surface of the monodispersed gold nanoparticles and used as a stabilizer for gold nanoparticle spheres. The MTT assay revealed that uniformly sized gold nanoparticles with non-toxic debris are essential for therapeutic applications. Furthermore, plaque-reduction assay has proved that the gallic acid modified gold nanoparticles have good virus inhibitory capability against herpes simplex viruses. Compared with clinic drug acyclovir, the functionalized gold nanoparticles do not produce any drug-resistant strains and can exhibit excellent viricidal properties by interfering with the virus attachment to Vero cells and inhibiting the spread of viral infection. Furthermore, gold nanoparticles are used as an emerging delivery carrier of various pharmaceuticals. Sei Kwang Hahn and his co-workers have prepared a hyaluronic acid gold nanoparticle and interferon complex for targeted treatment of hepatitis C virus infection [72] (Fig. 4). Compared with traditional treatment of hepatitis C infection, polyethylene glycol (PEG)-conjugated interferon  $\alpha$  (IFN $\alpha$ ) and hyaluronic acid (HA)-modified gold nanoparticles (HA–AuNP/IFN $\alpha$  complex) have exhibited higher stability after injection in human serum. Even at seven days after injection, the HA–AuNP/IFN $\alpha$  complex is still detectable in mouse liver, in contrast to the absence of the polyethylene glycol (PEG) conjugated interferon. This work demonstrates that the gold nanoparticle-based complex is a successful anti-HCV drug and superior to any commercially available chemical drugs.

Gold nanoparticles are a good scaffold for development of virus inhibitors, and functional gold nanoparticles were shown to suppress influenza virus, simplex herpes virus, and HIV [73]. For example, Christian Melander and his colleagues have demonstrated that multivalent gold nanoparticles can inhibit HIV fusion by multiple molecular interactions [74]. They mentioned that gold nanoparticles cannot inhibit viruses alone, and when covalently bound to other molecules that bind to the viruses, gold nanoparticles can exponentially increase the antiviral effects through multivalent interactions. Additionally, Javier and his collaborators have developed a series of dendronized anionic gold nanoparticles and found that dendronized AuNPs could inhibit HIV more effectively than dendrons alone. Their results showed that the presence of extra sulfur atoms in the dendrons and the coordination of the  $S(CH_2)_3SO_3$  moiety may hinder the aggregation of gold nanoparticles, making the modified gold nanoparticles more effective against HIV [75]. Rainer Haag et al. have reported that sialic acid functionalized gold nanoparticles can inhibit influenza virus infection by multivalent interactions [76]. Zanamivir and Oseltamivir are two well-known clinical drugs used to treat influenza virus infectious diseases. However, due to the high intrinsic mutation rate, it is highly possible for the influenza virus to develop resistance against those two drugs [77]. Fortunately, sialic acid coated gold nanoparticles can prevent the influenza viruses from attaching to their host cells, thereby reducing the possibility of drug resistance development. Overall, gold

nanoparticles provide both a scaffold for virus inhibition and an excellent way for developing antiviral chemical drugs. Interestingly, Rainer Haag and his collaborator have also found that the antiviral effect of gold nanoparticles is highly dependent on their sizes [78]. They demonstrated that surface area normalized polysulfated gold nanoparticles of diameters equal to or larger than the virus diameter could inhibit the binding between viruses and their host cells more efficiently than smaller particles. On average, larger sized gold nanoparticles were shown to be two orders of magnitude more efficient than smaller particles in inhibiting viral infections, probably due to different mechanisms.

### 3.4. Gold nanoclusters

Recent years have witnessed the rapid development of gold nanoclusters (Au NCs) composed of tens and hundreds of gold atoms whose size is comparable to Fermi wavelength of the electrons, usually less than 2 nm. Au NCs with a diameter close to 1 nm or sub-nanometer size possess interesting physicochemical properties while bulk gold does not. Due to the distinguished size between isolated atoms and larger nanoparticles, Au NCs have potential applications in optoelectronics, catalysis, biochemistry and biomedicine. Recently, Au NCs have proven to be effective fungicides. For instance, Xie and his collaborators have reported that Au NCs can kill both Gram-positive and Gram-negative bacteria [79]. They demonstrate that this wide-spectrum antimicrobial activity is attributed to the ultra-small size of Au NCs, which allows them to better interact with bacteria and cause a metabolic imbalance in bacterial cells after devouring Au NCs, leading to increased production of intracellular reactive oxygen species and thus killing the bacteria. Our group has discovered that Au NCs have certain viricidal properties and can prevent viruses such as PRRSV from entering their host cells [80]. We investigated the influences of glutathione-stabilized fluorescent Au NCs on viruses by plaque assay, indirect immunofluorescence assay, quantitative real-time polymerase chain reaction assay, and Western blot assay. Interestingly, Au NCs were found to selectively inhibit the proliferation and protein expression of PRRSV, but not for PRV. It was shown that Au NCs can directly inactivate PRRSV and block viral adsorption but produce no effect on viral genome replication (Fig. 5). In order to explore the effect of surface modification upon the antiviral performance of Au NCs, we synthesized two types of gold clusters with different surface modification: histidine stabilized Au NCs (His-Au NCs), and mercaptoethane sulfonate and histidine stabilized Au NCs (MES-Au NCs) [81]. It is His-Au NCs rather than MES-Au NCs that were found to strongly inhibit the proliferation of PRV, as indicated by the results of plaque assay, confocal microscopic analysis, quantitative real-time polymerase, Western blot assay, and chain reaction assay. These results demonstrate that surface modification is very effective in enhancing the antiviral abilities of functional nanoparticles.

### 3.5. Graphene oxide

Graphene oxide, a unique single-atom-thick and two-dimensional carbon material arranged in a hexagonal lattice, was discovered by two English scientists (Geim and Novoselov) in 2004, who were awarded the 2010 Noble Prize in physics [82,83]. Graphene oxide and its derivatives have recently received more and more attention due to their remarkable electrical, mechanical and thermal properties [84]. Aside from their biomedical applications, the antiviral properties of graphene oxide and its derivatives have also been extensively studied. For example, Tang and his co-workers found that graphene oxide was a promising candidate for virus prevention [85]. Their study indicated that the graphene oxide could effectively inactivate the pathogenic agent of hand-foot-and-mouth disease EV71 and endemic gastrointestinal avian influenza A virus H9N2 in a temperature-dependent manner. At room temperature 25 °C, the disinfection effect of graphene oxide treatment



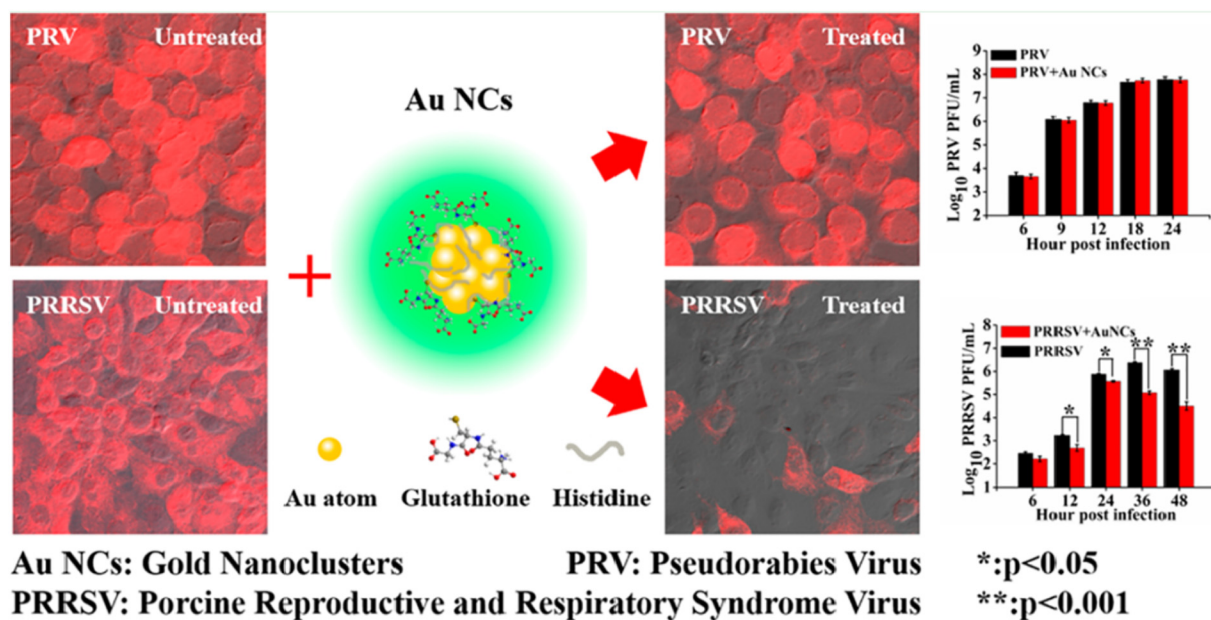


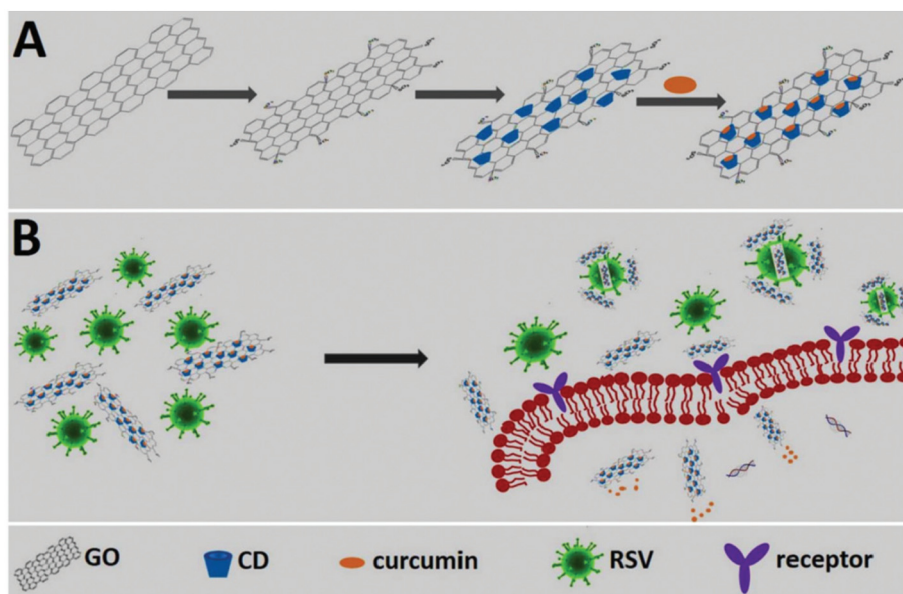
Fig. 5. Effects of glutathione-stabilized fluorescent gold nanoclusters on the proliferation of pseudorabies virus (PRV) and porcine reproductive and respiratory syndrome virus (PRRSV) (Reprinted with permission from Ref. 80 Copyright 2018 ACS). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

was weak; at physiological temperature 37 °C, the effect increased; as the temperature increased to 56 °C, the inactivation effect was much higher. They also discovered that the graphene oxide without any labeling or modification could destroy the virus by interaction. The results demonstrated that the disrupted virus was inserted into the edge and basal plane of graphene oxide, implying a general virus disruption effect based on the physicochemical interactions of graphene oxide with both capsid and envelope viruses. Furthermore, they found heating is an efficient way to enhance the capture and the denature effect due to the electron transfer and energy transfer properties of graphene oxide. The data have proved that without graphene oxide, the degradation of EV71 was not clearly visible within 15 min, while after 5 min of graphene oxide treatment, EV71 was totally undetectable. Likewise, the destruction of native H9N2 was insufficient even at 30 min whereas after only 5 min at 56 °C, the graphene oxide treatment completely degraded the virus. This virus prevention strategy can be further applied to a wide range of antiviral fields without any tedious procedures or causing any environment interference.

To improve its antiviral efficiency, graphene oxide is usually functionalized with other antiviral agents to form a synergistic virus prevention agent against the virus aggressive invasion. For instance, Huang and his collaborators developed a curcumin functionalized graphene oxide to combat the respiratory syncytial virus by loading a large amount of curcumin on the cyclodextrin functionalized graphene oxide composite [86] (Fig. 6). The curcumin loaded graphene oxide was confirmed to have a significant inhibitory effect on respiratory syncytial virus infection and high biocompatibility with host cells. The experimental data demonstrated that the composite could prevent respiratory syncytial virus from infecting the host cells by directly inactivating the virus and inhibiting the virus from attaching to host cells, coupled with prophylactic and therapeutic effects on the virus. The excellent synergistic antiviral capacity is attributed to the perfect combination of graphene oxide with curcumin, and this innovative composite has the potential use as an effective nanomedicine for the treatment of respiratory syncytial virus infection. The possible antiviral mechanisms of graphene oxide involve the following three ways: the curcumin functionalized graphene oxide can (i) inactivate the virus directly, (ii) inhibit viruses from attaching to host cells, and (iii) finally interrupt the virus replication. The multifunctional graphene oxide-based antiviral

agents provide a new insight into nanomedicine fabrication. Gedanken's group prepared a functional graphene oxide nanomaterial to inhibit herpes simplex virus type-1 from attaching to host cells [87]. Inspired by the cell surface receptor heparan sulfate, a negatively charged linear polymer composed of alternating moieties of hexuronic acid and glucosamine sulfated at various positions, the author designed a graphene oxide (GO) and partially reduced sulfonated GO (rGO – SO<sub>3</sub>) composite for suppressing the herpes simplex virus type-I (HSV-I) infections through a competitive inhibition mechanism. The results have shown that the GO and rGO-SO<sub>3</sub> had almost the same antiviral activity as that of heparan sulfate, suggesting the multiple simultaneous polyvalent interactions between GO, rGO-SO<sub>3</sub> and HSV-I contribute collectively to the strength and selectivity of the interaction compared to monovalent interactions, which influences the attachment and entry of most viruses to the cells. Further investigations demonstrated that the nanocomposite is effective in reducing viral infections, blocking attachment is the main mechanism for this interaction, and the presence of nanomaterials does not affect cell-to-cell diffusion. These intrinsic properties of GO and its derivatives will facilitate the development of safer and more effective antiviral nanodrugs with fewer side effects.

Graphene oxide quantum dots can also be used to construct antiviral therapeutic agents against viruses. Although still in the infancy, graphene oxide quantum dots-based nanoparticles have exhibited a great potential in the development of antiviral drugs. Iannazzo et al. probed target-specific HIV inhibition by conjugating graphene oxide quantum dots (GQDs) with non-nucleoside reverse transcriptase inhibitors, demonstrating that surface functionalization of GQDs with biocompatible targeting ligands can further improve their biocompatibility and therapeutic efficacy, facilitating the development of new anti-HIV agents with an ideal pharmacological effect [88]. Yang's group has fabricated fluorine functionalized graphene quantum dots as inhibitors against the amyloid aggregation of human islet amyloid polypeptide [89]. To our knowledge, some malignant infectious diseases can be caused by the misfolding and massive aggregation of viral proteins, such as transmissible spongiform encephalopathies and human Parkinson's disease, which can be prevented by this graphene quantum dot-based protein aggregation inhibitor due to its inhibition of prion virus.



**Fig. 6.** (A) The synthesis route of graphene oxide-based nanocomponent. (B) The inhibition mode of functional nanomaterial composites against RSV infection (Reprinted with permission from Ref. 86 Copyright 2017 RSC).

### 3.6. Mesoporous silicon nanoparticles

Intensive endeavors have been devoted to antiviral fight all over the world, including the use of some chemical drugs approved in clinical treatment [90–92]. However, some of those drugs fail to play an essential role in treating viral infectious diseases, probably due to the problems related to drug release efficiency. Antiviral drugs are known to locate their target tissues based on human blood circulation, which usually leads to low drug releasing efficiency and serious side effects. To circumvent this issue, mesoporous silicon nanoparticles are used as antiviral drug delivery carriers [93]. Compared with silver nanoparticles and gold nanoparticles, silicon nanomaterials are less cytotoxic and more biocompatible. Due to multiple porous structure, silicon materials can load drugs more easily than other nanostructures. Ross and his collaborators prepared glycosaminoglycan (GAGs) mimetic functionalized solid and mesoporous silica nanoparticles as antiviral agents to inhibit the entry of herpes simplex virus (HSV) type 1 and type 2 viruses into host cells [94]. The HSV entry begins with the attachment of viral glycoproteins to host cells, and GAGs are rich in sulfated groups like the heparan sulfate, with a hydrophobic and electrostatic interaction mechanism between HSV and GAGs. The authors designed GAG mimetic compounds containing sulfonate and hydrophobic groups, which can competitively bind to HSV and prevent HSV from entering their susceptible cells by blocking cellular attachment with remarkable viricidal activity. The mesoporous structure provides a foundation for future modifications to achieve the controlled release of antiviral drugs, and further research will focus on the relationship of the porous silicon nanostructures with drug loading and releasing efficiency. The results of this paper support the potential application of porous silicon nanoparticles as topical intravaginal microbicides against HSV infections, such as genital herpes or other infectious diseases, which are sensitive to inhibition by GAG mimetics. Another advantage of silicon nanoparticles is their low cytotoxicity. Silver nanoparticles are reported to have considerable cytotoxicity and may destroy host cells at a silver nanoparticle concentration above 2 mg/mL, while gold nanoparticles are more cytotoxic and may destroy host cells at a concentration above 0.2 mg/mL, in contrast to almost no cytotoxicity for silicon nanoparticles (SiNPs) when used as viricidal agents. Karamov et al. have investigated the antiviral activity of silicon nanoparticles against HIV and respiratory syncytial virus (RSV) and found the porous silicon nanoparticles exhibited excellent viricidal

capacity [95]. The strong inhibitory activity was detected at the SiNPs concentration below 0.1 mg/mL, which was significantly lower than the corresponding cytotoxic concentration. The obtained results are attributed to the non-specific interaction between SiNPs and viruses, resulting in the blocking of virions by SiNPs. Due to the unique porous structure, SiNPs can bind to viral proteins, which can effectively reduce the infectious virus strains and change the virus attack behavior. Therefore, SiNPs can be used as good prophylaxis agents against viruses, especially for those without any vaccines or drugs for treatment. The systematical antiviral mechanism of SiNPs is investigated by Cardoso's group [96] (Fig. 7). They synthesized the mesoporous silica nanoparticles with distinct surface groups and enabled the modified SiNPs to bind to viruses through hydrophobic interactions. As expected, the invasion abilities to host cells are much lower for the SiNPs-treated viruses than those untreated with SiNPs. This study indicated that the interaction between viruses and SiNPs causes drastic changes on their surface, which will greatly alter their attack behavior when attached to host cells. The unique porous structures of SiNPs endow their surface with abundant chemical groups and easy binding to various viral proteins, which is the most important mechanism for the viricidal activities of SiNPs.

With further study on the treatment of virus infectious diseases, many new nanoparticles have been developed to meet the challenges in clinic applications. For example, Venezuelan equine encephalitis virus (VEEV) poses a major public health threat due to its amenability for use as a bioterrorism agent and its severe consequences for human health [97]. ML336 is a recently developed chemical inhibitor against VEEV, showing effective inhibitory effect on VEEV infection in vitro and in vivo. However, its medical translation was hindered by its limited solubility and stability. To overcome these limitations, Negrete and his coworkers have developed lipid-coated mesoporous silica nanoparticles (LC-MSNs) with apparently improved solubility [98]. The large surface area of the MSN core promotes hydrophobic drug loading while the liposome coating retains the drug activity and increases the circulation time and biocompatibility, offering an ideal ML336 delivery platform. The results showed that LC-MSNs can load  $20 \pm 3.4 \mu\text{g}$  ML336/mg and then release  $6.6 \pm 1.3 \mu\text{g}$ /mg ML336 over 24 h. ML336-loaded LC-MSNs significantly prevented VEEV in vitro in a dose-dependent manner as compared to unloaded LC-MSNs controls, demonstrating that MSNs can obviously improve the targeting efficacy of drugs and have great potential as an antiviral candidate carrier for new medicine

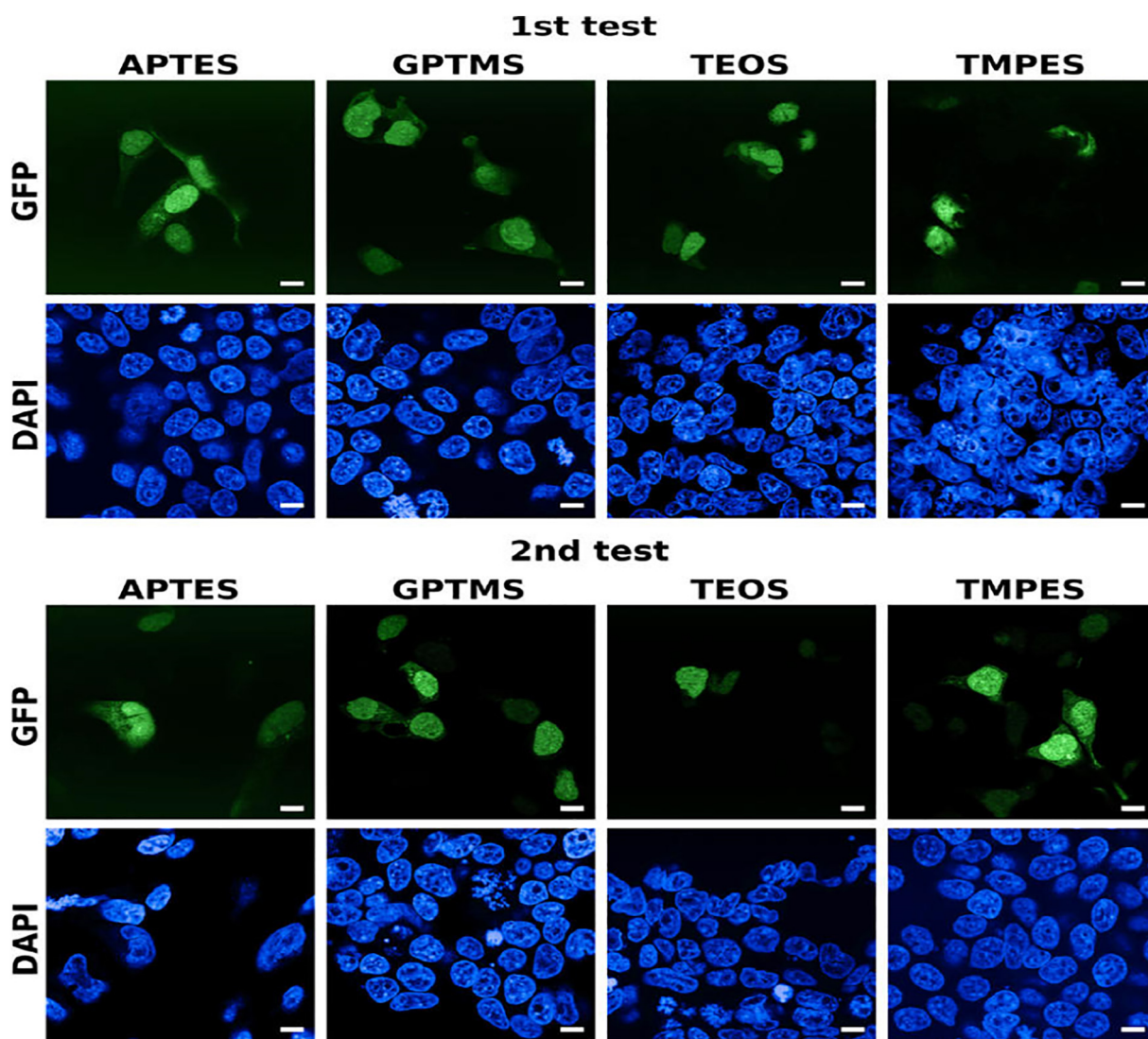


Fig. 7. Antiviral results by silicon nanoparticles. (1st test: silicon nanoparticles were incubated with the virus prior to infection. 2nd test: silicon nanoparticles were incubated with the cells before infection) (Reprinted with permission from Ref. 96 Copyright 2016 ACS).

development.

### 3.7. Polymers and dendrimers

Compared to mono compounds, scientists have found that polymers with long chains and branches have high antiviral capacity [99]. Due to the flexible molecular design, polymers can be prepared as arbitrary standards based on viricidal effects. Recently, various polymers have been fabricated to meet the needs of ubiquitous viral/bacterial agents. Among them, organotin compounds are a series of antiviral drugs with excellent performances. The first antiviral organotin compound was reported by Sadykh-Zade's group, who developed some organotin polymers derived from trimethyltin and triethyltin esters, which showed extraordinary antiviral activity due to hydrolysis of organotin moieties [100]. Later, Roner et al. mentioned that organotin polymers can be used as antiviral agents in a systematical review [101]. Organotin compounds were usually used as anti-tumor agents, but now many studies have shown that they have extraordinary antiviral properties. The organotin has a relative long retention time in patient blood circulation and shows even better effect than the clinical antiviral drugs of acyclovir and other antiviral drugs, which can be attributed to the following reasons: (i) polymers provide a large molecular weight and can be filtered out by kidney more slowly than small molecules, giving

rise to a longer retention time for targeting the infected issues in vivo; (ii) polymers have more condense structures and can offer much higher local concentration than small mono-compounds, thus facilitating a stronger binding between polymers and targets; (iii) reported evidence has demonstrated that various kinds of cells have little resistance to polymers, which is very significant in protecting host cells from invasion by viruses when using polymer-derived drugs; (iv) polymers have flexible structures and size so that they have more binding domains to the target viruses and inhibit them from attacking host cells. The inhibitory effect can be improved by changing the polymer subunits and their structures, which is mainly responsible for the higher antiviral capacity of polymers than small compounds and any other single nanoparticle-derived drugs.

To demonstrate the specific viral inhibition mechanism of organotin compounds, Roner et al. compared the antiviral capabilities of metal-containing polymers, including organotin and cisplatin-like polymers, two outstanding antitumor compounds [102]. The authors concluded that the compounds with tumor inhibition effect tend to possess viricidal properties. Experiments with these two polymers indicated that their excellent antiviral efficacy depends mainly on blocking viral DNA replication. Another important polymer is DNA, termed as nucleic acid polymer with a long backbone. Wedemeyer et al. have demonstrated that nucleic acid polymers can prevent the release of hepatitis B surface

antigen (HBsAg) particles by binding to the amphipathic alpha helix in the class I surface glycoprotein, thus capable of treating the disease of type D virus infection [103]. Moreover, the author also mentioned that the nucleic acid polymers can exhibit antiviral ability before and after the entry of virus to susceptible cells both in vitro and in vivo. The antiviral ability of other polymers was investigated by Whitten et al., who evaluated the viricidal performance of poly(phenylene ethynylene) (PPE)-based cationic conjugated polyelectrolytes (CPE) and oligo-phenylene ethynylenes (OPE), which were usually used as anti-bacterial agents [104]. Interestingly, the two polymers are also excellent candidates for antiviral applications, showing the same viricidal mechanism as the antibacterial agent. Under the UV-Visible light exposure, the CPEs and OPEs can produce singlet oxygen species, followed by the formation of more corrosive reactive oxygen intermediates, due to the  $\pi$  bonding system in the backbone of the compound. The singlet oxygen and subsequent ROS intermediates are known to be highly harmful to biomolecules, including DNA, RNA, and proteins. Through this mechanism, the CPEs and OPEs can exhibit remarkable viricidal performances. Furthermore, their structures and sizes can be chemically modified according to specific antiviral needs.

Polymers can be used not only as effective antiviral drugs, but also as co-factors for treatment of virus infectious diseases, such as antiviral drug carriers. Song and Haam et al. have developed amphiphilic copolymers comprising methoxy-poly(ethylene glycol)-block poly(phenylalanine) copolymers, which encapsulated mir-323a in the core and favipiravir in the exterior layer as both hydrophilic and hydrophobic antiviral agents [105]. This polymer-carried drug can effectively treat influenza A virus infectious diseases. Compared with naked drugs, polymer-carried drugs can solve three drug-targeting problems: (i) efficiently improving the solubility of antiviral drugs; (ii) prolonging the retention time of drugs in vivo; (iii) enhancing the uptake efficiency of drugs in cells. These advantages render polymers an excellent drug carrier in antiviral clinical applications. Therefore, polymers are being used in more and more antiviral drugs as antiviral coatings. For instance, Sierra's group used the self-assembly of amphiphilic dendrimers in water to fabricate micelles for encapsulating camptothecin as a therapy against the HCV [106]. The micelles can easily address at least three drawbacks of anti-HCV drugs: reducing the toxicity of those drugs, increasing the solubility of anti-HCV drugs in aqueous environment, and more importantly, maintaining the stability of anti-HCV drugs at physiological pH to enhance their antiviral activity, because camptothecin contains a lactone ring that is hydrolyzed at physiological pH. The experimental results have shown that the camptothecin-loaded dendrimer can inhibit HCV replication and exhibit much lower toxicity at a low drug concentration. It is worth noting that Kim's group has developed a kind of novel liver-targeted cyclosporine A-encapsulated poly (lactic-co-glycolic) acid (PLGA) nanoparticles, which could inhibit the replication of HCV both in vitro and in an HCV mouse model with excellent performance. The paper points out that targeting the host factor cyclophilin A (CsA) is essential for HCV replication; however, due to its immunosuppressive activity and severe side effects, the clinical applications of CsA as an antiviral agent have been limited worldwide. To overcome these drawbacks, they have successfully developed a liver-specific sustained drug delivery system by conjugating the liver-targeting peptide to PEGylated CsA-encapsulated PLGA nanoparticles. The clinical trial results have shown that the delivery system is highly specific to liver, thus contributing to the reduced immunosuppressive effect and toxicity profile of CsA. Moreover, the polymer nanoparticles could effectively inhibit viral replication with a sustained and prolonged anti-HCV effect, even after treatment withdrawal [107]. Currently, major attempts are being made to improve the antiviral activity of dendrimers. Daniel et al. has developed a triple combination of carbosilane dendrimers, tenofovir, and maraviroc as a potential microbicide to prevent HIV-1 sexual transmission [108]. By systematical investigation on the HIV target cells and topical issues, they concluded that the three-drug combination increases the antiviral potency and

works synergistically as a potential microbicide, which facilitates our understanding of the viricidal activity of dendrimers.

### 3.8. Other functional nanoparticles

Various nanoparticles have been explored in medical applications, such as cancer treatment and pathogen disease nursing, leading to the development of many new strategies against bacteria and viruses. RNA interference (RNAi) is one of such strategies to treat virus infectious diseases [109]. Basically, RNAi is a fundamental gene regulatory mechanism that is mediated by the RNA-induced silencing complex (RISC). Cao et al. reported an artificial nanoparticle complex that can effectively mimic the function of the cellular RISC machinery for guiding target RNA cleavage [110]. They designed a nanozyme for the treatment of HCV by actively cleaving HCV RNA in a sequence specific manner. This nanozyme is less susceptible to degradation by proteinase and can be effectively occupied by cultured human hepatoma cells. Meanwhile, the nanozyme is nontoxic to the cultured cells, and in a xenotransplantation mouse model under ambient conditions, it is shown not to trigger detectable cellular interferon response but have potent antiviral activity against HCV in cultured cells as well as in the mouse. Moreover, this nanozyme is easy to synthesize by a two-step strategy. In a typical experiment, gold nanoparticles are first functionalized with RNase A in a carbonate buffered solution at pH 9.6 and then modified with the anti-HCV oligonucleotide. The results have shown that DNA nanoparticles are of a precisely controlled size and structural conformation, with great potential in therapeutic treatments.

To develop broad-spectrum antiviral agents against various viral mutations, scientists tried to find new targets to suppress virus replications. Cholesterol biosynthesis within the infected cells is one of the promising targets of many viral systems, including HCV, HBV and HIV. Polyunsaturated liposomes (PLs) fabricated for intracellular, endoplasmic reticulum targeted in vivo drug delivery were modified to contain polyunsaturated fatty acids that perform an independent antiviral activity by reducing cellular cholesterol [111]. Treatment of HCV, HBV, and HIV infections with PLs significantly decreased viral infectivity and secretion. Furthermore, pretreatment of cells reduced the infectivity of both HCV and HIV by suppressing plasma membrane cholesterol levels. This work demonstrates that the antiviral activity in the system can inhibit viral infectivity by reducing virus-associated cholesterol, which is a viable way to suppress broad spectrum viral infections.

With the rapid development of nanotechnology, apart from the afore-mentioned nanoparticles, many other types of functional nanomaterials with antiviral activity have emerged recently. For instance, Palestino et al. prepared rare-earth upconverting  $Gd_2O_3:Tb^{3+}/Er^{3+}$  fluorescent nanoparticles as microcarriers of a Zika virus antigenic peptide with adjuvant properties [112]. Mazurkow et al. developed the spray-dried alumina granules modified with copper oxide nanoparticles and assessed the effect of copper oxidation state on virus removal capacity [113]. Hashemzadeh's group investigated the effect of copper oxide nanoparticles (CuO-NPs) on HSV-1 infection, and they found that copper oxide nanoparticles (CuO-NPs) have high inhibitory effect on herpes simplex virus type 1 (HSV-1), and the exposure of HSV-1 to CuO-NPs at the highest non-toxic concentration (100  $\mu$ g/mL) resulted in 2.8 log<sub>10</sub> TCID<sub>50</sub> reduction in infectious virus titer versus the virus controls [114]. Nabila et al. fabricated a curcumin-based nano emulsion to improve the solubility and cell uptake efficacy of curcumin, and they obtained an excellent dengue virus inhibitory result from the nano emulsion [115]. Derbalah et al. fabricated nickel oxide nanostructures (NONS) and evaluated their direct antiviral activity against cucumber mosaic virus (CMV) [116], and the results showed that cucumber plants treated with NONS could strongly suppress CMV infection versus non-treated plants. Huo et al. investigated the antiviral effect of zirconia (ZrO<sub>2</sub>) nanoparticles (NPs) against a highly pathogenic avian influenza virus [117], and the experimental data demonstrated that zirconia NPs

could well protect mice against the highly pathogenic avian influenza virus without any side effect. Ghaffari et al. developed zinc oxide nanoparticles (ZnO-NPs)-derived drugs for inhibition of H1N1 influenza virus infection [118], and they pointed out that PEGylated ZnO-NPs could be a novel, effective, and promising antiviral agent against H1N1 influenza virus infection. Titanium dioxide (TiO<sub>2</sub>) nanoparticles were revealed to inactivate the influenza virus H3N2 by directly destroying virus particles [119]. Nanoparticles have also been used as antiviral drug-carriers by self-assembling structures for prevention of Zika virus transmission [120]. In a word, those nanoparticles have exhibited superior capability in virus targeting and inhibition, as well as lower toxicity than chemical drugs in vivo. Currently, research on nanomaterials-based antiviral agents is still on the rise, and more and more promising materials will be used in antiviral treatments in the future.

#### 4. The antiviral mechanisms of functional nanoparticles

The whole virus infectious procedure mainly consists of attachment, penetration, replication and budding, while antiviral functional nanoparticles are intended to inhibit viruses by blocking or suppressing some of these steps. Herein, we will classify the different mechanisms of nanoparticles by their antiviral performance. The most direct way to suppress viruses is to inactivate them, and some of the nanostructures can interact with viruses, change their capsid protein structure and then dramatically reduce the virulence, which can be attributed to both physical and chemical mechanisms for decreasing the active virus number. To our knowledge, most of viral infections start with the attachment to host cells, usually by binding to the target acceptor protein. If nanoparticles can effectively inhibit the attachment, then host cells will be free from infection. Stellacci's group has designed a series of antiviral nanoparticles with long and flexible linkers mimicking heparan sulfate proteoglycans, the highly conserved target of viral attachment ligands (VALs), which can achieve efficient viral prevention through effective viral association with a binding simulated to be strong and multivalent to the VAL repeating units [121]. These particles are not cytotoxic and show in vitro nanomolar irreversible activity against herpes simplex virus, human papilloma virus, respiratory syncytial virus, dengue and lentivirus. Therefore, the functional nanoparticles can be used as a broad-spectrum antiviral agent to suppress the first step of viral infection, attachment. The second way to suppress viruses is blocking their penetration and entry to host cells by changing the cell surface membrane and protein structures. Haag and his collaborators have synthesized a series of water-soluble fullerene-polyglycerol sulfates (FPS) with different fullerene and polymer weight ratios and varying numbers of polyglycerol sulfate branches [122]. The combination of polyanionic branches with a solvent exposed variable hydrophobic core in FPS proves to be superior to analogs possessing only one of these features in preventing interaction of vesicular stomatitis virus coat glycoprotein with baby hamster kidney cells. Thus, development of blockings between viruses and host cells is an effective way to suppress virus infections. In the case of virus entry into cell, destroying their replication is the third effective strategy to inhibit the virus, which is usually achieved by suppressing the expression of certain enzymes which originally helped to complete the replication of virus DNA or RNA. The final strategy is to inhibit virus budding and excrete it from host cells. The offspring of a virus may be more virulent than its mother, and if functional nanoparticles prevent the virus from budding and greatly reduce the number of offspring viruses, the virulence will be reduced to an extraordinary degree. The typical antiviral mechanisms for functional nanoparticles are listed below in Table 1.

#### 5. Challenges and prospects

With the advantages of large surface-to-volume ratio, high surface reaction activity, and size-dependent optical and electronic properties, functional nanoparticles are being extensively explored in the field of

biosensors and biomedicines, and their viricidal activity has also been systematically investigated [125,126]. In this topical review, we have discussed the antiviral activities of quantum dots, gold nanoparticles and clusters, silver nanoparticles, graphene oxide, silicon materials and dendrimers as well as many other recently emerging nanoparticles. These functional nanoparticles can provide a novel platform for fabrication of biosafe and effective drugs for nanoscale treatment of virus infectious diseases in the future. Among these reviewed nanoparticles, carbon quantum dots modified with traditional Chinese medicines have a broad application prospect due to their remarkable biocompatibility and low toxicity. As a viricidal agent, they have exhibited superior and broad virus inhibition efficacy in both *in vitro* and *in vivo* models. Additionally, the nanoparticle drugs approved by the US Food and Drug Administration (FDA) will also be very popular in future clinic markets, such as gelatin nanoparticles and PLGA nanoparticles, due to their high stability as well as convenience in storage and transport [127,128]. Overall, more and more effective and safe nanodrugs are available to combat viruses. However, there are some important issues to be solved for nanoparticles. First, it is necessary to further improve their biocompatibility. Currently, dissolubility of nanoparticles decreases the releasing efficacy of many antiviral drugs, and effective synthesis procedure is one of the routes to enhance the biocompatibility of functional nanoparticle-based antiviral drugs. Secondly, targeting specific virus is a very challenging task, and improving the specificity of functional nanoparticles-based antiviral drugs is the key to solve this problem. Thirdly, it is essential to preserve the antiviral activity of nanoparticles when binding with viruses, and nanodrug structure design and fabrication protocol are the key to settle this issue. Fourthly, to date, the viricidal mechanism of functional nanoparticles is still largely unknown, especially for inhibition of drug-resistant viruses, despite several reports about the inhibitory effects of nanoparticles on drug-resistant virus strains. For instance, Gao and his collaborators discovered that iron oxide nanomaterial can be used as an enzyme for catalytic inactivation of drug-resistant H1N1, H5N1, and H7N9 subtype [129]. Lara et al. have demonstrated that silver nanoparticles can inhibit a wide variety of circulating human immunodeficiency virus (HIV-1) strains, including clinical isolates, T and M tropic strains, and resistant strains [130]. Fifthly, more efforts should be made to deliver the functional nanoparticles into the cells and tissues *in vivo* and find animal models to test the antiviral efficacy of functional nanoparticles. Sixthly, it is vitally necessary to expand the mutation range of target viruses and update nanostructures so that we can compete with any new virus strain to protect global public health. Finally, we cannot ignore the important issue of nanoparticle toxicity, thus the stability and degradation issues should be a constant research topic along with the development of functional nanoparticles [131,132]. Although low concentration of usage is probably safe and non-toxic towards active cells and tissues, it is still necessary to investigate the concentration limits of antiviral nanoparticles to host cells and host tissues, especially in human clinical trials. As shown in the previous results, the toxicity of most nanoparticles is dose-dependent and the antiviral activity also works in a dose-dependent manner. Therefore, optimization must be performed for each viricidal agent to obtain its optimal concentration.

Nowadays, with the unprecedented development and industrialization of nanotechnologies, large quantities of nanoparticles are produced in laboratories and industrial production lines every year, posing a huge challenge for us to address the biocompatibility and biosafety issues. Now, the amount-related toxicity of nanoparticles is being studied and will be resolved soon. It will not be long before various biosafe and effective antiviral drugs derived from functional nanoparticles can be used to protect and treat patients in clinical applications during a global pandemic.

**Table 1**  
Typical antiviral mechanisms for nanoparticles.

Nanomaterial	Virus	Mechanism	Reference
Graphene oxide	Respiratory syncytial virus	Directly inactivate virus and inhibit attachment	[86]
Nanogel	PRRSV	Shield attachment and penetration	[64]
Silver nanoparticle	Herpesvirus	Affect viral attachment	[63]
Graphene oxide	Herpesvirus	Attachment inhibition	[87]
gold nanoparticles	Herpesvirus	Prevent viral attachment and penetration	[71]
Nano-carbon	Herpesvirus	Inhibit virus entry at the early stage	[123]
Silicon nanoparticles	Influenza A	Reduce the amount of progeny virus	[124]
Ag <sub>2</sub> S nanoclusters	Coronavirus	Block viral RNA synthesis and budding	[44]
Gd <sub>2</sub> O <sub>3</sub> :Tb <sup>3+</sup> /Er <sup>3+</sup> nanoparticles	Zika virus	As antigen microcarriers for Zk2 peptide of ZIKV	[112]
Copper oxide nanoparticles	Herpes simplex virus type 1	Oxidation of viral proteins and degradation of viral genome	[114]
NiO nanostructures	Cucumber mosaic virus	Increase the expression of pod, pr1 and pal1 genes	[116]
Zirconia nanoparticles	H5N1 influenza virus	Promote the expression of cytokines	[117]
Zinc oxide nanoparticles	H1N1 influenza virus	Inhibit virus only after viral entry into host cells	[118]

### Declaration of competing interest

The authors declare no conflict of interest.

### Acknowledgement

This research was supported by the National Natural Sciences Foundation of China (31772785, 21305049), National Key Research and Development Program (2016YFD0500105).

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