Advances in Antiviral Material Development

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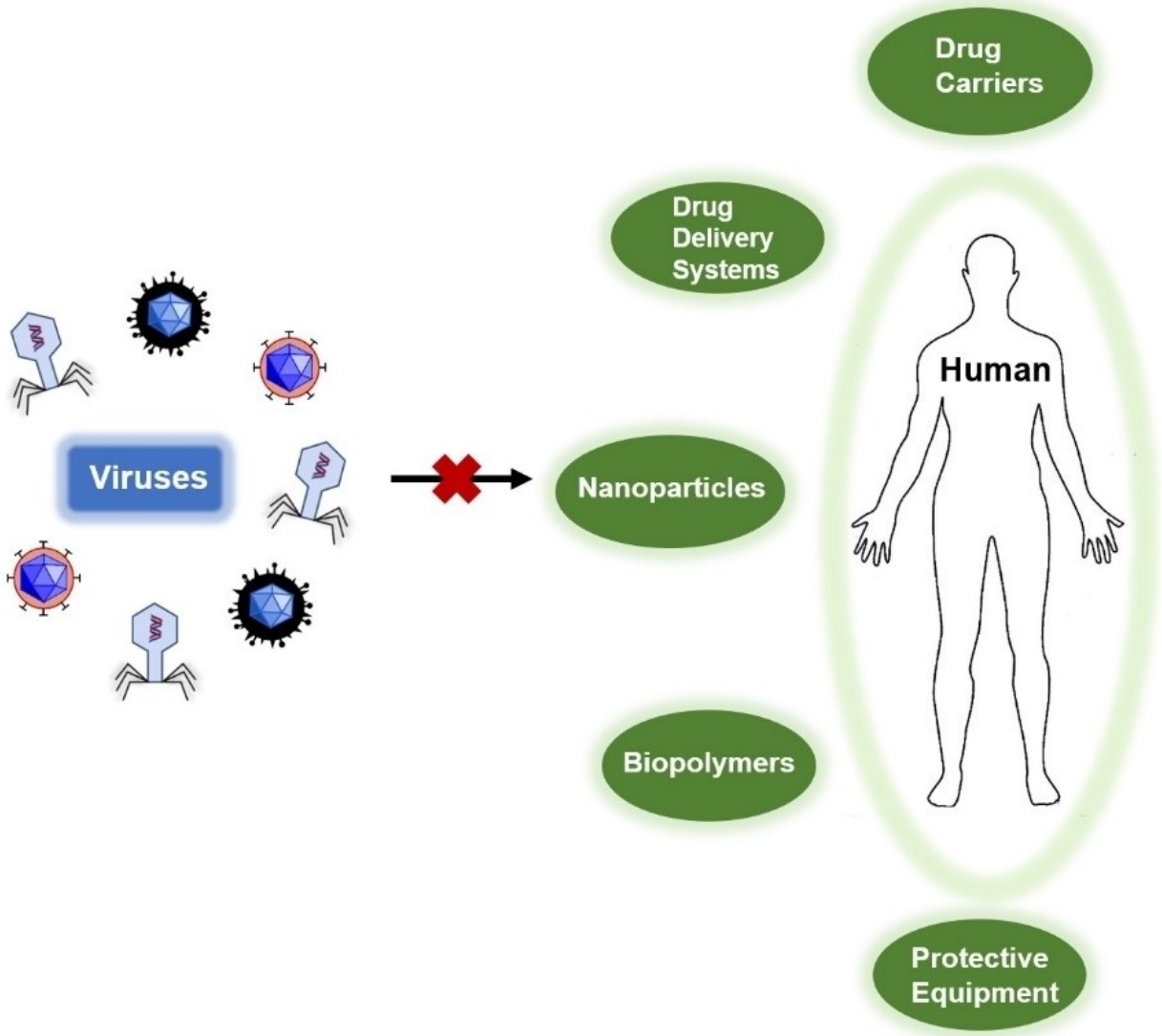

The rise in human pandemics demands prudent approaches in antiviral material development for disease prevention and treatment by effective protective equipment and therapeutic strategies. However, the current state of the antiviral materials research is predominantly aligned towards drug development and its related areas, catering to the field of pharmaceutical technology. This Review distinguishes the research advances in terms of innovative materials exhibiting antiviral activities that take advantage of fast-developing nanotechnology and biopolymer technology. Essential concepts of antiviral principles and underlying mechanisms are illustrated, followed by detailed descriptions of novel antiviral materials including inorganic nanomaterials, organic nanomaterials, and biopolymers. The biomedical applications of the antiviral materials are also elaborated based on the specific categorization. Challenges and future prospects are discussed to facilitate the research and development of protective solutions and curative treatments.

1. Introduction

Human society is entering a new pandemic age fueled by factors such as the rise in global travel, intensive urbanization, deforestation and changing agricultural practices, all of which increase the possibility of human exposure to animal species that carry potentially deadly viral infections.[1] Human enteric viruses pose a serious threat for disease transmission leading to illness and death, as the human species are unlikely to have immunity to the emerging viruses.[2] A variety of pathogenic viruses have existed and evolved to cause severe harmful impacts, e.g., severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) epidemics. Besides, H5 N1 may be evolving faster than our ability to understand it, becoming harder to predict the occurrence of a human pandemic.[3] The global mortality rate of H5 N1 was 63%, peaking as high as 82% in Indonesia.[2] The worldwide epidemic of the Hong Kong influenza (H3 N2) in 1968 was reported to be a recombinant virus between human and animal/avian virus, and was even not a mutant virus as previously reported.[4] Thus, human pandemics can result from numerous undetected avian influenza strains in existence that may arise out of recombination at any point in time.[4]

In this highly connected world, new viruses are able to spread rapidly, causing devastating effects that science must retool to encounter the possible pandemic threats.[1] Research is vital in developing the technology, systems, and services required to achieve universal health care.[5] The conventional methods of prevention involve vaccines and antiviral drugs. However, the development of a vaccine for a new strain could take from few months to several decades; meanwhile, the virus could spread globally and substantially affect the health care system and the global economy.[6] To date, there have been numerous reports and publications on antiviral materials. Biomedical applications of antiviral materials dominate the literature over food applications.[7] However, antiviral materials have not been widely applied in commercial use for personal protection and safety. Influenza viruses have claimed the lives of millions, causing annual epidemics and occasional pandemics.[6a] In cases of fast-moving pathogens such as influenza viruses and coronaviruses, one of the most basic protective strategies is to prevent viral transmission *via* human contact and aerial discharge. The current state of the protective care products offers surgical or N95 protective masks that, in most instances, are insufficient to provide adequate protection against viral transmission since the virus is small enough to penetrate the microfibers of most masks.[8]

Viruses are acellular obligate parasites. The life cycle of a virus, or rather, viral replication cycle, consists of six basic stages: attachment, penetration, uncoating, replication, assembly, and virion release (Figure 1).[9] Based on the two different virion release methods: lysis and budding, viruses are categorized into cytolytic and cytopathic, respectively. In terms of structures, viruses can be separated into an enveloped and a non-enveloped structure. The enveloped viruses have primarily lipid envelopes, which are less stable in the environment. On the contrary, the non-enveloped viruses are more stable in wastewater and surfaces and remain resistant to disinfectants.[10] Generally, antiviral behaviors could be divided into two categories. One is by interfering in the viral replication cycle as therapeutic agents. The other is by acting as a protective shield against viral infections.

Nanotechnology and biopolymer technology have demonstrated to be thriving to deliver essential changes to the development of antiviral therapeutics.[11] The research on antiviral technologies such as the use of metal nanoparticles,[12] carbon-based nanomaterials,[13] organic nanomaterials,[14] nanocomposites,[15] and biopolymers[16] cast new light onto the development of antiviral protective solutions. For example, the antiviral properties of the nanoparticles are attributed to their charge, size, shape, surface functionality and composition, forcing interference with the viral replication cycle.[11a] Hence, in this review, we evaluate the latest published literatures on the antiviral materials that exhibit potential as either protective shields or therapeutic agents to prevent or alleviate viral infection. The review also provides information on the current

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state of the developments in the biomedical applications of the antiviral materials. Challenges and future prospects are discussed in the end to facilitate the research and development of protective solutions and curative treatments.

2. Antiviral principles and mechanisms

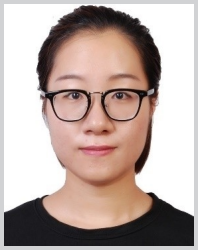
2.1. Viral entry inhibition

Inhibition action prior to viral entry is one of the most attractive approaches against viral infection because the extracellular intervention is relatively accessible. The attachment of virus to host cells and viral entry are recognition interactions involving specific components on viruses' surface and receptors on the host cell membrane,[17–18] which are promising targets for viral entry inhibition.

Inactivation of viruses prior to entry is the most direct antiviral strategy. This antiviral mechanism is proved *via* indirect evidence, frequently. Yang et al. reported a study about antiviral activities of curcumin (CCM) modified silver nanoparticles, showing that the modified silver nanoparticles (AgNPs) inhibited respiratory syncytial virus (RSV) infection *via* direct inactivation of viral envelope glycoproteins.[19] Also, Speshock et al. reported that the interactions of AgNPs with Tacaribe virus (TCRV) could inhibit arenavirus infection at the early stage of viral replication cycle.[20]

As a matter of fact, plenty of materials play their antiviral roles *via* blockage of viral entry.[13d,21] Similar to the virus inactivation mechanism, researchers observed the antiviral activities at the early state prior to viral entry and made the speculation upon different results or behaviors. For example, Barras et al. reported a type of surface-functionalized carbon dots (CDs) that could interfere with the entry of herpes simplex virus type 1 (HSV-1).[22] Their results indicated that the modified CDs prevented HSV-1 infection at certain concentrations and by specifically acting at the early stage of viral entry. However, they also claimed that CDs might make a difference in limiting viruses spreading from cell to cell. Gao et al. reported a study on 3,6-sulfated chitosan (36S) inhibiting human papillomavirus (HPV).[21a] They claimed that the 36S might directly bind to the viral capsid proteins and thus block HPV adsorption.

Antiviral agents can also take effect *via* interference with the virus-cell binding process. Research about polysaccharide-



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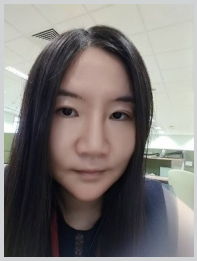

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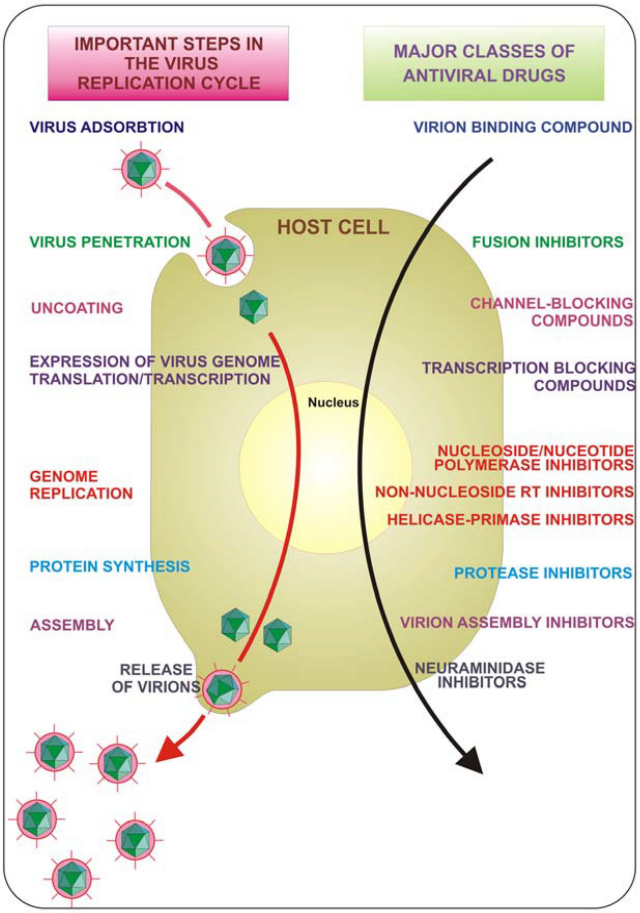

Figure 1. Key steps in the viral replication cycle that provide antiviral targets. Reproduced from reference [17] with permission from the Multidisciplinary Digital Publishing Institute.

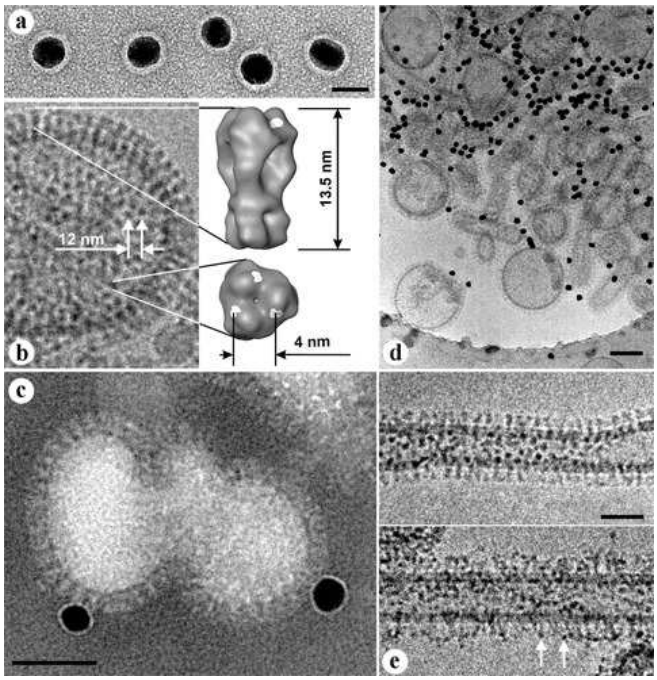

Figure 2. a) AuNP 16 (14 nm), scale bar is 20 nm. b) Influenza A X31 virion. c) Cryo-TEM preparation of influenza A virions after 60 min incubation with AuNP 16, scale bar is 50 nm. d) Preparation as in (c). e) Cryo-TEM preparations of influenza A virions before (top) and after (bottom) 60 min incubation with AuNP 14 (2 nm), scale bar is 50 nm. Reproduced from reference [24] with permission from Wiley-VCH.

coated AgNPs against monkeypox virus showed that the modified 10–80 nm particles were capable of blocking virus-cell binding and penetration.[23] As shown in Figure 2, Papp et al. reported a study on the inhibition of influenza virus infection using multivalent sialic-acid-functionalized gold nanoparticles (AuNPs). This study demonstrated a relatively clear mechanism: the receptor of the target virus fusion protein is sialic acid receptor while the modified multivalent sialic-acid-functionalized AuNPs are expected to compete the binding process and thus inhibit the viral infection.[24] Similar mechanisms were reported in multiple studies, where the specific mechanisms were called competition for the binding of virus to the cell, interfaces with viral attachment, preferential binding to the cell proteins, and inhibition of binding to specific receptors.[25] Despite their slightly different description, the speculated mechanisms are rather similar: antiviral materials compete or inhibit the binding process between viruses and host cells and thus inhibit viral infections.

Specifically, another paradigm can be introduced for enveloped viruses, targeting viral fusion process. Enveloped viruses are one of the major causes of human viral diseases and the viral entry process of all enveloped viruses involves membrane fusion.[26] Vigant et al. summarized this particular aspect in their review article.[26] Briefly, the fusion process consists of viral attachment *via* cell surface receptors as well as conformation changes of protein and components. Both proteins involve in the fusion process and lipids on virus and host cell membranes are potential targets for broad-spectrum antiviral agents. Relevant antiviral strategies are gaining more attention since the outbreak of COVID-19, as researchers are looking for similarities among pathogenic viruses instead of only developing traditional point-to-point methodology.[27] Numerous antiviral agents targeting the viral envelope were reported, including titanium dioxide (TiO_2) nanomaterials,[28] silica nanoparticles (SiNPs),[29] liposomes,[30] peptides,[31] etc. For example, Jackman et al. reported a therapeutic strategy that introduced potential membrane-active peptides targeting against mosquito-borne viruses.[32] Badani et al. summarized recent studies of peptide entry inhibitors against enveloped viruses.[33] Detailed examples will be introduced in the following sections.

It should be noted that many of those mechanisms were speculation or preliminary conclusion from limited *in vivo* or *in vitro* experiments. Various materials show clear antiviral activity against targeted viruses and are speculated that they affect the early stage of viral replication cycle. Although the limited evidence is insufficient to confirm a specific single antiviral mechanism of these materials, the importance of previous studies remains beneficial as the materials exhibited antiviral behavior in the well-designed experiments. Moreover, under various circumstances, multiple mechanisms are effective

at the same time.[13d] A single antiviral material can also exert inhibitory effects against multiple virus species with different antiviral mechanisms.[13c]

2.2. Inhibition of other steps from viral replication cycle

Antiviral agents can target at various stages of the viral replication cycle after viral entry. It includes inhibition of viral nucleic acid synthesis; transcription of mRNA *via* antisense nucleotides; translation and transcription in the nucleus (DNA-based viruses) or cytoplasm (RNA-based viruses); protease, integrase, protein synthesis at Golgi and endoplasmic reticulum; uncoating of virus; envelope formation; virus release, and lytic process (cytolytic viruses manipulate apoptosis process and spread from cell to cell). Besides, agents can also target indirect system such as immune system for host defense modification. A large number of antiviral agents taking effects after viral entry are well-designed upon their behaviors towards specific steps. Some materials serving as drug carriers may have even clearer antiviral mechanisms.[34] For example, Zhu et al. investigated the antiviral effect of drug-loaded single-walled carbon nanotubes (SWCNTs) against grass carp reovirus (GCRV). The carbon nanotubes served as carriers while the loaded ribavirin functioned as the primary antiviral agent targeting viral RNA-dependent RNA polymerase.[35]

Ghaffari et al. reported on the antiviral activity of zinc oxide nanoparticles (ZnO NPs) against H1 N1 influenza virus. The *in vitro* experiments showed that the modified ZnO NPs exhibited antiviral properties when added for 1 h after viral infection, indicating the inhibitory effect occurred after viral entry.[36] Tavakoli et al. reported a study of antiviral materials targeting virus genome. The copper oxide nanoparticles they synthesized exhibited significant antiviral activities against herpes simplex virus type 1 (HSV-1) *via* oxidation of viral proteins or degradation of viral genome. Although various antiviral activities were observed at the stages after viral entry, the evidence to identify the exact antiviral mechanisms was still insufficient and remains to be further developed in the future.[37]

3. Detailed description of various antiviral materials

3.1. Inorganic nanomaterials

Currently, numerous types of inorganic nanomaterials, such as metallic nanoparticles, carbon-based nanomaterials and silica nanoparticles, have intrigued tremendous interest in biomedical applications because of their attractive physical and chemical characteristics, including superior biocompatibility, good stability, unique structures, large surface-area-to-volume ratios.[38] As shown in Table 1, it was found in many studies that inorganic nanomaterials exhibited comparable or even stronger antiviral effect when compared with traditional pharmaceutical ingredient,[39] significantly improved the antiviral drug delivery efficiency as nanocarriers,[40] or exerted synergistic effect against viruses when in combination with antiviral drugs.[41] Although most of the inorganic nanomaterials possessing antiviral activities were reported to be biocompatible, their potential toxic effects on humans and the environment still require additional attention. For example, AuNPs are generally more biocompatible when compared with AgNPs.[42] One of the possible toxic mechanisms may be due to the release of silver ions from AgNPs and the exact mechanism is still under debate.[43] In this section, we mainly focus on the inhibitory effect of inorganic nanomaterials against various viruses as well as different strategies used to enhance their antiviral activity, stability and biocompatibility.

3.1.1. Silver nanoparticles

AgNPs are one of the most extensively researched classes of metallic nanomaterials used for antiviral applications. Numerous studies have reported that AgNPs exhibit broad-spectrum antiviral efficacy on different stages of the viral replication cycle.[17,44] Recently, Du et al. developed biocompatible glutathione-capped Ag_2S nanoclusters (NCs), serving as a highly efficient antiviral agent against porcine epidemic diarrhea virus (PEDV). Mechanism analysis (Figure 3) showed that Ag_2S NCs inhibited the synthesis of viral negative-strand RNA and viral budding. In the meantime, Ag_2S NCs also induced the production of IFN-stimulating genes and upregulated proinflammation cytokines expression. Their findings suggested that Ag_2S NCs can become a promising antiviral agent in the treatment of other types of coronavirus, such as SARS and MERS coronavirus.[45]

Apart from exhibiting direct antiviral activities, AgNPs were also reported to exert enhanced antiviral effect when modified with pharmaceutical ingredients. For instance, curcumin is an active component of turmeric, which was known as a type of antiviral and antimicrobial agent. However, its poor bioavail-

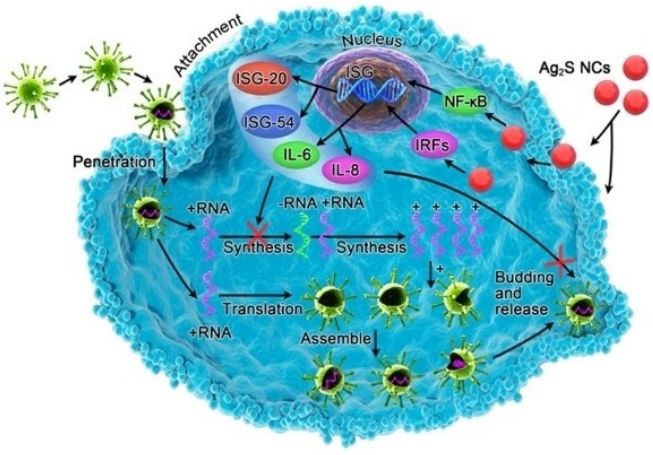

Figure 3. Possible antiviral activity of glutathione-capped Ag_2S NCs. Reproduced from reference [45] with permission from the American Chemical Society.

Table 1. Antiviral inorganic nanomaterials.

Type of Nanomaterials	Nanomaterials Characteristics	Virus	Antiviral mechanism	References
AgNPs	Amantadine-modified silver nanoparticles	H1 N1	Prevent viral attachment to the host cell; inhibit caspase-3 mediated apoptosis *via* ROS generation	Li et al., 2016[67]
	Silver nanorods conjugated with sodium 2-mercaptoethane sulfonate	HIV,HSV-1	Inhibit viral replication	Etemadzade et al., 2016[68]
	AgNPs decorated by oseltamivir	H1 N1	Block viral entry and inhibit ROS-mediated signaling pathways	Li et al., 2016[41]
	Curcumin modified silver nanoparticles	RSV	Direct virus inactivation	Yang et al., 2016[47]
	AgNPs functionalized with zanamivir	H1 N1	Inhibit the neuraminidase activity of the H1 N1 virus, resist virus-induced apoptosis of the host cells	Lin et al., 2017[69]
	Electrochemical-synthesized AgNPs	Poliovirus	Inhibition of viral binding to RD cells	Huy et al., 2017[70]
	AgNPs with a size of 20–25 nm	Bovine herpesvirus-1 (BoHV-1)	Inhibit viral replication	El-Mohamady et al., 2018[71]
	Tannic acid modified AgNPs	HSV-2	Enhance anti-HSV-2 immune response	Orłowski et al., 2018[72]
	Green synthesis of AgNPs from medicinal plants	Chikungunya virus (CHIKV)	–	Sharma et al., 2019[73]
	Poly-vinylpyrrolidone (PVP) coated biopure AgNPs	RSV	Attach to viral glycoproteins and block viral entry	Morris et al., 2019[74]
Ag_2S NCs	Glutathione-capped Ag_2S NCs	PEDV	Blockage of viral RNA synthesis and budding; activate immune system	Du et al., 2018[45]
AuNPs	HA-AuNP /interferon α complex	HCV	Enhance innate immune response	Lee et al., 2012[50]
	AuNPs conjugated with thiolated raltegravir molecules	HIV-1	Inhibit HIV integrase	Garrido et al., 2015[40]
	Pectin-reduced AuNPs carry antiretroviral drug zidovudine	HIV	Target HIV reservoir sites	Borker et al., 2017[75]
	Gallic acid stabilized monodispersed AuNPs	HSV-1, HSV-2	Interfered with virus attachment and proliferation	Halder et al., 2018[76]
	Delivery of antisense peptide nucleic acids by AuNPs	Bovine viral diarrhea virus (BVDV)	Inhibit the translation and replication of the virus	Ghaffari et al., 2019[77]
	AuNPs synthesized by using garlic extract	Measles virus (MeV)	Block virus directly and inhibit virus replication	Meléndez-Villanueva et al., 2019[229]
AuNCs	Glutathione-stabilized fluorescent AuNCs	PRRSV	Direct PRRSV inactivation and blockage of viral absorption	Bai et al., 2018[51]
CuO	Nearly spherical CuO NPs with an average size of 40 nm	HSV-1	Oxidation of viral proteins or degradation of the viral genome	Tavakoli et al., 2020[78]
Cu_2O	Spherical Cu_2O NPs with an average size of 45 nm	HCV	Interaction with virion surface	Hang et al., 2015[79]
Cu_2O	Solid-state copper(I) compounds	H1 N1, bacteriophage Qβ	Denature protein structures on viral surfaces	Minoshima et al., 2016[80]
	CuI NPs ranging 100–400 nm	FCV	Capsid protein oxidation	Shionoiri et al., 2012[81]
CuI	CuI NPs with an average size of 160 nm	H1 N1	Degradation of viral proteins	Fujimori et al., 2012[82]
TiO_2	TiO_2 nano-colloids synthesized by sonochemical method	NDV	Destroy lipid in viral envelope	Akhtar et al., 2019
SiNPs	Silicon nanoparticles prepared by grinding of porous silicon	HIV, RSV	Virions blockage and inactivation	Osminkina et al., 2014[83]

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Table 1. continued

Type of Nanomaterials	Nanomaterials Characteristics	Virus	Antiviral mechanism	References
SiNPs	Surface-modified SiNPs	HIV	Interaction with specific virus envelope	Silva et al., 2016[84]
Mesoporous SiNPs	Acyclovir-Loaded and glycosaminoglycan functionalized mesoporous SiNPs	HSV-1, HSV-2	Inhibition of viral entry and DNA replication.	Lee et al., 2018[85]
Mesoporous SiNPs	Lipid-coated and ML336-loaded mesoporous SiNPs	Venezuelan equine encephalitis virus (VEEV)	Virus inactivation by chemical inhibitor	LaBauve et al., 2018[66]
	Micro–nano filopodia-like ZnO structures	HSV-1	Trap the virions and block viral entry	Mishra et al., 2011[86]
	ZnO tetrapod micro-nanostructures	HSV-2	Block viral entry and neutralize HSV-2 virions	Antoine et al., 2012[87]
ZnO	PEGylated ZnO NPs	HSV-1	Direct interaction with virus, trap the virions and subsequently block viral entry	Tavakoli et al., 2018[21c]
	PEGylated ZnO NPs	H1 N1	Inactivate virus after viral entry	Ghaffari et al., 2019[36]
Fe_3O_4 NPs	Polymer coated superparamagnetic Fe_3O_4 nanoparticles	H1 N1	Inhibition of viral RNA synthesis	Kumar et al., 2014[88]
Fe_3O_4 NPs	Glycine coated Fe_3O_4 NPs	H1 N1	Preferential binding to the protein knobs of influenza virus	Kumar et al., 2019[89]
Magnetic NPs	Aptamer-conjugated iron oxide nanoparticles	HCV	Bind to E1E2 glycoprotein of HCV and lower the viral load	Delaviz et al., 2015[90]
	Selenium nanoparticles (SeNPs) functionalized with oseltamivir	H1 N1	Inhibition of caspase 3-mediated apoptosis *via* ROS generation	Li et al., 2017[91]
	SeNPs loaded with zanamivir	H1 N1	Suppress the activation of caspase-3 and cleavage of PARP; down-regulate p38 and JNK signaling pathways	Lin et al., 2017[92]
SeNPs				
	SeNPs decorated by ribavirin	H1 N1	Resist caspase-3 apoptotic pathway	Lin et al., 2018[93]
	SeNPs functionalized with amantadine	H1 N1	Depress cell apoptosis *via* ROS-mediated AKT signaling pathways	Li et al., 2018[94]
	Glycodendrofullerenes with 36 mannoses	EBOV	Blockage of DC-SIGN mediated viral entry	Luczkowiak et al., 2013[95]
Fullerene				
	Pyridine/pyridinium-type fullerene derivatives	HIV	Inhibit HIV reverse transcriptase activity	Yasuno et al., 2015[96]
	C_{70} fullerene derivatives 2a-c	HIV-1	Inhibit viral maturation by interrupting Gag and Gag-Pol processing	Castro et al., 2016[97]
	Fullerene derivatives 1,2,3	HIV-1	Inhibit HIV-1 replication	Martinez et al., 2016[98]
	Fullerene derivatives 1a-e	HCV	Inhibit HCV NS3/4 A protease and NS5B polymerase activity	Kataoka et al., 2016[99]
	Mannosylated 3D fullerenes C_{60}	EBOV	Interfere with lectin-mediated EBOV infection through multivalent interaction	Illescas et al., 2017[54]
Fullerene				
	Multivalent disaccharide/[60] fullerene nanoballs	Zika virus (ZIKV), dengue virus (DENV)	Blockage of DC-SIGN mediated viral entry	Ramos-Soriano et al., 2019[100]
	Chlorofullerenes $C_{60}Cl_6$ and $C_{70}C_{l8}$	HIV-1, HIV-2	Inhibit HIV-1 attachment and entry to host cells	Kraevaya et al., 2020[101]
SWCNTs	SWCNTs loading HIV-1 IN inhibitor, 5CITEP	HIV-1	Disrupt the DNA binding channel of HIV-1 integrase (IN)	Zhang et al., 2013[57]
MWCNTs	Highly hydrophilic carboxylated MWCNTs loading antiretroviral drugs CHI360 and CHI415	HIV-1	Strong interaction with viral enzyme	Iannazzo et al., 2015[13b]
SWCNTs	SWCNTs loaded with ribavirin	GCRV	Direct inhibition of the viral RNA polymerase	Zhu et al., 2015[35]

Table 1. continued

Type of Nanomaterials	Nanomaterials Characteristics	Virus	Antiviral mechanism	References
MWCNTs	Tyrosinase immobilized MWCNTs	HSV-1, HSV-2, coxsackievirus type B3 (Cox B3), cytomegalovirus (CMV)	Inhibition of virus replication	Botta et al., 2015[102]
SWCNTs	Isoprinosine delivery with SWCNTs	Nervous necrosis virus (NNV)	Activation of immune response	Zhu et al., 2019[103]
GO	GO and partially reduced sulfonated GO (rGO–SO_3)	HSV-1	Inhibition of viral entry	Sametband et al., 2014[104]
GO	GO conjugated with PVP	PRV, PEDV	Inactivate virus *via* structural destruction	Ye et al., 2015[13c]
GO	Reduced GO modified with sulfonated magnetic nanoparticles	HSV-1	Virion capture and photothermal therapy	Deokar et al., 2017[105]
GO	β-cyclodextrin (CD) functionalized GO loading curcumin	RSV	Directly inactivate the virus and inhibit viral attachment	Yang et al., 2017[58]
Graphene	Graphene derivatives covered with polyglycerol sulfate and alkyl chains	HSV-1	Interact with virus and destroy viral membrane	Donskyi et al., 2019[106]
CDs	CDs modified with boronic acid or amine	HSV-1	Blockage of viral entry	Barras et al., 2016[107]
	Cationic CDs by using ascorbic acid as carbon precursor	PRV, PRRSV	Induce immune response to inhibit viral replication	Du et al., 2016[108]
	Graphene-like CDs derived from citric acid and modified with boronic acid	HIV-1	Blockage of viral entry	Fahmi et al., 2016[109]
	CDs modified by surface passivation molecules	Human norovirus virus-like-particles (VLPs)	Inhibition of VLPs' binding to HBGA receptors	Dong et al., 2017[110]
	Cationic CDs by using curcumin as carbon precursor	PEDV	Blockage of viral entry, viral RNA synthesis and virus budding; suppression of ROS accumulation; inhibition of virus replication by activating immune system	Du et al., 2018[61]
	Cationic CDs by using benzoxazine monomers as carbon precursor	Japanese encephalitis virus (JEV), ZIKV, DENV, porcine parvovirus (PPV), adenovirus-associated virus (AAV)	Directly interact with virions; might limit the transmission of the virus	Huang et al., 2019[60]
	CDs derived from curcumin	EV71	Block the attachment of EV71 virus to the cell; inhibit virus replication	Lin et al., 2019[111]
	CDs derived from ethylenediamine/citric acid and postmodified with boronic acid ligands; CDs derived from 4-aminophenylboronic acid	Human Coronavirus (HCoV)	Inhibit viral entry; interfere with virus replication	Łoczechin et al., 2019[112]

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ability and low solubility in water become a major limitation for further biomedical applications.[46] Yang et al. reported that CCM could act as a reducing and capping agent to prepare uniform and stable AgNPs without using organic solvents. The experiments revealed that CCM modified AgNPs could exert synergistic antiviral effect against the RSV *via* direct virus inactivation.[47] Other studies also explored the combinational antiviral potential of the AgNPs and common antiviral drugs. Li et al. decorated AgNPs with Oseltamivir (Ag@OTV), which exhibited significant antiviral efficacy against H1 N1 infection. The underlying mechanism indicated that Ag@OTV could block viral entry and, more importantly, inhibit reactive oxygen species (ROS)-mediated signaling pathways to reduce cell apoptosis. The above findings exhibited the great potential of utilizing antiviral drug-modified AgNPs in the treatment of various types of viruses.[41]

3.1.2. Gold nanoparticles

AuNPs usually possess large surface-area-to-volume ratios with a diameter ranging from 1 to 100 nm, allowing conjugation of various drugs or ligands.[48] In comparison with other types of metallic nanomaterials that may release heavy metals during the treatment, AuNPs possess superior biocompatibility and facile preparation approaches.[49] The above advantages make AuNPs become attractive materials for antiviral applications. Lee et al. designed a hyaluronic acid-gold nanoparticle/interferon α (HA-AuNP/IFNα) complex, serving as an efficient IFNα delivery platform with long circulation time. They discovered that the complex remained in murine liver tissue for more than 7 days postinjection, therefore enhancing innate immune response to HCV infection in liver tissue.[50] Bai et al. reported that the glutathione-stabilized fluorescent gold nanocluster (AuNCs) showed different antiviral influences on pseudorabies virus (PRV) and porcine reproductive and respiratory syndrome virus (PRRSV). The results showed that AuNCs could selectively inhibit PRRSV (RNA virus) propagation by the direct viral inactivation and blockage of viral absorption but not that of PRV (DNA virus), indicating the possibility of applying AuNCs in the treatment of RNA virus infection.[51]

3.1.3. Carbon-based nanomaterials

Carbon-based nanomaterials, such as fullerenes, carbon nanotubes (CNTs), graphene oxide (GO), or carbon dots, are among the most widely investigated nanomaterials possessing antiviral properties.

3.1.3.1. Fullerenes

Fullerenes are allotropic forms of carbon with hollow spherical, ellipsoid, or tubular structures.[52] The fullerene family has raised considerable interest in antiviral applications due to its distinctive physical and chemical properties. Illescas et al. prepared 3D fullerene C60 with a spherical shape, which could act as a biocompatible scaffold for the multivalent presentation of functional carbohydrates.[53] They demonstrated that the mannosylated fullerenes could interfere with lectin-mediated Ebola virus (EBOV) infection *via* a multivalent manner.[54] Fullerenes and their derivatives were also reported as potential human immunodeficiency virus type 1 (HIV-1) inhibitors. Castro et al. synthesized novel cationic C70 derivatives that exhibited over 99% HIV-1 inhibition rate. Further, it was the first time to prove that the fullerene derivatives could interfere with viral maturation by impairing Gag and Gag-Pol processing.[55]

3.1.3.2. Carbon nanotubes

Carbon nanotubes as novel nanomaterials have shown intriguing applications in the biomedical field. They usually serve as drug carriers due to their functionalized surface with multiple drug binding sites and their capacity to penetrate cellular membranes.[56] Iannazzo et al. prepared highly hydrophilic carboxylated multiwalled-carbon nanotubes (ox-MWCNTs) and the same materials loading antiretroviral drugs CHI360 and CHI415. They proved that both ox-MWCNT and MWCNT–C-CHI360 could have strong interaction with viral enzyme and act as potential HIV-1 inhibitor.[13b] Zhang et al. also explored the antiviral activity of CNTs against HIV-1. They discovered that CNTs could not only disrupt the DNA binding channel of HIV-1 integrase (IN) but also stably carry HIV-1 IN inhibitor molecules, exhibiting enhanced inhibitory effect as a dual-functional agent against HIV infection.[57]

3.1.3.3. Graphene oxide

GO and its derivatives have been broadly investigated for biomedical applications owing to their unique physicochemical properties. For example, Ye et al.[13c] reported that the GO nanosheets showed strong antiviral effect against PRV and PEDV, due to their extraordinary single-layer structure and negative surface charge. Based on the antiviral effect of GO, Yang et al. loaded CCM on the surface of β-cyclodextrin functionalized GO and explored their synergistic antiviral effect against RSV infection. The results showed that CCM loaded GO could effectively suppress RSV infection through direct virus inactivation and viral attachment inhibition.[58]

3.1.3.4. Carbon dots

CDs are an intriguing type of fluorescent carbon nanomaterial with a size below 10 nm.[59] The surface functionalization of CDs significantly enables them to interact closely with the interface in various biological systems.[60] Though the antiviral research of CDs is still in the initial stage, studies carried so far have already shown the promising antiviral activity of CDs that derived from various carbon precursors. Du et al. synthesized cationic CDs by using CCM as a single-layer carbon precursor and observed that

the CCM–CDs exhibited outstanding antiviral activity against PEDV infection. The mechanism analysis revealed that CDs could inhibit virus entry, suppress the synthesis of negative-strand RNA within the virus, hinder the budding of the virus and prevent the accumulation of ROS caused by PEDV infection. In addition, this material could also inhibit viral replication by stimulating the host cells to produce proinflammatory cytokines genes and interferon-stimulating genes (Figure 4). The results suggested that CCM–CDs carry the great potential to be developed into a multi-target antiviral agent in the future.[61]

3.1.4. Other types of inorganic nanomaterials

Other inorganic nanomaterials made of copper, zinc, titanium, silica, iron and selenium were also reported with various antiviral activities, mainly including viral entry inhibition, intrinsic virucidal effect and delivery of antiviral drugs. For instance, SiNPs with hydrophobic/hydrophilic surface properties can interact with specific virus envelope that has similar surface properties. It prevented the contact between the host cell receptors and viral envelope, and significantly reduced viral transduction ability.[62] Similarly, Hang et al. proved that cuprous oxide nanoparticles (CO-NPs) could inhibit HCV infection *via* interaction with virion surface, therefore interfere with viral attachment and entry.[63] Also, Tavakoli et al. reported that PEGlated ZnO NPs showed higher antiviral effect against the H1 N1 influenza virus and HSV-1 than that of bare ZnO NPs, indicating PEGlation is an effective approach to increase antiviral ability and reduce cytotoxicity.[21c,36] Moreover, Akhtar et al. synthesized titanium dioxide nano-colloids (TiO_2-NCs) *via* sonochemical method. The antiviral experiments of TiO_2-NCs against Newcastle disease virus (NDV) showed virucidal efficacy at a minimum dose of 6.25 μg/ml, and the possible mechanism of virus inactivation was by lipid damage in the viral envelope.[64] Mesoporous silica nanoparticles (MSNs) have been widely used as drug delivery systems owing to their large surface area, tunable pore structure, size and shape, as well as ease of synthesis and modification.[65] Recently, LaBauve et al. developed lipid-coated MSNs loading antiviral molecule ML336 against the Venezuelan equine encephalitis virus (VEEV). The MSNs core significantly increased hydrophobic drug loading while the lipid coating retained the loaded drug, achieving sustained drug release and enhanced material biocompatibility.[66]

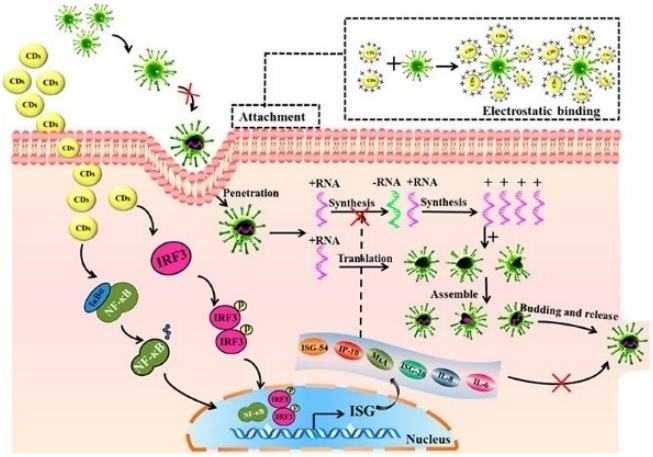

Figure 4. Possible antiviral mechanism of CCM-CDs against PEDV infection. Reproduced from reference [61] with permission from the American Chemical Society.

3.2. Organic nanomaterials

Organic nanomaterials are equipped with favorable properties such as good biocompatibility, biodegradability, colloidal stability and easy modification, owing to their size, morphology as well as surface characteristics.[113] The organic nanomaterials, including polymeric nanoparticles, lipid-based nanomaterials, dendrimers and micelles, are also extensively evaluated for their antiviral properties. Their inherent virucidal characteristics and capabilities to load therapeutic agents make them suitable candidates for effective virus treatment.

3.2.1. Polymeric nanoparticles

Polymeric nanoparticles are usually made of natural or synthetic polymers (Table 2) with a size ranging from 10 to 1000 nm.[114] Antiviral drugs can be either encapsulated in the polymeric matrix or absorbed on the surface to increase their bioavailability, prolong blood circulation time and reduce the possible side effect. Li et al. reported a unique cocktail therapeutic strategy for antiviral treatment. They developed biodegradable polymeric nanoparticles to trap reverse transcriptase inhibitor and conjugate with HIV-1 fusion inhibitor, revealing combinational virucidal effects against HIV-1. Besides, the results also showed improved intracellular uptake, lengthened blood circulation time and controlled release.[14a] Polymeric nanoparticles can also inhibit virus replication *via* ROS regulation. Kim et al. synthesized poly(aniline-co-pyrrole) polymerized nanoregulators (PASomes) which can control ROS levels *in vitro*. After the downregulation of intracellular ROS, virus propagation was significantly suppressed in Madin-Darby Canine Kidney (MDCK) cells.[115] Besides, Jamali et al. reported that siRNA-loaded chitosan (CS) nanoparticles effectively targeted virus nucleoprotein to reduce virus infections. Moreover, they also indicated that the intranasal administration of CS/siRNA nanoparticles showed therapeutic effect on mice attacked with a lethal dose of influenza virus, revealing the antiviral activity *in vivo*.[116]

3.2.2. Lipid-based nanomaterials

Liposomes are vesicular systems consisting of unilamellar or multilamellar phospholipid bilayers.[117] They have received much attention in the biomedical area owning to their outstanding biocompatibility, biodegradability, drug loading capacity and low toxicity. For example, ganciclovir (GCV) is applied for the treatment of retinitis caused by cytomegalovirus

Table 2. Antiviral organic nanomaterials.

Type of Nanomaterials	Nanomaterials Characteristics	Therapeutic Agents	Virus	Antiviral mechanism	References
Polymeric nanoparticles	PLGA nanoparticles encapsulating combination of antiretroviral drugs	Maraviroc, etravirine, raltegravir	HIV-1	Inhibit reverse transcriptase; block viral entry; inhibit integrase	Jiang et al., 2015[129]
	PEG-PLA-NPs encapsulate HIV-1 entry inhibitor and conjugate with reverse transcriptase inhibitor	DAAN-14f, T1144	HIV-1	Inhibit HIV-1 entry and transcription	Li et al., 2016[14a]
	Poly(aniline-co-pyrrole) polymerized nanoregulators	–	H1 N1, H3 N2, H9 N2	ROS regulated inhibition of viral propagation	Kim et al., 2017[115]
	Chitosan nanoparticles loaded with siRNA	siRNA-1496	H1 N1	Inhibit influenza virus replication	Jamali et al., 2018[116]
Polymeric nanoparticles	L-HSA conjugated PLGA NPs encapsulating antiviral drug	Lamivudine	HBV	Inhibit HBV polymerase and terminate viral DNA chain synthesis	Dhoke et al., 2018[130]
	Efavirenz-loaded PLGA NPs modified by transferrin receptor-binding peptide	Efavirenz	HIV	Target at the blood-brain barrier and release antiviral drug	Martins et al., 2019[131]
	Prodrug-loaded PLGA NPs	Raltegravir prodrug	HIV	Antiretroviral drug delivery	Creighton et al., 2019[132]
	Nanodecoy with polymeric core and host cell membrane coating	–	ZIKV	Prevent viral entry by trapping ZIKV	Rao et al., 2019[133]
Liposomes	Liposome-mediated RNA sensor delivery and expression	Retinoic acid-inducible gene-I	HBV	Induce immune response and inhibit HBV replication	Sato et al., 2015[134]
	Engineered liposomes as nanocarriers for antiviral agent	Ivermectin	DENV	Inhibit DENV replication	Croci et al., 2016[135]
	Antibody fragments grafted liposomes encapsulating dapivirine	Dapivirine	HIV-1	Neutralization of HIV-1 by binding to virus envelope glycoprotein	Wang et al., 2016[136]
	Lipid raft-like liposomes loading chimeric entry-inhibitor peptide	Chimeric peptides	HIV-1	Target HIV-1 gp41 and block viral entry	Gómara et al., 2017[137]
	Single-layer and multi-layer liposomes conjugated with S-NeuAc-α (2-6)-di-LacNAc	–	H1 N1	Block viral entry into MDCK cells	Cheng et al., 2018[138]
	Anti-RSV peptide-loaded liposomes	RF-482	RSV	Inhibit the RSV fusion and block viral entry	Joshi et al., 2018[139]
	Cationic liposomes incorporated with stearylamine	–	Baculovirus, HSV-1	Interact with the lipid envelope of viruses	Tahara et al., 2018[118]
	Transferrin (Tf)-conjugated liposomes	Ganciclovir	Cytomegalo-virus (CMV)	Inhibit the expression of CMV glycoprotein B	Asasutjarit et al., 2020[14b]
Solid lipid nanoparticles	Solid lipid nanoparticles bearing short hairpin RNA	shRNA74	HCV	Silencing of HCV replicon	Torrecilla et al., 2016[140]
	Solid lipid nanoparticles encapsulating HIV-1 protease inhibitor	Ritonavir	HIV-1	Inhibit virus production by using HIV-1 protease inhibitor	Javan et al., 2017[141]
Solid lipid nanoparticles	Solid lipid nanoparticles with a drug loading of 67.44%	Acyclovir	HSV-1	Sustained-release of antiviral drug	Kondel et al., 2019[120]
Planar lipid bilayers	Discoidal phospholipid bilayers wrapped by two copies of amphipathic membrane scaffold protein	–	H1 N1	Perforate the viral envelope and cause virus inactivation	Kong et al., 2019[121]
Dendrimers	Multivalent glycodendrimers bearing different carbohydrates or glycomimetic DC-SIGN ligands	bis-benzylamide 4	HIV, DENV	Block DC-SIGN mediated uptake of DENV; inhibit HIV *trans*-infection	Varga et al., 2014[142]

Table 2. continued

Type of Nanomaterials	Nanomaterials Characteristics	Therapeutic Agents	Virus	Antiviral mechanism	References
	Dendrimers with polyphenolic core and 24 sulfonate surface groups	–	HCV	Prevent virions absorption to the target cell	Sepúlveda-Crespo et al., 2017[143]
	Anionic PEG-citrate G2 dendrimer conjugated with multi-epitopic HIV-1 vaccine candidate	Multi-epitopic rHIVtop4	HIV-1	Induce Th1 immune responses	Abdoli et al., 2017[144]
	6′-sialyllactose-polyamidoamine (6SL-PAMAM) conjugates	–	H1 N1	Inhibit virus attachment and viral entry	Kwon et al., 2017[124]
	Ammonium-terminated amphiphilic Janus dendrimers	Camptothecin	HCV	Inhibit NS3 protease of HCV and restrict virus replication	Lancelot et al., 2017[145]
	Biocompatible G1 and G2 anionic citrate-PEG-citrate dendrimer	–	HIV	Blockage of viral attachment	Kandi et al., 2019[146]
	Polyanionic carbosilane dendrimers with a polyphenolic core and sulfonate or carboxylate end-groups	–	HIV-1	Virions inactivation and gp120 shedding	Sepúlveda-Crespo et al., 2018[14c]
	Anionic poly(alkylideneamine) dendrimers with carboxylate and sulfonate terminal groups	–	HIV-1	Blockage of viral entry by interacting with target proteins on the virus	Maciel et al., 2019[147]
	3′-sialyllactose- and 6′-sialyllactose-conjugated PAMAM dendrimers	–	IAV	Host-specific inhibition of IAV infection	Günther et al., 2020[148]
	Stearic acid-g-chitosan oligosaccharide micelle conjugated with antiviral drug	Acyclovir	HBV	Inhibit the expressions of hepatitis B surface antigen (HBsAg), hepatitis B e antigen (HBeAg) and HBV DNA	Huang et al., 2011[149]
Micelle	Cross-linked polymeric micelles loading antiviral agent	Camptothecin	HCV	Inhibition of HCV replicon	Jiménez-Pardo et al., 2015[150]
	Camptothecin-loaded amphiphilic polymeric micelles	Camptothecin	HCV	Inhibit HCV replication	Concellón et al., 2016[151]
	Chitosan-g-stearic acid micelles delivering DNAzyme	DrzBS	HBV	Suppress HBV S gene expression	Hong et al., 2019[128]

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(CMV). Asasutjarit et al. developed transferrin (Tf)-conjugated liposomes to deliver GCV *via* intravitreal injection and topical instillation. After Tf receptors-mediated endocytosis, the drug-loaded liposomes effectively inhibited the expression of CMV glycoprotein B, serving as a promising antiviral agent in the CMV retinitis therapy.[14b] Tahara et al. prepared a kind of cationic liposomes incorporated with stearylamine (SA) and proved their antiviral activity against recombinant baculovirus without loading active pharmaceutical ingredients. They demonstrated that the binding of SA liposomes to host cell membranes prevented viral entry and the antiviral activity of SA liposomes on HSV-1 is comparable to that of antiviral drug acyclovir.[118]

Solid lipid nanoparticles (SLN) consist of lipids that are solid at body temperature, such as fatty acids and triglycerides. They have advantages including lower toxicity, lower cost, higher stability, broader available source, higher drug loading capacity compared with that of synthetic polymeric nanoparticles and liposomes.[119] Kondel et al. prepared acyclovir SLN to treat HSV infection and demonstrated that a single dose of this formulation had comparative antiviral efficacy to the multiple-dose regiment of traditional acyclovir.[120]

Another interesting study reported a novel virucidal nanodisc which was a self-assembled discoidal planar lipid bilayer wrapped by two copies of amphipathic membrane scaffold protein (MSP) and modified with sialic acid on the surface. Mechanistically, the nanodiscs could bind to influenza virions *via* sialic acid interaction and then co-endocytosed into host cells. Under low pH endosomal environment, the nanodiscs effectively perforated the viral envelope and lead to virus inactivation.[121]

3.2.3. Dendrimers

Dendrimers are spherical macromolecules consisting of a central core and three-dimensional branched architecture with abundant end groups.[122] The interior cavity is suitable for drug encapsulation while the exterior surface can be easily conjugated with drugs and targeting ligands.[123] The use of functionalized dendrimers as antiviral agents has been widely explored. For instance, a study has shown that sulfonate-ended carbosilane dendrimers presented virucidal activity against HIV-1 infection through virions inactivation and gp120 shedding.[14c] Kwon et al. investigated the virucidal effect of multivalent 6′-sialyllactose-polyamidoamine (6SL-PAMAM) conjugates against influenza A virus (IAV). These conjugates resisted H1 N1 induced hydrolysis and protected 75% of mice from fatal attack with H1 N1, exhibiting the potential to be further developed as IAV inhibitors in virus treatment. Apart from the inherent antiviral activity of functionalized dendrimers, they also act as efficient nanocarriers for drug delivery.[124] Lancelot et al. reported a type of amphiphilic Janus dendrimers consisting of two dendritic blocks with different end groups. The result showed that these dendrimers could encapsulate camptothecin while maintaining the activity of the drug. From the antiviral studies, the Janus dendrimers exerted effective anti-HCV activity at low camptothecin concentration.[125]

3.2.4. Micelles

Micelles are colloidal systems synthesized from amphiphilic copolymers with particle size at 5–100 nm range.[126] The inner core formed by hydrophobic blocks can encapsulate drugs with poor water solubility, while the outer shell formed by hydrophilic blocks can be readily functionalized with various chemical groups.[127] Over the past years, micelles have attracted considerable attention as a drug delivery system. Hong et al. synthesized a DNAzyme called DrzBS which has the potential to inhibit HBV S gene expression *via* sequence-specific mRNA cleavage. However, the application of this enzyme was limited due to the lack of an exogenous delivery system. To overcome this challenge, they constructed chitosan-g-stearic acid (CSO-SA) micelles to effectively deliver DrzBS for HBV gene therapy. The results indicated that, compared with common transfection reagent LipofectamineTM, the DNAzyme delivered by micelles exhibited higher HBV inhibition rate and even prolonged therapeutic time to 96 h.[128]

3.3. Nanocomposites

Nanocomposites can be defined as heterogeneous materials with at least one component that has one, two or three dimensions of nanoscale size.[152] Using combinational nanomaterials for the antiviral applications can effectively integrate the advantages of each component in the nanocomposites, which may exhibit fascinating and potent antiviral activity (Table 3). For instance, Du et al. prepared silver nanoparticle-modified graphene oxide (GO-AgNPs) nanocomposites and investigated the antiviral effect of the material on the replication of PRRSV. The results indicated that GO-AgNPs effectively impeded PRRSV infection and exerted stronger antiviral effect than single GO and AgNPs, suggesting great potential of developing hybrid nanomaterials for antiviral applications.[153] Besides, nanoscale TiO_2 is one of the most popular photocatalysts possessing strong oxidizing ability under UV light.[154] Zan et al. first investigated the photocatalysis effect of TiO_2 nanoparticles and TiO_2-coated ceramic plate on HBsAg, which is involved in the attachment of HBV to hepatocytes. Both materials showed a destructive impact on HBsAg, suggesting their potential use as HBV inhibitor and providing feasible ideas to develop TiO_2 based nanocomposites for antiviral applications.[15a] Recently, Monmaturapoj et al. modified TiO_2 on the surface of hydroxyapatite and significant antiviral activity of HA/TiO_2 composite against H1 N1 was observed. They demonstrated that the virus was firstly absorbed onto the surface of HA, followed with ROS generation from TiO_2 under UV radiation that directly inactivated the virus.[155] In another study, Ishiguro et al. deposited copper ion on their previously developed TiO_2-coated cordierite foam for air cleaner, which exhibited stronger antiviral and antibacterial

Table 3. Antiviral nanocomposites.

Nanocomposites	Virus	Antiviral mechanism	References
TiO_2-coated ceramic plate	HBV	Inactivate HBV by photocatalysis effect	Zan et al., 2007[15a]
TiO_2 and DNA nanocomposites *via* polylysine (PL) linker	H1 N1, H5 N1, H3 N2	Target conservative regions of viral RNA; inhibit virus reproduction	Levina et al., 2016[160]
TiO_2-modified hydroxyapatite	H1 N1	ROS-induced virus inactivation	Monmaturapoj et al., 2018[155]
Silver-doped TiO_2 nanocomposites	H1 N1	Inactivate virus by enhanced photocatalytic reaction	Moongraksathum et al., 2019[161]
Cu^{2+}/ TiO_2-coated cordierite foam	Qβ bacteriophage T4 bacteriophage	Inactivate virus by enhanced photocatalytic reaction	Ishiguro et al., 2013[156]
Cu^{2+} incorporated in zeolite-textile materials	AIV H5 subtypes	Destruction of virions by Cu^{2+}	Imai et al., 2012[15b]
AgNPs/CS composites	H1 N1	Interact with virions and block viral entry	Yasutaka et al., 2013[162]
Polyquaternary polyphosphonium-oligochitosans (PQPOC) decorated with AgNPs	Hepatitis A virus (HAV), Noroviruses (NoV), and CoxB4.	AgNPs bind to virions active sites; interaction between PQPOC and viruses; chitosan-induced viral RNA degradation inhibits virus replication	Sofy et al., 2019[163]
AgNPs-modified GO	Infectious bursal disease virus (IBDV), feline coronavirus(FcoV)	Block viral entry and interfere with viral membrane fusion	Chen et al., 2016[164]
AgNPs-modified GO	PRRSV	Inhibition of viral entry and proliferation	Du et al., 2018[153]
Nanosilver based anionic linear globular dendrimer	HIV-1	Inhibition of virus replication	Ardestani et al., 2015[165]
Nanohybrids with SWCNTs, MWCNTs, and carbon nanohorns (SWCNHs) as scaffolds connecting to glycofullerenes	EBOV	Block DC-SIGN mediated viral entry	Rodríguez-Pérez et al., 2018[166]
Nanofibrous membranes consist of electrospun nanofibers and the daylight-active photosensitizers	T7 bacteriophage	ROS-induced virus inactivation	Si et al., 2018[159]
Quaternized chitosan nanofibers containing graphene	PPV	Bind and remove virus in solution	Bai et al., 2013[167]
Chitosan-chondroitin sulfate nanocomplex encapsulating tenofovir	HIV-1	Inhibit viral reverse transcriptase	Wu et al., 2016[168]
PLGA-CS coated nanoparticles loading two antiretrovirals	HIV-1	–	Makita-Chingombe et al., 2016[169]
Zidovudine loaded PVP/SA-PEG nanoparticles	HIV	–	K. S. et al., 2018[170]
S-Linked sialyloligosaccharides bearing liposomes and micelles	H1 N1	Block viral entry into the MDCK cells	Yeh et al., 2015[171]

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activities than that of TiO_2-coated cordierite foam.[156] Copper ions were also incorporated in zeolite-textile materials and showed high and rapid inactivation of the avian influenza virus (AIV) H5 subtypes.[15b]

Nanofibers are a type of nanoscale fibrous material with high surface-to-volume ratio, facile surface functionalization and excellent mechanical properties, which have gathered great interest for applications in different biomedical fields.[157] When mixed in nanocomposites, nanofibers usually exhibit desired synergistic effect in combination with other components. Bai et al. prepared quaternized electrospun chitosan nanofibers containing graphene, which exerted excellent virus removal efficacy by binding up to 95% of porcine parvovirus. The addition of graphene can increase nanofiber formation and also the reduction of virus.[158] Lately, Si et al. also reported a fascinating study of antiviral nanocomposites. They fabricated a novel daylight-driven rechargeable nanofibrous membranes (RNMs) with virucidal activities through the integration of electrospun nanofibers and the photosensitizers. The photoactive RNMs can rapidly produce and accumulate ROS under daylight and release them under dim light or dark environment. With their high ROS production rate, durable activity and high biocidal efficacy, the RNMs possess great potential to serve as a biocidal layer on protective equipment.[159]

3.4. Antiviral biopolymers

3.4.1. Saccharides

Monosaccharides,[172] oligosaccharides[173] and polysaccharides[174] and their derivatives[175] are found to possess attractive properties, such as low toxicity, biocompatibility as well as antiviral efficacy. There exist numerous review papers discussing the structural properties and antiviral activities of saccharides, especially the widely studied oligosaccharides and polysaccharides.[175–176] Some latest research findings are illustrated in this review, and further details can be found in relevant references.

Among various marine organisms, seaweeds, also known as algae, are the most abundant source of polysaccharide, especially sulfated polysaccharides.[177] Carrageenans are linear sulfated polysaccharides extracted from red seaweeds, which have been widely investigated as an antiviral agent.[178] Boulho et al. applied both conventional and microwave-assisted extraction (MAE) methods to harvest carrageenans from *Solieria chordalis* and explored their antiviral ability. Results indicated that by using MAE methods, the extracted carrageenans exhibited better antiviral ability against HSV-1, equal to that of antiviral drug acyclovir.[179] Guo et al. reported that iota-carrageenan (CG) displayed potent antiviral activity against PRRSV by blocking viral entry and inhibiting virus-induced NF-κB activation, which is essential for viral gene transcription and replication.[21b] Another type of well-known sulfated polysaccharides are fucoidans obtained from brown seaweeds. Recent studies have shown that fucoidans can exhibit antiviral properties. For example, Ponce et al. extracted fucoidans from brown seaweed *Scytosiphon lomentaria* and then isolated heavily sulfated galactofucans and uronofucoidans by cetrimide fractionation. They demonstrated that galactofucans exhibited significant antiviral activity against HSV-1 and HSV-2 infection while uronofucoidans showed no effect.[180] Sun et al. also reported that fucoidans possessed anti-HSV-2 activity by interfering with the absorption of virions to the host cells.[174] Generally, as shown in Figure 5, the possible antiviral mechanism of seaweed polysaccharides could be the prevention of virus adsorption into the host cells and/or inhibition of the new virion production inside the host cells.[175]

Chitosan is a natural biocompatible and biodegradable biopolymer derived from chitin deacetylation.[181] Sulfated chitosan has shown intriguing biological properties including antiviral effect.[182] Gao et al. developed 36S derived from marine polysaccharides and demonstrated its broad anti-HPV activities. 36S may directly block HPV entry by interacting with viral capsid protein. In addition, it may also interfere with the cellular PI3 K/Akt/mTOR pathway and therefore suppress cell autophagy.[21a] Besides, sulfated chitosan extracted from the cuttlebone of *Sepia pharaonic* was confirmed with antiviral effect against NDV by binding to virus receptors to prevent viral proliferation in the avian bloodstream.[183]

Cyclodextrins are natural cyclic oligosaccharides mainly composed of six to eight glucopyranoside units, with unique ring structure, internal hydrophobic cavity and hydrophilic external surface.[184] The above properties make cyclodextrins become potent candidates in the treatment of viral infection *via* drug delivery, direct virucidal action or synergistic therapy. Recently, Jones et al. developed a nontoxic cyclodextrin modified with sulfonic acid, exhibiting irreversible virucidal activity against a wide range of heparan sulfate-dependent viruses and posing a high barrier for the emergence of drug resistance.[185]

In summary, the structural diversity and complexity of saccharides and their derivatives could contribute their antiviral activities at different stages of viral infection processes, revealing considerable potential in future clinical transformation.

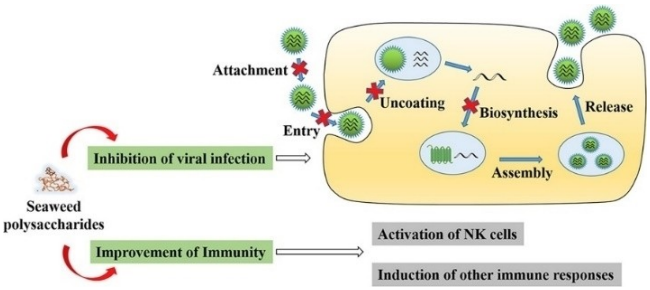

Figure 5. The antiviral activities and mechanisms of seaweed polysaccharides. Reproduced from reference [175] with permission from Elsevier.

3.4.2. Peptides

Antiviral peptides have received much attention over the last few years because of their increasing discoveries of antiviral properties. Such peptides can derive from natural sources, such as bacteria, plants and animals, or can be rationally designed and synthesized.[186] They have been reported to target different stages of the virus replication cycle, and the primary mechanism can be summarized as follows: First, some peptides can interact with the virus or host cells, block viral attachment and prevent viral fusion. Second, several types of peptides present direct biocidal activity by disrupting virus envelope. Third, specific peptides can interact with viral polymerase complex or stimulate immune response to inhibit viral replication.[187] Lately, several reviews have comprehensively introduced the studies of antiviral peptides,[186–188] readers may refer to those reviews for detailed information. In this section, we mainly focus on the latest development of antiviral peptides.

Recently, Mechlia et al. investigated the anti-rabies activity of dermaseptins S3, S4 and their derivatives, which are excreted from amphibian skin glands. The results have shown that dermaseptins not only disrupted the viral envelope before viral entry but also affected downstream stages of the virus replication cycle after infection. Data also showed that S4 M4 K exhibited the highest therapeutic effect that protected 50–60% infected mice from lethal challenge with Rabies virus (RABV).[16b] In another study, poly-gamma-glutamic acid (γ-PGA), an anionic polypeptide generated from *Bacillus* species, showed its antiviral efficacy against norovirus infection. After oral administration, γ-PGA can interfere with viral entry and increase IFN-β production, which can effectively suppress virus replication in host cells.[189] Also, β-defensins, a family of endogenous cysteine-rich and cationic peptides, demonstrated broad-spectrum antiviral properties against various viruses, especially influenza virus.[187b,190] Zhao et al. synthesized different peptides derived from mouse β-defensin-4 and discovered that peptide P9 effectively inhibited influenza A virus (H1 N1, H3 N2, H5 N1, H7 N7 and H7 N9) and coronavirus (SARS-CoV and MERS-CoV). Mechanism analysis revealed that P9 bound to viral envelope glycoproteins, entered into the cells with the virus and prevented endosomal acidification, which impeded membrane fusion and viral RNA release.[191]

In addition, rationally synthesized peptides have also been extensively explored for their antiviral effect. Zhao et al. developed a type of dual-functional peptide TAT P1, loading defective interfering genes (DIG-3) of influenza virus. On the one hand, the delivered DIG-3 significantly suppressed virus replication through cell transfection. On the other hand, the vector TAT P1 showed intrinsic antiviral activity by preventing endosomal acidification.[192] This study has paved the way for developing transfection vectors as promising therapeutic agents in virus treatment.

Besides, membrane-active peptide has received much attention over the past years in terms of developing antiviral agents. Many medically important viruses are equipped with lipid envelopes derived from host cell membranes, which play a crucial role in viral structural integrity and become attractive targets for membrane-active peptide.[193] For example, α-helical (AH) peptide is known as a broad-spectrum antiviral agent against a wide range of enveloped viruses *via* lipid membrane destabilization.[194] Recently, Jackman et al. demonstrated a promising antiviral strategy named 'lipid envelope antiviral disruption' (LEAD), using AH peptide as the template (Figure 6). The engineered peptide could penetrate through the blood-brain barrier and preferentially target at Zika virus, resulting in significantly reduced viral infection in mice model.[31] Previous studies indicated that AH peptide possesses unique size-selective disruptive behavior,[194–195] which can form pores in highly curved membranes (e.g., small vesicles, viral envelopes) and subsequently contribute to membrane lysis after reaching a critical pore intensity.[196] It was further identified that the flexible conformation of AH peptide enables it to exhibit higher membrane targeting selectivity compared with C5 A peptide.[197] The above findings suggest that LEAD strategy opens the door to the treatment of mosquito-borne or other types of enveloped virus infection in a feasible approach.

4. State of the art in current antiviral biomedical applications

Infectious diseases caused by viruses are still a major threat to public health and associated with significant economic losses throughout the world.[198] As of 20 August 2020, there have been over 22 million confirmed cases of COVID-19 with 3.5% mortality rate.[199] The successful synthesis (including biosynthesis) of those fascinating antiviral materials may provide new insights into the development of antiviral protection solutions, potential antiviral agents, antiviral drug carriers and antiviral drug delivery systems.

4.1. Protective equipment against aerosol and droplet based viral entry

Proper antiviral protection can effectively prevent infectious disease, reduce economic losses and save lives.[200] Viruses can spread among humans through direct or indirect contact to

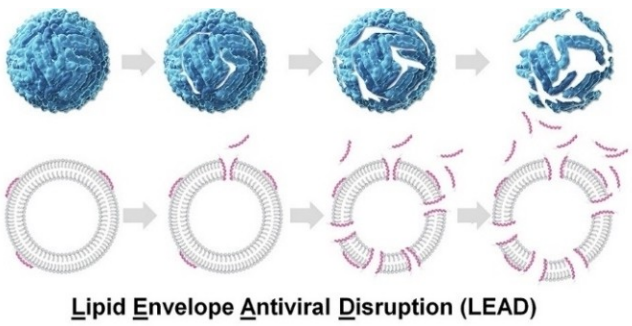

Figure 6. Scheme illustration of LEAD antiviral strategy. Reproduced from reference [197] with permission from the American Chemical Society.

blood and other body fluids and/or exposure to respiratory aerosols or droplets from infectious individuals.[201] If there is no vaccine for the specific virus, the best way to prevent spread and infection is to avoid being exposed to the viruses.[202] Non-pharmaceutical interventions, such as facemasks, goggles, gloves, and protective suits have been used to protect against virus infection during a pandemic.[8b,203]

As most viruses range in size from 5 to 300 nm, the pore sizes of materials are critical for antiviral protection.[204] The moisture-proof plastic and rubber are commonly used for the fabrication of goggles and gloves, respectively. Compared with goggles and gloves, protective suits require more soft and comfortable permeable materials.[205] However, porous materials are insufficient for antiviral protection. An antiviral material layer is required for protective suits by providing contact killing against virus either in aerosol or in liquid forms.[206] The antiviral nanoparticles have been mechanically infused into textiles for protective suits and other protective products.[159,207]

Facemasks and respirators are the key pieces of personal protective equipment (PPE) that are generally applied for the protection from the viruses transmitted by respiratory aerosols and droplets.[208] Reusable cloth masks have been widely used by general public and even health care workers globally, particularly in Asia.[209] The efficacy of cloth masks against specific virus infectious threats such as influenza and coronavirus could be extremely limited. And thus, the common practices such as reuse of masks are discouraged on the basis of public health judgment. Therefore, cost-effective antiviral materials are preferred as the raw materials for disposable facemasks to lower the risk of severe illness from virus infection.

Currently, medical masks are recommended for the public to prevent respiratory virus infections.[210] The medical masks, also known as surgical masks, are typically three layers that include outer, barrier and inner layers in sequence. The outer and inner layers are made of non-woven fabric materials, and the barrier layer is made of a melt-blown material. The barrier layer acts as the filter that prevents the virus as well as other microbes and particles from entering or exiting the mask. To increase the antiviral effectiveness, antiviral nanoparticles, such as silver, copper and zinc nanoparticles have been coated as a film on the outer layer of masks to rapidly destroy viruses before entering the barrier layer.[159,207, 211] Furthermore, an additional antiviral layer has also been developed using antiviral materials to co-support with other conventional layers. The antiviral layer, which placed between outer layer and barrier layer could be made from hybrid materials, such as silver nanoparticle-containing fibers, silver-containing polymer nanocomposites.[212] The design of an antiviral medical mask is shown in Figure 7. The main functions of outer layer, antiviral layer, barrier layer and inner layer are trapping viruses and penetration of air, inactivating or killing viruses, filtration of air, and final barrier, respectively.

Besides the medical masks, protective respirators have also been used for antiviral applications.[213] The respirators are tight-fitting protective devices with superior antiviral properties when compared to the medical masks.[214] The N95 respirators have been certified to filter at least 95% of particles that are

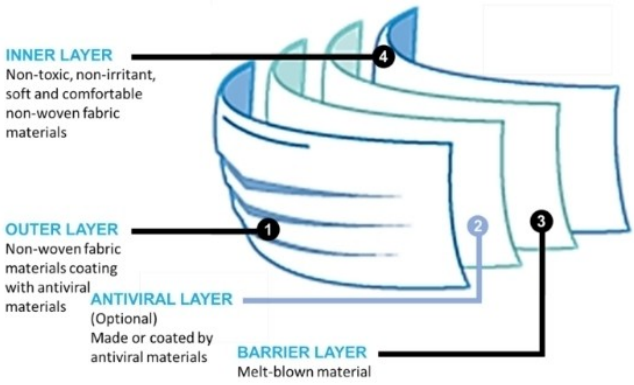

Figure 7. The design of medical masks against viruses

recommended to the healthcare workers to wear for prevention from contracting the virus.[215] Antiviral materials, such as copper oxide nanoparticles could be impregnated into N95 respirators or coated on the surfaces of N95 respirators with an antiviral layer to further enhance the antiviral performance.[216] Furthermore, elastomeric respirators are reusable devices with exchangeable cartridge filters that offer a viable protection option to healthcare workers for updating respiratory protection programs.[217] Obviously, the application of nanomaterials, nanocomposites or biopolymers with antiviral properties to the structure of elastomeric respirators could offer many potential advantages, such as enhanced antiviral efficiency, reduced disinfection frequency, and extended wear time.[218] For instance, the graphene containing chitosan nanofibers and daylight-driven rechargeable nanofibrous membranes mentioned in the previous section would become suitable candidates in the filter design.[158–159]

4.2. Potential antiviral agents

The emergence of various viruses has increased the demand for potential antiviral agents, which can be used to treat viral infections.[219] The antiviral agents are different from viricides and should be relatively harmless to the hosts.[220] Nowadays, researchers are working on expanding the scope of antiviral agents to different viruses, such as coronavirus, HIV, HBV, HCV, HSV, and influenza A and B viruses.[220b,221] However, it is difficult to design safe and effective antiviral agents without damaging host biological cells. Furthermore, the emergence of widespread drug resistance and viral mutation makes developing antiviral agents even more difficult. Research on potential antiviral drugs must therefore be continued, and all possible strategies should be challenging.

Some antiviral materials, especially biopolymers are promising candidates as antiviral agents.[7,222] Most biopolymers are isolated from natural sources, which possess low toxicity, less side-effects, renewable supply and biodiversity. These biopolymers could offer complementary and overlapping mechanisms of antiviral action by inhibiting viral replication and/or viral genome synthesis. Compared with standard combinatorial

chemistry, these biopolymers have higher chemical diversity and biochemical specificity, providing an important opportunity to find new lead structures that are bioactive against a wide range of viruses. In addition, the structures of the biopolymers can lead to chemical modification with improved antiviral activities.[223]

In recent years, researchers have confirmed that some polysaccharides,[222b,222c][224] proteins,[225] peptides,[226] polyphenols,[227] poly-and oligonucleotides[228] and some natural products derived materials[229] possess antiviral activities and wide-ranging beneficial therapeutic effects. Specifically, the polysaccharides have emerged as an essential antiviral agent, both *in vitro* and *in vivo*. Due to unparalleled chemical diversity, polysaccharides offer unlimited opportunities for new antiviral agents.[222b,c,230] Recently, the polysaccharides were reported as a novel strategy for inhibiting or slowing down the viral infection without cytotoxic effects. The polysaccharides, particularly sulfated polysaccharides, demonstrated to have antiviral bioactivities against multiple viruses, such as coronavirus, DENV, influenza virus, poliovirus, HSV and varicella-zoster viruses.[230]

Nevertheless, more studies on structure-activity relationships, mechanism of action, drug metabolism, molecular simulation, and combinatorial chemistry are required for better utilization of those biopolymers for biomedical applications. Besides, some biopolymers, such as sulfated polysaccharides, polyphenols and peptides, can be used as synergistic enhancers to boost the effect of other antiviral drugs.[231] The synergistic effect can reduce the therapeutic dose and toxicity of antiviral drugs, and minimize or delay the induction of antiviral resistance.

4.3. Antiviral drug carriers

Currently, antiviral drugs suffer from low antiviral efficacy, low compound solubility, low bioavailability when administered in conventional dosage forms. Short half-lives of active compounds, undesired systemic toxic and side effects hinder the development of antiviral drugs.[232] A variety of carrier systems have been developed for antiviral drugs to improve the effectiveness and specificity of them. By far, the most widely studied antiviral drug carriers are biodegradable materials and nanomaterials. Besides physical immobilization and encapsulation, the conjugation of antiviral drugs to biodegradable polymeric carriers is usually designed by the presence of covalent bond between the water-soluble polymer and the antiviral drug molecule. The concept of polymer-drug conjugates opens up a new perspective for drug carriers in modern pharmacy.[233] Compared with conventional antiviral drugs, the antiviral effectiveness of polymer-drug conjugates can be achieved by either part of the polymeric backbone or the side chains, which offer several attractive advantages, such as improved water solubility and stability, controlled administration, and improved pharmacokinetics and biodistribution. To develop antiviral polymer conjugates, several biodegradable polymers are currently being studied, such as poly(N-(2-hydroxypropyl)methacrylamide), lignins, (glycol)proteins, deoxynucleotide and biocompatible dendrimers for reduced cytotoxicity and enhanced activity of antiviral drugs.[234]

Advances in nanotechnology have a profound impact on drug carriers, leading to the development of nanomaterials with larger loading capacity and higher targeting accuracy for the treatment of viral diseases.[235] Nanomaterials with antiviral intrinsic activity can be considered drug carriers to enhance the effectiveness of antiviral drugs by synergistic effects. However, they are often related to solubility and bioavailability issues. To overcome these limitations, biodegradable nanoparticles, such as lipid-based nanoparticles and biopolymeric nanoparticles have been commonly used as carriers for antiviral drug delivery in the treatment of various viruses. By using these nanocarriers, it is possible to overcome the problems of many antiviral drugs in conventional dosage forms, which may help to address solubility and dissolution issues, increase the bioavailability of drugs, protect sensitive drugs from degradation, reduce adverse side effects, improve tissue tolerance to drugs and reduce treatment costs.[34b,236]

4.4. Antiviral drug delivery systems

As viruses are characterized by rapid replication within host cells and carry the ability to attack any part of the host cell, the clinical efficacy of antiviral drugs and their bioavailability becomes more critical considerations in the treatment of viral infections.[237] This makes it difficult to find targets for antiviral drugs that can interfere with the viruses without harming the host cells. In recent years, more and more new antiviral drugs have entered the pharmaceutical market. Therefore, various antiviral drug delivery systems have been used for drug site-specific targeting to enhance the effectiveness of the treatment. The targets are not only specific cells, but also specific organelles for antiviral and antiretroviral therapy. Figure 8

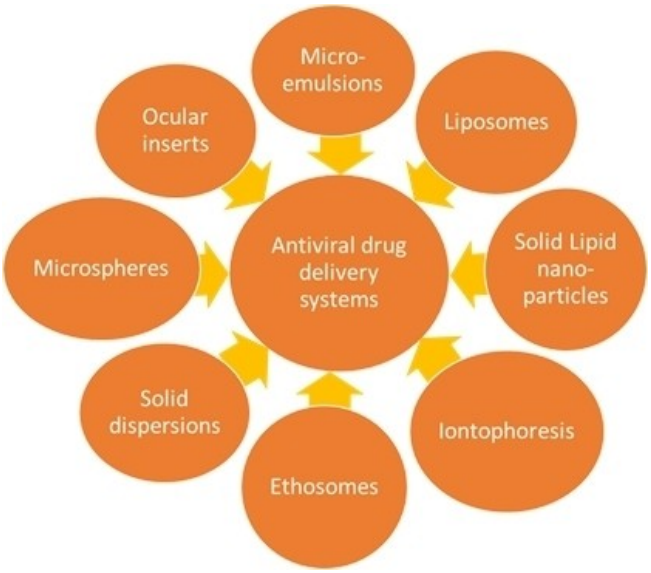

Figure 8. Schematic diagram of antiviral drug delivery systems. Reproduced from reference [238] with permission from Medknow.

outlines the drug delivery systems most commonly studied for antiviral and antiretroviral therapy.[238]

Among the different materials of drug delivery systems being currently investigated by pharmaceutical scientists, "smart" polymer biomaterials hold a great potential for antiviral drug delivery.[239] As an essential feature of human body systems is their ability to change important properties in response to tiny environmental signals, the development of "smart" polymer biomaterials with biomimetic properties could be applied as intelligent antiviral drug delivery systems. "Smart" polymers, or stimuli-responsive polymers in a more scientific term, are capable of altering their chemical and/or physical properties upon exposure to external stimuli.[239–240] These materials have been intensively studied over the years for on-demand drug deliveries. The schematic representation of "smart" polymers as a drug delivery system for the transport of active antiviral drugs is shown in Figure 9. Inspired by viruses trafficking from endo-lysosomes, "smart" polymers have been used as an effective drug delivery system. The stimuli-responsive degradation properties of "smart" polymers have shown great possibilities in exhibiting enhanced release of antiviral therapeutics into targeted cells, even the specific organelles.[241]

5. Challenges and future prospects

In general, nanomaterials have been used as cost-effective biomedical materials for developing antiviral protective solutions. Antiviral biopolymers exhibit equivalent potential for antiviral applications due to their inherent low toxicity, broad-spectrum antiviral activity, high specificity, effectiveness, wide acceptability, biodegradability, and relatively low production costs.[11c,242] All the efforts dedicated to the synthesis and characterization of these antiviral materials have paved the way for various biomedical applications. However, it was highlighted that dosage regulation and effectivity need to be addressed before industrial-scale applications.[7] Most studies were in the preliminary stages of testing and implementation. For challenging biomedical applications, such as using antiviral drug carriers and antiviral drug delivery systems, it has been found that the current antiviral materials are far from meeting all the clinical requirements. Nevertheless, antiviral biodegradable nanomaterials and "smart" polymer biomaterials are still expected to solve the related biomedical problems and accelerate the transition to clinical applications.

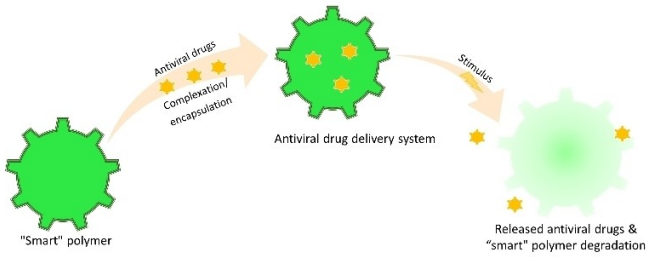

Figure 9. Schematic representation of a "smart" polymer-based delivery system for the transport of active antiviral drugs.[239–240]

On the one hand, the most important limitation observed is that most of the conclusions derived were based on the observations from the *in vitro* antiviral studies. Further exploration into *in vivo* studies with animal and clinical testing are essential to progress towards real biomedical applications. On the other hand, the complexity of interactions during the antiviral activity limits the ability to understand the antiviral mechanism. Currently, most of the reported mechanisms are based on speculations. Although the results from the antiviral studies were conclusive, the underlying mechanism of action remains unresolved due to the lack of sufficient evidence. Profound understandings of the antiviral mechanisms would facilitate precise antiviral material development.

The reviewed candidates for the antiviral applications demonstrate significant potential in the fight against future viral pandemics. The use of different virus strains and types further complicates the correlation among studies. The most common viral strains used are HIV and HSV, which restrict the application scope of antiviral materials. It would be ideal to develop and test the antiviral materials on certain viruses that represent each viral category. A universal protocol for such studies would facilitate the applications to a broader spectrum of viral pathogens. It was emphasized that there is an urgent need to develop more effective antiviral therapies to reduce morbidity and mortality.[243] A concerted effort is essential to focus the research towards specific goals of achieving the antiviral materials with desired performance.

Amidst the viral infections, there are numerous unexplained factors that determine interspecies transmission, reassortment, human-to-human transmission, and exposure-to-infection ratio of the novel viruses.[3,6a] The opportunity to observe real-time virus evolution would provide us with invaluable information on the factors that determine pathogenicity and/or transmissibility.[6a] The availability of immense amount of data from the previous pandemics can aid along with the help of automation, artificial intelligence and bioinformatics to direct the development of the research area. In the case of H5 N1, Yong reported that 99.9% of the exposed population with antibodies carried in their blood failed to develop the disease. However, rapid viral replication was observed in infected people.[3] The cases were clustered within the genetically susceptible blood relatives while others possessed genetic variants that protected them.[3] The complications in understanding the pattern of viral infection need resolution.

The economic cost of the pandemics is high with the loss of lives, loss in productivity, social disruption, and incurred government and medical expenses. For example, the economic cost of the 1957 and 1968 pandemics combined was $32 billion (in 1995 dollars).[244] Hence, it is essential for governments and interested institutions to venture and invest in active research addressing the gap in the field. In principle, the H5 N1 can become airborne and unpredictable.[3] Preparedness for such an airborne pandemic could prevent large-scale implications. The development and/or evolution of novel viruses are predicted to be imminent that would increase the number of pandemics in

the future. The probability of pandemic occurrence increases over time.[244–245] Moreover, the higher the frequency of pandemics the greater the failure of containment efforts due to the shortage of workforce and resources.[245] Hanvoravongchai et al. studied the pandemic preparedness and health system challenges of six Asian countries including Thailand, Indonesia, Taiwan, Lao PDR, Cambodia and Viet Nam.[246] The shortage of highly skilled workers, insufficient stockpiles of the antivirals and PPE were some of the resource challenges attributed to the developing countries. Unfortunately, it is also suggested that the human understanding of the emergence of pandemics is incomplete and may not be as frequent as indicated by scientists.[245]

Further, a WHO report stated that creativity and imagination are essential to the research enterprise with new ideas emerging to resolve health problems.[5] It emphasized that the constraints are in the means to implement these ideas and highest quality research into dependable and practical applications to facilitate better health. Research investments are attained by demonstrating results from translatable scientific investigations into accessible and affordable health services. It will be ever more arduous and convoluted to develop antiviral materials with the emergence of new virus strains. The development of novel methods of treatment or inhibition would eventually be overcome by nature (in this case, viruses) over time. Hence, this fight against the viruses will be never ending.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: antiviral materials · biopolymers · drug delivery · nanoparticles · viruses

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