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Review article

Antiviral polysaccharide and antiviral peptide delivering nanomaterials for prevention and treatment of SARS-CoV-2 caused COVID-19 and other viral diseases

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ABSTRACT

Antiviral peptides and antiviral polysaccharides can play a major role in the prevention and treatment of emerging viral health problems. These antiviral compounds are biocompatible, environmentally friendly, non-toxic, and cost-effective, yet are poorly water soluble and vulnerable to enzymatic (protease) degradation within the aggressive intercellular microenvironment. Therefore, they should be properly protected and delivered to viruses and host cells by the well-designed nanocarriers that mimic viruses in terms of size, morphology, and smart function. This literature review is meant to introduce the latest advances (mainly within the past five years) in antiviral nano-assemblies comprising antiviral peptides or antiviral polysaccharides. To the best of our knowledge, there is no similar study in the literature that has solely and sufficiently investigated such antiviral nanomaterials partially or totally derived from nature. The rational classification of microorganism-, plant-, and animal-derived antiviral polysaccharide and antiviral peptide delivering nanomaterials and exploration of their relevant applications will clarify the promising capacity of these state-of-the-art materials for a number of technologies developed to inactivate viruses.

1. Introduction

Over the past few decades, rapid advances in science and technology have led to significant progress in the healthcare industry. However, still many infectious viral diseases continue to exist, result in human death, and impose negative social consequences. COVID-19 pandemic, a new

coronavirus disease that began in 2019, has sparked a global health disaster. It is a respiratory infectious disease induced by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and has swiftly spread to become a pandemic in 2020 [1,2]. Compared to the SARS pandemic that took place more than a decade ago, COVID-19 features a higher risk of transmission due to its larger reproductive

Abbreviations: AI, Avian influenza; Alg, Alginate; ASP, Angelica sinensis polysaccharide; AVA, Anthrax Vaccine Adsorbed; BBR, Berberine; BoHV-1, Bovine herpesvirus type 1; CG, Carrageenan; CHIKV, Chikungunya virus.; CNC, Nanocellulose; CNT, Carbon nanotube; CS, Chitosan; CSFV, Classical swine fever virus; CV, Coxsackievirus; DEV, Duck enteritis virus; DENV, Dengue virus.; DHAV, Duck virus hepatitis; EBOV, Ebola virus; EGCG, Epigallocatechin gallate; EO, Essential oil; EV71, Enterovirus 71.; EVD, Ebola virus disease.; FIPV, Feline infectious peritonitis virus; FUC, Fucoidan; GA, Gallic acid; GAG, Glycosaminoglycan; Gly, Glycylrrhizic acid; H5N1, Asian avian influenza A virus.; HAV, Hepatitis A virus; HCMV, Human cytomegalovirus.; HCV, Hepatitis C virus.; HIV, Human immunodeficiency virus.; HP, Heparin; HPV, Human papillomavirus.; HRV, Human rhinovirus; HS, Heparin sulphate; HSV, Herpes simplex virus.; IAV, Influenza A virus; IBDV, Infectious bursal disease virus; IBV, Influenza B virus; INF, Influenza virus; JEV, Japanese encephalitis virus; JUNV, Junin virus; LF, Lactoferrin; LSDV, Lumpy skin disease virus; MEL, Melittin; MLV, Murine leukemia virus; MuV, Mumps virus; MWCNT, Multiwalled carbon nanotube; NDV, Newcastle disease virus; NiV, Nipah virus; NP, Nanoparticle; OA, Oleanolic acid; PACA, Poly(alkyl cyanoacrylate); PCV2, Porcine circovirus type 2; PEI, Polyethyleneimine; PGA, Polyglycolic acid; PICA, Poly(isobutyl cyanoacrylate); PLA, Polylactic acid; PLGA, Poly(lactic-co-glycolic acid); PMMA, Polymethyl methacrylate; PRRSV, Porcine reproductive and respiratory syndrome virus; PS, Polystyrene; PV, Poliovirus; PVA, Polyvinyl alcohol; QD, Quantum dot; RdRp, RNA dependent RNA polymerase; RES, Resveratrol; RSV, Respiratory syncytial virus; RT, Reverse transcriptase; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2.; SIt, Sitagliptin; SIV, Simian immunodeficiency virus; SuHV-1, Porcine herpesvirus type 1; TA, Tannic acid; TMV, Tobacco mosaic virus; VACV, Vaccinia virus.; VSV, Vesicular stomatitis Indiana virus; VZV, Varicella-zoster virus; YFV, Yellow fever virus; ZIKAV, Zika virus.

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number than that of SARS (COVID-19: 2.9 > SARS: 1.77) [3]. Within a week of infection, mild COVID-19 symptoms, including dizziness, headache, fever, and cough might be cured [1], while the symptoms of severe infection are mainly reflected in very intensive respiratory problems and in most cases lead to death [4].

In addition to COVID-19, there are many other kinds of viruses such as Ebola virus (EBOV), dengue virus (DENV), Human immunodeficiency virus (HIV), Nipah virus (NiV), coronavirus (CoV), and influenza virus (AI) (avian flu H5N1) that cause serious health problems [5]. Therefore, there is an urgent need to efficient antiviral therapies to address viral infections. Among them, development of nature-derived antiviral nanomaterials has contributed significantly to the field of antiviral therapy.

To inhibit the transmission of viruses, materials science plays a crucial role. Antiviral natural materials, such as antiviral peptides and antiviral polysaccharides, destroy the virus' structure and disrupt its infection mechanism [6,7]. However, the crisis of pathogen resistance to most antiviral agents necessitates the identification and development of new antiviral materials. These materials need to possess hypotoxicity, specific activity, biocompatibility, and high bioavailability [8]. In this regard, the materials obtained from natural sources are typically the most optimum candidates. In a large number of natural compounds, antiviral ingredients are made by microorganisms or as a result of their interaction with hosts [8]. Such natural bioactive components are effective in killing viruses or inhibiting their growth and multiplication through various mechanisms. Natural materials have drawn researchers' attention due to their numerous benefits over man-made materials. They are widely available from various biological sources, easily accessible, durable, chemically stable, renewable, non-toxic, and non-polluting. With the growing number of investigations into the antiviral properties of natural materials, recently, nature-derived antiviral materials have become popular to prevent or treat viral diseases (Fig. 1a). The data shown in Fig. 1a were extracted from "Web of Science" database based on the keywords of "antiviral OR anti-viral" combined with "natural material OR nature-derived material OR natural product". This search led to 2129 studies carried out between 2000 and 2022. Fig. 1a shows that the number of relevant publications grew more rapidly from 2019 to 2021, most likely due to the epidemic of COVID-19. Interestingly, the number of publications over these three years accounts for almost 50% of the total number of publications from 2000 to 2020, indicating the increasing importance of natural antiviral materials in fighting against the COVID-19 pandemic.

Despite different merits of natural materials for antiviral purposes, they are poorly water soluble, delicate, and vulnerable to biological (enzymatic) degradation within body [9]. Therefore, they can hardly reach target cells or virus to play their engineered role. The most promising strategy to protect such bioactive agents is their encapsulation or hybridization within/with nanocarriers, as is similarly done for the nanotechnology-based messenger RNA vaccines, e.g., lipid nanoparticle-based mRNA vaccines from Moderna and Pfizer–BioNTech (mRNA-1273 and BNT162b2, respectively). Since all viruses *per se* are nanoscale pathogens [10], nanotechnology has developed as a potent technique for enhancing the antiviral effect of natural materials and protecting them against possible degradation pathways *in vivo* [11]. The network map in Fig. 1b was constructed by using VOSViewer to show the frequency of occurrence and co-occurrence association of the keywords extracted from the 2129 studies reflected in Fig. 1a. Seventy-five terms related to nature-derived materials, antiviral activity, and nano-scale application were manually filtered. Fig. 1b represents the strong correlation between antiviral properties, natural materials, and nano-scale applications. The yellow and blue clusters contain natural materials with antiviral activity, while the green and purple clusters are associated with antiviral activity of the materials as well as targeted viruses. Eventually, the red cluster represents the applications of natural antiviral nanomaterials.

2. Mimicking viruses; a strategy to develop effective theranostic nanotools

Getting to know the (replication) mechanisms of action of viruses and their features has helped scientists propose nanobiotechnological tools capable of neutralizing their harmful effects. With an evolution process as old as millions of years, viruses have learned how to adapt themselves for efficient penetration into cells and for survival inside cells. They perfectly activate, hamper, or modify the defence mechanisms of hosting biological systems [12]. They transmit their genes into cells in a highly efficient manner that has inspired researchers to develop non-infectious recombinant viral vectors with potential applications for gene-therapy [13,14].

Despite the similarity of the life cycle of CoVs within host cells (Fig. 2), several features of SARS-CoV-2, SARS-CoV, and MERS-CoV are distinct [15]. This discrepancy leads to diverse uptake and processing mechanisms inside host cells. The virion initially attaches to the host cell via interaction between its S protein and cell's specific receptor [15].

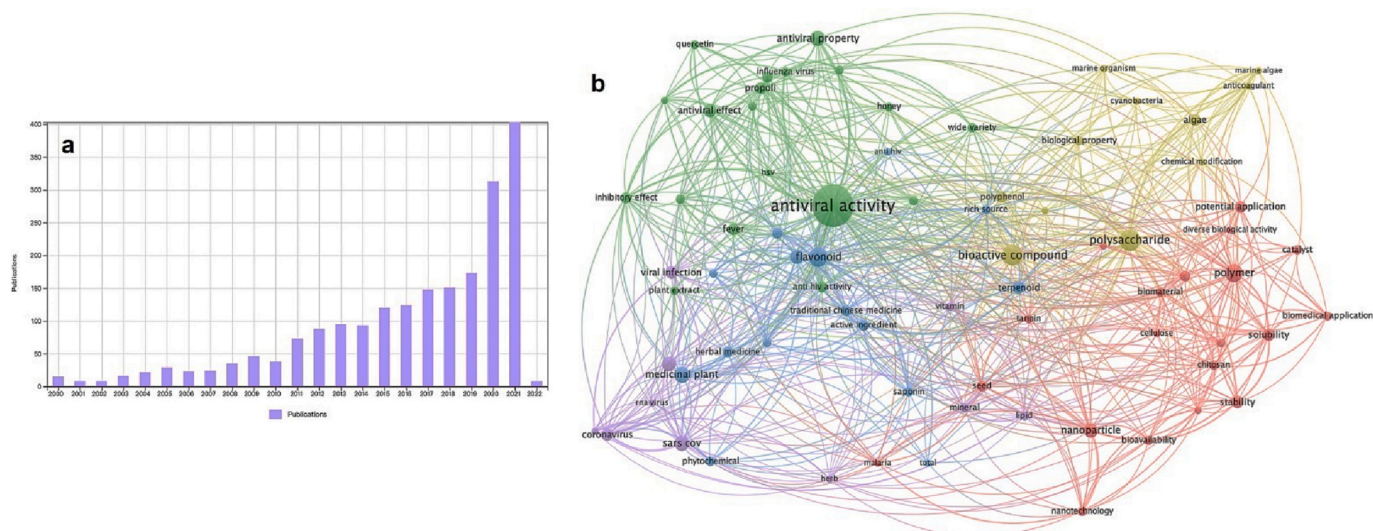


Fig. 1. a) Annual growth of the number of publications on nature-derived antiviral materials (data collected from Web of Science in January 2022). b) The network map for keyword occurrence in the 2129 studies carried out from 2000 to 2021 for nature-derived nanomaterials with antiviral activity.

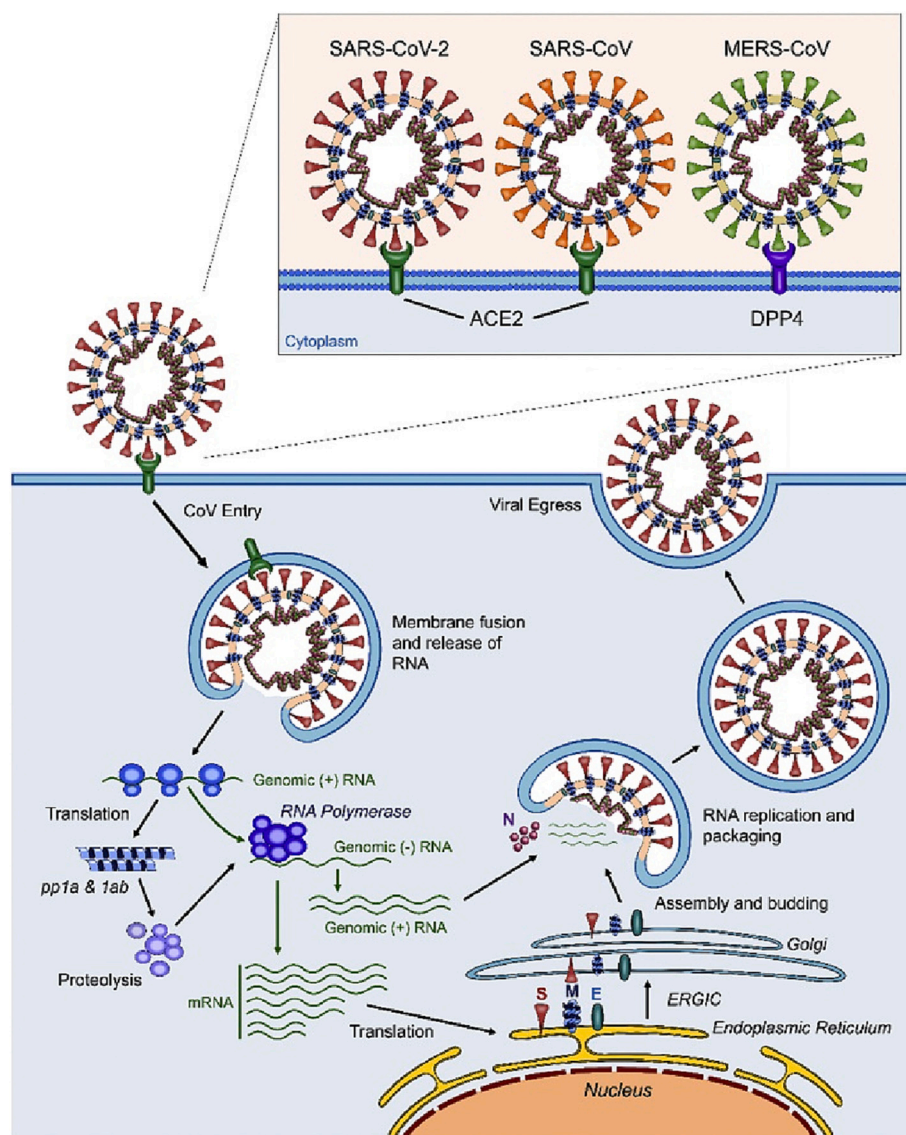


Fig. 2. Schematic illustration of the replication pathways of SARS-CoV, SARS-CoV-2, and MERS-CoV in different steps: (a) virus binds to the specific cell receptor (ACE2 or DPP4 depending on the virus type), (b) virus enters into the cell through endocytosis, (c) viral envelope fuses with the endosomal membrane of the host cell and viral RNA is subsequently released, (d) non-structural proteins including RNA-dependent RNA polymerase (RdRP) are translated and RNA is replicated, (e) structural viral proteins are translated at endoplasmic reticulum–golgi intermediate compartment (ERGIC), (f) replicated RNA is packaged into new virions and eventually (g) viral egress. Reproduced under terms of the CC-BY license. [15] Copyright 2020, Elsevier.

SARS-CoV and SARS-CoV-2 attach to the cell receptor, angiotensin-converting enzyme 2 (ACE2), that is predominantly available in lung. Additionally, this receptor can be found in the intestine mucosal cells, endothelial cells of veins and arteries, immune cells and cerebral neurons, and the tubular epithelial cells of kidney and renal tubules [16–24]. Differently, MERS-CoV attaches to the cell receptor of dipeptidyl peptidase 4 (DPP4) which is also called as cluster of differentiation 26 (CD26). This cell receptor is available on epithelial cells in liver, kidney, small intestine, alveoli, and prostate and also on activated leukocytes, human dendritic cells, and macrophages and T-cells [19,25–33].

Upon fusion of viral envelope with the endosomal membrane of the host cell, viral genome is secreted into cytoplasm. Afterwards, viral RNA is translated and thereby RNA replicase-transcriptase complex (aka, RdRP) is produced [19]. Such a product itself creates transitional full-length negative-sense (–) RNA copies, that are subsequently employed as templates for the development of full-length positive-sense (+) RNA genomes [15]. A larger extent of genome translation provokes the generation of viral proteins. Thereafter, originating from N-proteins and viral genomic RNA present in cytoplasm, viral nucleocapsids form. This process is followed by enlarging of the structural proteins and nucleocapsid in the lumen of ERGIC and leads to creation of new virions. The as-formed virions are later egressed (released) via exocytosis [15].

Imitating the gene transfer ability and extensive infection tendency of viral vectors, a plethora of nanosystems have been designed that can serve for nanomedicine [34–36]. Discovery of the molecular mechanisms whereby such vectors perform, has enabled the development of delivery platforms for various nanomedicine fields, e.g., cancer therapy and regenerative medicine [37]. The inspiration from virology has not only been limited to delivery nanosystems, but also extended to the creation of therapeutic tools to overcome dangerous viral diseases. In this regard, nature-derived antiviral agents have been largely incorporated into virus-like nanostructures (capsules) to prevent and to likely treat such catastrophic diseases. To be more specific, SARS-CoV-2 is known to infect various cells via the attachment of its S protein to the ACE2 receptor present on host cells [38]. Therefore, any strategy to inhibit this binding through blockage of S-protein or ACE2 receptor could be efficient in prevention of viral diseases. In this regard, the NPs containing antiviral peptides and antiviral polysaccharides have been validated to be effective. In this review, we aim to present an updated overview on the nature-derived nanomedicine technologies developed to suppress viral activities, e.g., to inhibit their attachment to host cells or their replication within the host cells. To the best of our knowledge, there are no similar reviews in the literature describing the nanoconjugates of antiviral peptides and antiviral polysaccharides. These nanotherapeutics that have been developed for the prevention and

treatment of diverse viral diseases will be elaborated from various perspectives of design, composition, and mechanisms of action. As will be discussed later, such technologies, particularly those based on antiviral peptides, are limited in number. Therefore, a larger attention from research community should be paid towards these advanced nanomedicines to discover new formulations with superior antiviral efficiency, given their promising therapeutic potentials.

3. Antiviral nanomaterials with natural origins

Natural polymers and peptides are produced by living cells. They are abundant in biomass and are easily obtained from a variety of natural sources including animals, plants, marine organisms, fungi, etc. [39–41]. Due to the promising characteristics of natural polymers/peptides such as biocompatibility, reproducibility, biodegradability, abundance, non-toxicity, and cleanness, many of them have been spotlighted for antiviral therapeutics [40,42–44]. Combining nanotechnology and natural polymer/peptide technology, the nanomaterials delivering natural bioactive constituents have demonstrated a superior protective/therapeutic performance to prevent, alleviate, or eradicate viral infections [42].

3.1. Antimicrobial peptide (AMP) delivering nanomaterials

AMPs have been widely recognized as a potential solution against harmful microorganisms [45]. They are naturally occurring short oligopeptides found in microbes, plants, and animals and act as a major element of their immune system. Such materials play a pivotal role in the organism's early immunological response to damage and infection [45–47]. Therefore, they are also known as host defence peptides (HDPs) [48]. Up to now, more than 5000 different AMPs have been reported in the data repository of antimicrobial peptides (DRAMP) [49], including phaseococcin (from runner bean seeds), cecropin A (from moth), melittin (from bees), clavansins (from *Styela clava*), defensins, cathelicidins (from mammals), among others [50]. Despite their structural diversity, there are many overlaps in physicochemical properties of AMPs. For instance, they are cationic and amphipathic, with the net charges of +2 and +9 at the neutral pH range [51,52]. These characteristics are promising for their interaction with cell membrane, microbial surface, and internal structure [43]. Thus, a diverse range of microorganisms, especially fungi, bacteria, and viruses are effectively eliminated or prevented from proliferating [52].

Owing to the limitations of the currently available therapeutic compounds for viral diseases, research on new antiviral materials has gained substantial attention these days [46,53]. The pathogenicity re-emergence and viral resistance caused by long-term and widespread utilization of antivirals are becoming major challenges for clinical virus infection control [54,55]. With further discovery of antiviral properties of AMPs, they have been recently considered as candidate drugs for antiviral therapeutics [55]. Advantageous over conventional antiviral drugs, AMPs are insensitive to microbial resistance development, and show a broad-spectrum antimicrobial activity [56]. However, despite the clinical application of various peptide antibiotics, e.g., daptomycin (i.e., a cyclic anionic lipopeptide), gramicidin (i.e., a linear polypeptide obtained from *Bacillus brevis*), colistin (polymyxin E, derived from *Bacillus polymyxa*), and polymyxin B (a lipopeptide which is derived from *B. polymyxa*), AMPs are still at the pre-clinical stage [57,58]. In this regard, a number of AMPs are under various clinical trials, though, likely in vivo toxicity and challenging scalability at an industrial scale might delay the clinical translation of such antimicrobial agents [59].

AMPs' antiviral activity is reflected in the following aspects: First, they block viral attachment by interacting with viruses and binding to virus targets on the surface of host cells [47,50]. Second, the cationic nature of AMPs promotes the electrostatic interaction between AMPs and the negatively charged cell membrane, but their hydrophobicity allows them to get into the hydrophobic core of cell membranes, thereby

offering a direct biocidal effect by rupturing the membrane and lysing the cells [44,60]. Third, AMPs either react directly with various proteins on the virus surface or activate the immune system in cells, which can hamper the replication and transmission of virus by suppressing the expression of viral genes and inhibiting their translation or immunomodulatory activities [47,61]. AMPs are known virucidal when handicapping viral particles or occupying the protein link site within the host cell membrane, thereby challenging cell-virus interaction and adsorption [62]. They might interfere in the other phases of the viral cycle and disrupt viral gene expression [63,64]. Accordingly, AMPs offer a wide range of therapeutic functions against viral infections.

AMPs can effectively inhibit the infection by many DNA and RNA viruses, such as influenza A virus (IAV), human cytomegalovirus (HCMV), herpes type 1 (HSV-1), HIV, vesicular stomatitis Indiana virus (VSV), and Junin virus (JUNV) [49]. For instance, dendrimer LTP (((Arg)2Lys)2Lys)2Lys-Ala-Cys) peptides and synthetic linear peptides of SA-35 (Met-Ile-Thr-His-Gly-Cys-Tyr-Thr-Arg-Thr-Arg-His-Lys-His-Lys-Leu-Lys-Lys-Thr-Leu) have been proven to offer a profound antiviral effect towards the respiratory syncytial virus that engenders viral disease in children [65]. These peptides commonly feature homogenous distribution of positive charge and the presence of poor amphipathic amino acid moieties. In the synthesis of such peptides, particular bioactive cationic, helical parts of the respiratory syncytial virus receptor's structure, nucleolin, has been employed [65]. López-Martínez et al. [66] synthesized nine peptides based on the conserved region of viral spike protein (hemagglutinin). These peptides effectively inhibited avian influenza virus and human swan strains, most likely due to the interference of the peptide between the host cell surface and viral spike protein. Chen et al. [67] considered a different part of viral spike protein, i.e., neuraminidase, which contributes to the replication of the virus, for the synthesis of an octapeptide (errKPAQP). This peptide performs as a neuraminidase inhibitor and challenges viral replication. Neuraminidase and hemagglutinin are two principal glycoproteins involved in viral fusion and can be targeted by AMPs [67,68]. Matsubara et al. [69] devised c01(GWYKGRARPVSAVA) and c03(RAVWRHSVATPSHSV) pentapeptides, based on the specific attachment of hemagglutinin to ganglioside GM3 containing Neu5Ac α 2-3Gal which is present on the cell surface receptor. These peptides were subsequently acylated using a C18 group that could enhance their assembly and their multivalent attachment to influenza virus. Multivalent peptides could be also effective in the treatment of SARS-CoV-2 [70]. Kwon et al. [71] have also shown that 6-sialyllactose-polyamidoamine is multivalent and can inhibit influenza and H1N1 infection.

Despite all the mentioned merits that AMPs offer to inhibit viral activity, their physicochemical characteristics such as low water solubility (hydrophobic peptides), poor stability (due to vulnerability to environmental conditions, e.g., light, oxidation, and degradation by proteases), and toxicity (interaction with blood components during intravenous administration) limit their application in antiviral treatments [72]. Recent advances in biotechnology, particularly in nanomedicines, have led to the development of AMP encapsulated polymeric nanocarriers [2]. Such peptide nanomedicines have been shown to possess decreased cytotoxicity, less degradation rate, and increased targeting efficiency [73,74]. The AMP nanomedicines improve the antimicrobial effect of AMPs and control their enhanced permeability and retention effect (EPR) [75]. As shown in Fig. 3a&b, there are two main classes of AMP nanomedicines; passive and active. Such strategies can shield AMPs against a harmful external environment, delay their degradation rate by enzymes, ensure their safe arrival to target, and reduce the immunological response [76].

The strategy of encapsulation of AMPs into drug delivery nanosystems for an antiviral purpose has been mainly applied to two kinds of AMPs, melittin (MEL) and LL-37.

MEL is a natural AMP commonly found in bee venom [80]. MEL's antiviral activity for a number of viruses, particularly HSV and HIV, is due to the direct lysis of virus membrane [81,82]. Al-Rabia et al. [83]

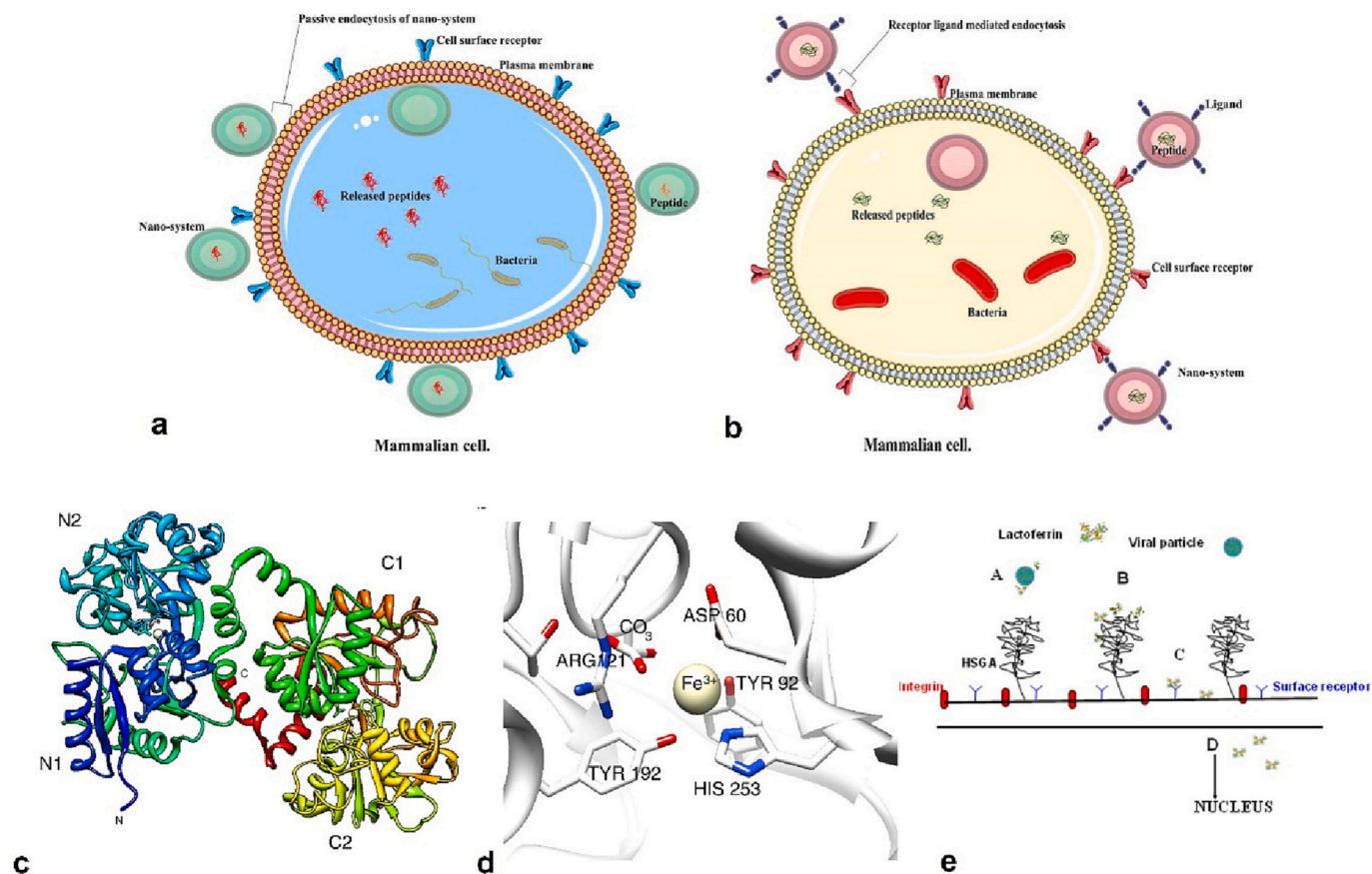


Fig. 3. a) Passive AMP delivery into an infected cell, which can be controlled only by size and shape of the nanocarrier. b) Active AMP delivery into an infected cell, which can be achieved by surface modifications. Reproduced under terms of the CC-BY license. [77] Copyright 2018, Frontiers. c) Structure of bovine lactoferrin (bLF) with 2-lobe, 4-domain polypeptide. d) Canonical Fe-binding pocket site of LF. Reproduced with permission. [78] Copyright 2012, Elsevier. e) Different mechanisms by which LF prevents viral infections: binding to (A) viral particles, (B) acetyl heparan glycosaminoglycan (HSGA) and (C) viral receptors; (D) Intracellular localization. Reproduced with permission. [79] Copyright 2011, MDPI.

made nanoconjugates comprising of MEL and sitagliptin (SIT) as an efficient formulation against SARS-CoV-2. As shown by the authors, 50% viral inhibition is achieved at SIT-MEL concentration (IC_{50}) of $8.439 \mu\text{M}$, which is notably lower than the IC_{50} of SIT and MEL (16.14 and $15.73 \mu\text{M}$) alone, thus exhibiting an improved antiviral effect. Interestingly, the NP diameter of SIT-MEL complex increases with its concentration. This feature enables tailoring of the delivery performance (e.g., absorption and entrance into cells, cellular internalization, and intracellular localization).

LL-37, a human cathelicidin AMP and a 37 amino acid C-terminal peptide domain, shows an antiviral effect towards a wide range of enveloped viruses, including IAV [84], Respiratory syncytial virus (RSV) [85], vaccinia virus (VV) [86], Hepatitis C virus (HCV) [87] and HIV [88] through destruction of viral capsids and inhibition of DNA replication [53,54]. Lee et al. [89] investigated the efficacy of LL-37 containing silica NPs incorporated into collagen (supplemented with a network of 2-methacryloyloxyethyl phosphorylcholine (MPC)-poly(ethylene glycol) diacrylate (PEGDA)) to suppress the viral activity of HSV-1. In this study, LL-37 was shown to significantly reduce the HSV-1 infectivity in human corneal epithelial cells (HCEC) after 72 h of continuous-release, owing to its cumulative, protective effect [89]. Additionally, while maintaining its antiviral activity against HSV-1, effectively encapsulated LL-37 was released over a period of 22 days, which was 7 days longer than that of other allografts. While this AMP could slow down the spread of HSV-1 in ocular cells and inhibit binding of HSV-1 to cells, it was unable to completely inactivate the virus after being internalized by the cells [89].

Lactoferrin (LF) is an iron-binding (80 kDa) glycoprotein, first

identified in cow's milk. It is abundantly available in milk, plasma, and neutrophils of human, mice, pig, and other mammals [45,53]. LF is a positively charged protein whose structure is based on a polypeptide chain with a positively charged N-terminal domain [90]. The LF chain consists of two circular loops linked to 3 spiral α -helices, each one with an iron ion binding site [53], Fig. 3c&d. LF can reversibly chelate two ferric ions (Fe^{3+}) per molecule with high affinity. This capability preserves Fe^{3+} ions even under highly acidic conditions (e.g., pH 3). As a result, it controls the free iron concentration in body fluids in the range of $10\text{--}18 \text{ M}$ and thus hampers precipitation of iron hydroxide, generation of ROS, and growth of microorganisms [79,91]. As a crucial part of the innate immune defence, LF has been demonstrated to offer promising antiviral potentials for both human and animals [92]. The antiviral mechanism of LF varies depending on the type of virus (Fig. 3e). LF can inhibit virus-host interaction through direct binding with virus particles including rotavirus, poliovirus, herpesvirus, and human hepatitis C virus, thus preventing infection of host cells [90]. It can also inactivate HIV [93] and restrict the respiratory syncytial replication in host cells [94]. Lang et al. [95] reported that LF plays an inhibitory role against the attachment of SARS-CoV (via spike proteins) to host cells. In this regard, Hu et al. [96] proved that LF offers a notable antiviral activity against many types of commonly occurring coronaviruses. In general, they showed that LF has a broad-spectrum antiviral activity and effectively inactivates HCoV-229E, SARS-CoV-2, HCoV-NL63, and HCoV-OC43 in vitro. They also verified that compared to human LF, bovine LF is more effective.

Similar to other AMPs, nanoencapsulation of active LF into nanocarriers enhances its antiviral efficacy [47]. As mentioned earlier, due to

physicochemical properties and poor stability of peptides and proteins in the complex body fluid environment, AMPs including LF cannot exert proper antiviral effects in human body alone [2,53]. To address this shortcoming, their derived nanomedicines, i.e., AMP encapsulated/conjugated nanocarriers could be more demanded [2,72,73,90,91]. In this regard, in a very recent study, LF was conjugated with Ag and Au NPs to inhibit the attachment and entry of HSV-1 and 2 in human keratinocytes [97]. A relevant *in vivo* study using HSV-2 infected mice showed that treatment with LF-Ag/Au NPs further reduces virus titers in spinal cord and vaginal tissue compared to the control case based on LF alone. The animal models treated with LF-Ag/Au NPs also upregulated IL-1 β , IFN- γ , CXCL9, and CXCL10 in vaginal tissues.

There are many AMP nanomedicines that are being researched for preventive or therapeutic purposes. In this regard, various challenges such as a low encapsulation rate in nanoformulation, changes in morphology and activity of peptide after encapsulation, and difficulties in finding a suitable nano-delivery system still exist [2,46]. Table 1 tabulates some examples for AMP delivery nanosystems. It is worthy to note that majority of such nanomedicines have been aimed to act as antibacterial agents. The number of antiviral peptide delivering nanocarriers is notably limited and therefore this subject could be a high potential research area in future.

3.2. Antiviral polysaccharide delivering nanomaterials

Polysaccharides are another class of nature-derived compounds with

antiviral potentials. Polysaccharides feature a large molecular mass comprising 10 monosaccharide chains, interconnected by glycosidic bonds [112]. The emergence of SARS-CoV-2 pandemic has led to an increased research interest towards polysaccharides derived from natural sources because of their favourable antioxidant, antibacterial, and immunomodulatory properties [113]. Furthermore, polysaccharides are optimally biodegradable and safe (biosafety) and provide potent antiviral activity via interfering with virus' life cycle. When delivered by nanocarriers, these advantages become further prominent [114]. Therefore, they can play a crucial role as antiviral nanomaterials and in drug delivery nanosystems [115]. Depending on their origin, polysaccharides are mainly classified as: microbial, plant, and animal polysaccharides.

3.2.1. Microbial polysaccharides

Microbial polysaccharides, produced via the metabolism of microorganisms, have been shown to offer antitumor, antioxidant, antibacterial, and anti-inflammatory properties [116]. Additionally, they provide notable therapeutic effects as antiviral medicines against viral infectious illnesses, particularly novel coronaviruses [117].

Marine sulfated polysaccharide (SP) is a negatively charged microbial polysaccharide that is found in the cell walls of seaweeds (marine microalgae). This polysaccharide has recently drawn a large interest because of its superb antiviral activity [118]. Carrageenan (CG) is a linear sulfated polysaccharide produced by certain red algae (e.g., *Gigartina*, *Stellaria*, *Solieria*, *Agardhiella*, etc. [119]). CG is composed of

Table 1
Some examples for AMP delivering nanosystems.

AMP	Nanocarrier	Size (nm)	Application	Synthesis	Ref.
WLBU2	Liposome with NHS-PEG ₂₀₀₀ -DSPE	136.6 \pm 1.6	Antibacterial activity against <i>MRSA</i> and <i>P. aeruginosa</i>	Film-hydration-extrusion	[98]
LL-37	PEGylated liposome	106.8 \pm 10.1	Enhanced stability as well as bioactivity against HSV-1	Thin film hydration	[99]
Nisin	Partially purified soybean phosphatidylcholine liposome	190, 181 and 148	Antimicrobial activity against <i>Listeria monocytogenes</i> ATCC 7644	Reversed-phase and hydration film method using probe-type and bath-type ultrasound	[100]
F12W-magainin 2 [D]-H6L9	Phosphatidylcholine liposome (R + D)-Lip	–	–	Thin film hydration method	[101]
P34	Partially purified soybean phosphatidylcholine liposome	115–140	Tumor inhibition effect	Film dispersion method	[102]
DP7-C (Chol-suc-VQWRIRVAVIRK-NH2)	Soybean phosphatidylcholine liposome	150	Antibacterial activity against pathogenic and food spoilage bacteria	Thin film hydration method	[103]
Tilapia hepcidin 2–3	PEGylated liposome	~100	Treatment of <i>MRSA</i> infection	Thin film hydration method	[104]
Nisin	PG NPs	103.56 \pm 3.29	Tumor inhibition effect	Thin film hydration method	[105]
SET-M33	Single-chain dextran NPs	60–90	Antibacterial activity against food spoilage bacteria	Dissolution of PG in sodium acetate buffer, then addition of β -amylase and later ethanol	[106]
OA1	Ag NPs	18	Antibacterial activity	Controlled addition of a dithiol cross-linker to methacrylate-functionalized dextran precursor polymer.	[107]
Esculentin-1a(Esc1–21)	Au NPs	12–14	Antibacterial activity	SET-M33 peptide was conjugated with dextran NPs via non-covalent interactions.	[108]
RBRBR (R: Arginine, and B: L-4-phenyl-phenylalanine)	Chitosan NPs	14	Topical treatment of epithelial infections and healing of the injured tissue	Addition of Ag NPs to the aqueous solution of OA1	[109]
MEL	SIT NPs	121.13 \pm 1	Antibacterial activity	PEG conjugated Au NPs were surface functionalized with EDC-sulfo NHS and the AMP was coupled with the assembly while incubated in MES.	[110]
LL-37	Silica NPs	77.42	Antiviral activity against SARS-CoV-2	Ionotropic gelation method	[83]
PEP and/or TAT	Au NPs	–	Antiviral activity against HSV-1	Co-dissolution of MEL and SIT in a phosphate buffer	[89]
LF	Ag/Au NPs	10.1 \pm 1.7	Gene delivery to mesenchymal stem cells with antibacterial ability	Drop-wise addition of TEOS to LL-37 solution containing cyclohexane and triton.	[111]
		10	Antiviral activity against HSV-1 and HSV-2	Au NPs were mixed with TAT or PEP or TAT/PEP mixture solutions	[97]

NHS-PEG2000-DSPE: 1,2-Distearoyl-sn-glycero-3-phosphoethanolamine-N-[3-(N-succinimidyl-oxyglutaryl)aminopropyl(polyethyleneglycol)-2000-carbamyl], MRSA: methicillin-resistant *Staphylococcus aureus*, *P. aeruginosa*: *Pseudomonas aeruginosa*, PEG: polyethylene glycol, HSV-1: herpes simplex type 1, PG: Phytoglycogen, MES: 2-(N-morpholino)ethanesulfonic acid, EDC: 1-Ethyl-3-(3-dimethylaminopropyl)-carbodiimide, Sulfo-NHS: N-hydroxysulfosuccinimide, SIT: Sitagliptin, MEL: melittin, SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2, TEOS: tetraethyl orthosilicate.

repeating disaccharide units with alternating 3-linked β - d-galactopyranose and 4-linked α -galactopyranose or 3, 6-anhydro- α -galactopyranose [120]. Depending on the chemical composition and degree of sulphation, CG is classified in three types (Fig. 4a). CG has been shown to induce a considerable viral inhibition activity by occupying the viral envelope location and by preventing the virus particle from physically attaching and entering the host cell (Fig. 4b). As a result, CG can inactivate many kinds of viruses such as HSV, human rhinoviruses (HRVs), varicella-zoster virus (VZV), human papillomavirus (HPV) [121], hepatitis A virus (HAV) [122], and porcine herpesvirus type 1 (SuHV-1) [123].

CG based nanomaterials show improved antiviral properties compared to CG alone and thus have found a larger number of pharmaceutical and biomedical applications [114]. Thanks to their large availability, non-toxicity, and biodegradability, CG oligosaccharide can be employed as a reducing agent for biosynthesis of noble metal NPs, thereby forming, e.g., a CG-Au nanoconjugate [124]. As seen in Fig. 4c, such nanoconjugates can be further functionalized by S or N protein from CoV through protein corona formation and eventually perform as a CoV NP vaccine [125].

In addition to CG, many other algae derived polysaccharides exhibit antiviral effects (Fig. 5a). For instance, Fucoindan (FUC) and ulvan are two other polysaccharides obtained from brown and green algae, respectively [127]. Their antiviral mechanism is similar to that of CG and is broad spectrum. This property would be further augmented when

such algal polysaccharides are coupled with other natural polymers and compounds (e.g., drugs) in a nanoformulation [121]. These natural nanocomposites are extensively employed for medical applications such as adjuvants for vaccines, drug delivery, and tissue engineering [114]. In this regard, Tsai et al. [128] synthesized FUC- trimethyl chitosan (TMC) NPs with negative or positive surface charge as adjuvants of Anthrax Vaccine Adsorbed (AVA) to raise its immunogenicity efficiency. Both classes of NPs showed high cell viability for JAWS II dendritic cells, A549, and L929 cells. However, the positively charged NPs had a lower internalization level than their negatively charged counterparts (Fig. 5b&c), yet stimulated the release of pro-inflammatory cytokines including IL-4, IFN- γ , and IL12p40. Fig. 5d shows that both types of NPs were able to deliver the drugs within nucleus and cytoplasm. According to in vivo tests using A/J mice, the positively charged NPs with AVA cargo induced a proper immune response reflected in a larger IgG anti-PA antibody titer compared to AVA with CpG oligodeoxynucleotides and led to complete (100%) protection when tested by anthracis spores. Additionally, PA-specific IgG1 and IgG2a analysis validated that the positively charged FUC-TMC NPs notably provoked humoral immunity.

3.2.2. Plant polysaccharides

Plant polysaccharides are the most abundant class of polysaccharides and in fact constitute the major fraction of all biomasses. Plant polysaccharides are largely available in the plant cells' walls and are comprised of diverse monosaccharides, thus possessing different

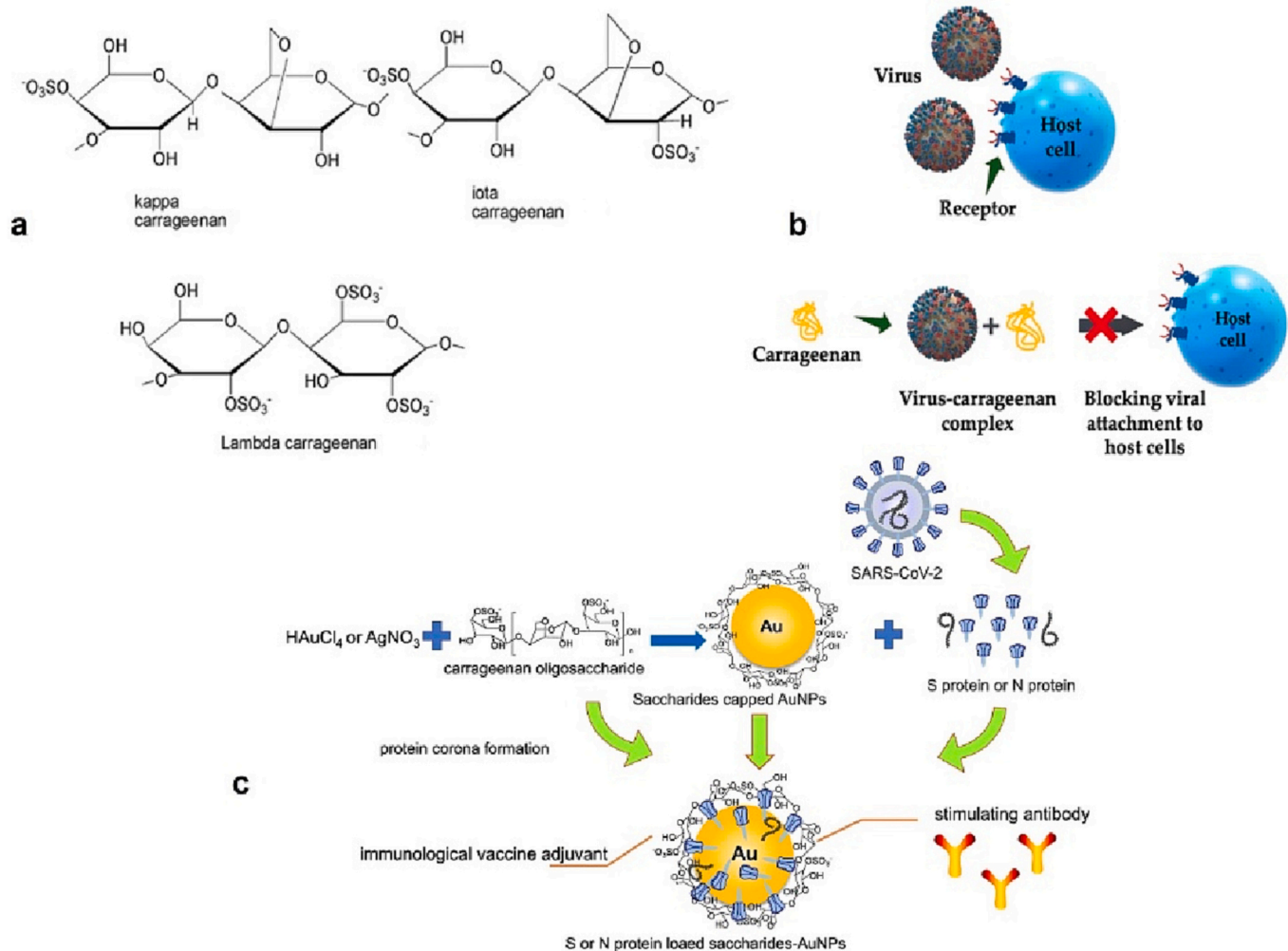


Fig. 4. a) The chemical structure of CG in three different compositions and sulfation degrees, known as kappa, iota, and lambda. Reproduced with permission. [126] Copyright 2017, Elsevier. b) Antiviral mechanism of CG. Reproduced under terms of CC license. [121] Copyright 2020, MDPI. c) Schematic illustration of the synthesis of CG-Au nanoconjugates loaded with S/N protein of CoV. Reproduced with permission. [125] Copyright 2020, Elsevier.

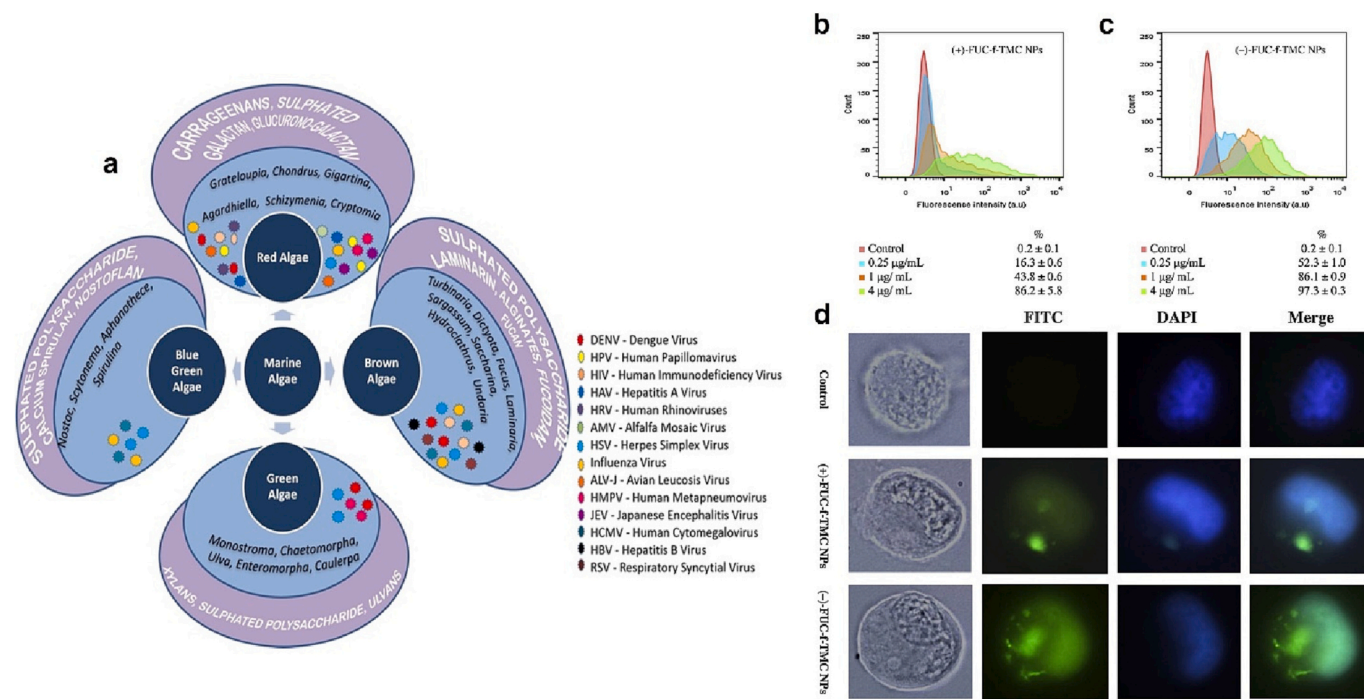


Fig. 5. a) Schematic classification of antiviral algal polysaccharides derived from red, brown, green, and blue green marine algae with different genera (Grateloupia, Laminaria, Fucus, Ulva, Nostoc, etc.). The derived polysaccharides (CG, ulvans, FUC, alginates, nostoflans, xylans, etc.) demonstrate a broad spectrum antiviral effect against a plethora of viruses. Reproduced under terms of CC license. [129] Copyright 2021, Elsevier. Flow cytometry data of JAWS II DCs co-cultured with different amounts of positively(b)/negatively (c) charged FUC-TMC NPs after 16 h. (d) Fluorescence dye staining and imaging of JAWS II DCs after co-culture with positively/negatively charged FUC-TMC NPs after 16 h. It is worthy to note that nuclei of the cells were stained with DAPI and are shown in blue. Reproduced with permission. [128], Copyright 2020, Elsevier. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

structures [130]. Due to their capacity to inactivate various viruses, plant polysaccharides are known as a promising source for prospective medicines. In the continuous pursuit of effective antiviral medicines, many Indian plant polysaccharides and Traditional Chinese Medicine (TCM) polysaccharides have been shown to be fatal against viruses (Table 2 and 3). In a recent study, Panavir®, a polysaccharide extracted from potato branches, was proven to be effective in treatment of the SARS-CoV-2 disease [131]. In general, plant polysaccharides can be regarded as promising therapeutic compounds against COVID-19 [132].

The main parameters that govern the antiviral activity of plant polysaccharides include molecular mass, conformation, sugar composition, branching arrangement, and chemical functionalization [132]. In this regard, sulfated galactofucan and glucuronomannan have been proven to more strongly bind to spike glycoproteins of SARS-CoV-2 compared to heparin, indicating the crucial role of polysaccharide's structure. Additionally, the position and density of sulfate groups affect the binding ability of sulfated polysaccharides to viral proteins [132]. In general, by disrupting the replication cycle of virus or stimulating the human immune reaction, plant polysaccharides can potentially suppress viral infection [152]. Fig. 6a illustrates various antiviral mechanisms of

Table 2
Antiviral activities of Indian plant polysaccharides.

Polysaccharide	Antiviral activities	Ref.
<i>Portulaca oleracea L.</i>	HSV-2	[133]
<i>Grateloupia indica</i>	HSV	[134]
<i>Calendula officinalis</i>	HIV	[135]
<i>Scinaia hatei</i>	HSV	[136]
<i>Rhizophora apiculata</i>	HIV	[132]
	SIV	
<i>Azadirachta indica</i>	PV-1	[137]
	BoHV-1	[138]

SIV: Simian immunodeficiency virus, PV-1: Poliovirus type 1, BoHV-1: Bovine herpesvirus type 1.

Table 3
Antiviral activities of Traditional Chinese Medicine polysaccharides.

Polysaccharide source	Antiviral activities	Ref.
<i>Astragalus</i>	PCV2	[139]
	HBV	[140]
	PRRSV	
	CSFV	
	DHAV	[141]
<i>Lycium barbarum</i>	IBDV	[142]
	PCV2	[143]
<i>Gelidium cartilagenium</i>	NDV	[144]
	IBV	[145]
<i>Angelica sinensis</i>	MuV	
	MLVs	[146]
	PCV2	[147]
<i>Sophora subprostrate</i>	PCV2	[148]
<i>Rehmannia glutinosa</i>	PCV2	[149]
<i>Chuanminshen violaceum</i>	DEV	[150]
<i>Chickweed</i>	HBV	[151]

PCV2: Porcine circovirus type 2, PRRSV: Porcine reproductive and respiratory syndrome virus, CSFV: Classical swine fever virus, DHAV: Duck virus hepatitis, IBDV: Infectious bursal disease virus, NDV: Newcastle disease virus, IBV: Influenza B virus, MuV: Mumps virus, MLV: Murine leukemia virus, DEV: Duck enteritis virus.

plant polysaccharides against SARS-CoV-2 that is an enveloped virus containing a positive-stranded RNA genome. In this virus, there are four different structural proteins including membrane, envelope, spike, and nucleocapsid [132]. The virus diffuses into the host cell through a complicated, multi-step process, beginning with interaction between the virus and surface receptors of the host cell. This interaction leads to fusion of the envelope with the host cell's membrane mediated by viral S proteins [132]. Sulfated polysaccharides electrostatically bind to the surface of virus, thereby minimizing its transmissibility or inactivating the virus. Sulfated polysaccharides are highly negatively charged and

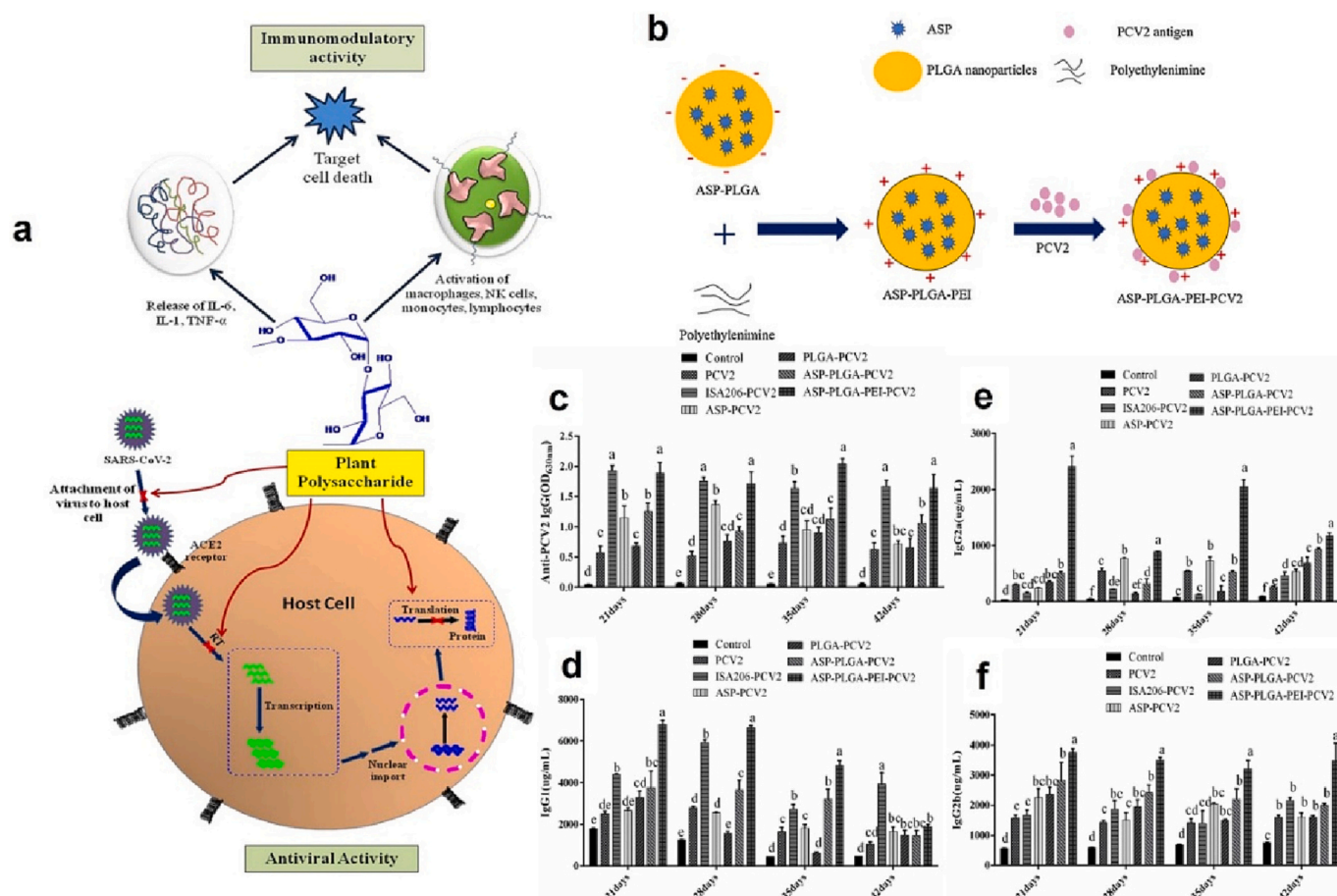


Fig. 6. a) Schematic illustration of the likely immunomodulatory and antiviral mechanism of plant polysaccharides against SARS-CoV-2. Reproduced with permission. [132] Copyright 2021 Elsevier. b) Schematic presentation of the preparation process of ASP incorporated PEI-PLGA and the derived vaccine NPs, PCV2 loaded ASP-PEI-PLGA. Serum IgG antibody response of the mice vaccinated with PCV2 loaded ASP-PEI-PLGA: c) PCV2-specific IgG titers and the amount of antibody isotypes of d) IgG1, e) IgG2a, and f) IgG2b after exposure to the vaccine NPs at different intervals. Reproduced with permission. [147], Copyright 2019 Elsevier.

thus can challenge the adsorption of virus or its invasion by covering the positively charged surface of the host cell [153]. These polysaccharides can also potentially inhibit the transcription and/or replication of virus on a host cell. Upon invasion of virus into the host cell, plant polysaccharide can stimulate host macrophages and NK cells, thereby provoking the release of immune cytokines. As a result, the plant polysaccharide activates the innate immunity and indirectly applies an antiviral effect [132]. Additionally, plant polysaccharides can induce an innate immune activity in a host cell via NO production, upregulation of interleukins (IL-6 and IL-12) and TNF- α in macrophages via binding to TLR-2, and activation of MAPK cells and NF- κ B [132].

It is well-known that activating the immune system with immunomodulating agents assists the body in adapting to virus prior to a significant illness, thus making the whole treatment more controllable [154]. Many plant polysaccharides can indirectly exert an antiviral activity by activating the body's immune system. Although they per se have no fatal impacts on the virus during infection, they can pre-regulate the immune response and prepare the immune system to defend against viral attacks or alleviate the symptoms and accelerate recovery. Plant polysaccharides can be used as adjuvants in NP vaccines, thereby enhancing the immune response, reducing the amount of viral antigen, safeguarding antigen and medication from degradation, and optimizing their bioavailability [155,156]. By coupling them with vaccines, plant polysaccharide adjuvants support vaccine antigens to induce or to augment a stronger immune response. Moreover, a long-term immune memory is achieved that can raise the efficacy of the vaccine and provoke the immune system [118]. In this regard, Gu et al. [156,157]

encapsulated angelica sinensis polysaccharide (ASP) in poly (lactic-co-glycolic acid) (PLGA) NPs to establish a drug delivery system. Compared to PLGA NPs, ASP-PLGA NPs dramatically increased the proliferation rate of T- and B- lymphocytes and induced a higher CD4+ to CD8+ T cell ratio. These outcomes implied the superior immune-enhancing ability of ASP-PLGA NPs as a novel drug delivery system [157]. In a subsequent study, Gu et al. [147] developed positively charged polyethyleneimine (PEI) coated PLGA NPs incorporating ASP (ASP-PEI-PLGA) as an adjuvant to amplify the antiviral efficiency of PCV2 vaccines (Fig. 6b). The NPs carrying PCV2 antigen elicited a more robust, long-lasting humoral immune response in mice compared to six control groups (Fig. 6c). In addition, they largely increased the amount of antibody isotypes IgG1, IgG2a and IgG2b (two latter are associated with a Th1-biased immune response) (Fig. 6d-f). The results confirm that PCV2 antigen-loaded ASP-PEI-PLGA NPs dramatically boost humoral and cell-mediated specific IgG immune function.

It is worthy to note that the synthesis of plant polysaccharide delivering nanosystems is often challenging. Moreover, translation of such experimental ideas into clinical products is a difficult task. To meet this objective, the mechanism of interaction between polysaccharide nanocarriers and living cells should be further explored. Additionally, more systematic and comprehensive processing techniques are needed to match the quality standards.

3.2.3. Animal polysaccharides

The third class of polysaccharides is animal polysaccharides that are obtained from various sources such as sea creatures' shell (chitin and

chitosan) and mammalian tissues (glycosaminoglycans, e.g.).

Chitosan (CS) is a naturally derived cationic amino-polysaccharide that consists of d-glucosamine and N-acetyl-d-glucosamine monomers linked by randomly distributed β -(1,4) bonds [158]. It is in fact a deacetylated derivative of chitin, an abundant polysaccharide in nature (Fig. 7a) [159,160]. This natural renewable polysaccharide has the advantages of degradability, hydrophilicity, mucosal adhesion, biocompatibility, and bioactivity [115]. Driven by the COVID-19 crisis, CS' antiviral action has garnered more interest in the recent years [161–163]. Through the interaction with angiotensin-converting enzyme II (ACE2), SARS-CoV-2 can enter and thus infect the human respiratory epithelial cells. It has been shown that β -CS can firmly attach to ACE2, thereby blocking it against the attachment of SARS-CoV-2's receptor binding domain (RBD) [164]. Sulphated CS-oligosaccharide compounds have been also proven to effectively hamper the contact between HIV-1gp120 and CD4+ surface receptors of host cells, thereby limiting virus–host cell fusion and viral entry into the host cell [165]. On the other hand, thanks to the electrostatic attraction between the negatively charged surface of viruses and the positively charged groups of CS, the infectious ability of virus is minimized and/or virus is killed through disruption of its protective membrane [166]. The antiviral activity of CS can be schematically explained by the mechanisms shown in Fig. 7b.

Various antiviral activities of CS have enabled the development of a variety of therapeutic or preventive nanotools, particularly over the course of viral pandemics. Fig. 7c summarizes the potential contributions of CS to fighting against viral diseases. CS NPs can also be used as drug delivery nanosystems and antiviral vaccine formulations. Fig. 7d schematically lists the merits of CS NPs as drug nanocarriers. In this regard, Gu et al. [168] developed antibody immobilized CS NPs as carriers for small interfering RNA (siRNA). The as-synthesized nanosystem was aimed to release siRNA over the blood-brain barrier and in

particular, into HIV-infected brain astrocytes to inhibit HIV replication. The dual antibody (anti-Tf and anti-B2 antibody) functionalized CS NPs were shown to be more effective in terms of cellular uptake and gene silencing than their neat counterparts are. Rather than a NP delivery material, CS has been also employed to coat liposome nanocarriers containing the antiviral drug of Triazavirin [169].

Glycosaminoglycans (GAGs), also known as mucopolysaccharides, are naturally derived linear polysaccharides that consist of repeating disaccharide units [170]. Mucopolysaccharides are largely available in mucous and perform as viscous lubricants [171]. GAGs are found throughout the body and expressed mainly in intracellular compartments, extracellular space, and on the surface of cell membranes [113,125]. With different repeating disaccharide units, GAGs are classified as: heparin (HP)/heparin sulphate (HS), chondroitin/dermatan sulphate, hyaluronan, and keratan sulphate [113,172]. Among these classes of GAGs, HP and HS have been shown to possess a proper potential as antiviral drugs [113]. Both HP and HS bind to viruses, thereby preventing or limiting pathogen invasion [125]. They can potentially inactivate a variety of viruses, including DEN [173], Japanese encephalitis virus (JEV) [173], HSV-1 and HSV-2 [174], influenza H5N1 [175] and HIV [176]. Additionally, it has been shown that HS proteoglycans can show an antiviral effect towards HCoV-NL63 [177]. In the presence of soluble HS, virus entry into a host cell is inhibited via its interaction with HS. HCoV-NL63 virus binds to HS on cell surface and thus its adhesion to host cell is completely hampered [177]. The SARS-CoV-2 spike protein can also firmly react with HP and HS. Therefore, acetyl heparin and heparin-derived medicines could have antiviral effects against SARS-CoV-2 [113,178,179]. The negatively charged sulfate groups of GAGs can electrostatically attract arginine residues of the virion binding S1 subunit with a positive charge, thereby limiting the virus adsorption to host cells [113]. This possibility could be regarded as the basis of creation of an antiviral GAG layer-by-layer (LBL) nano-

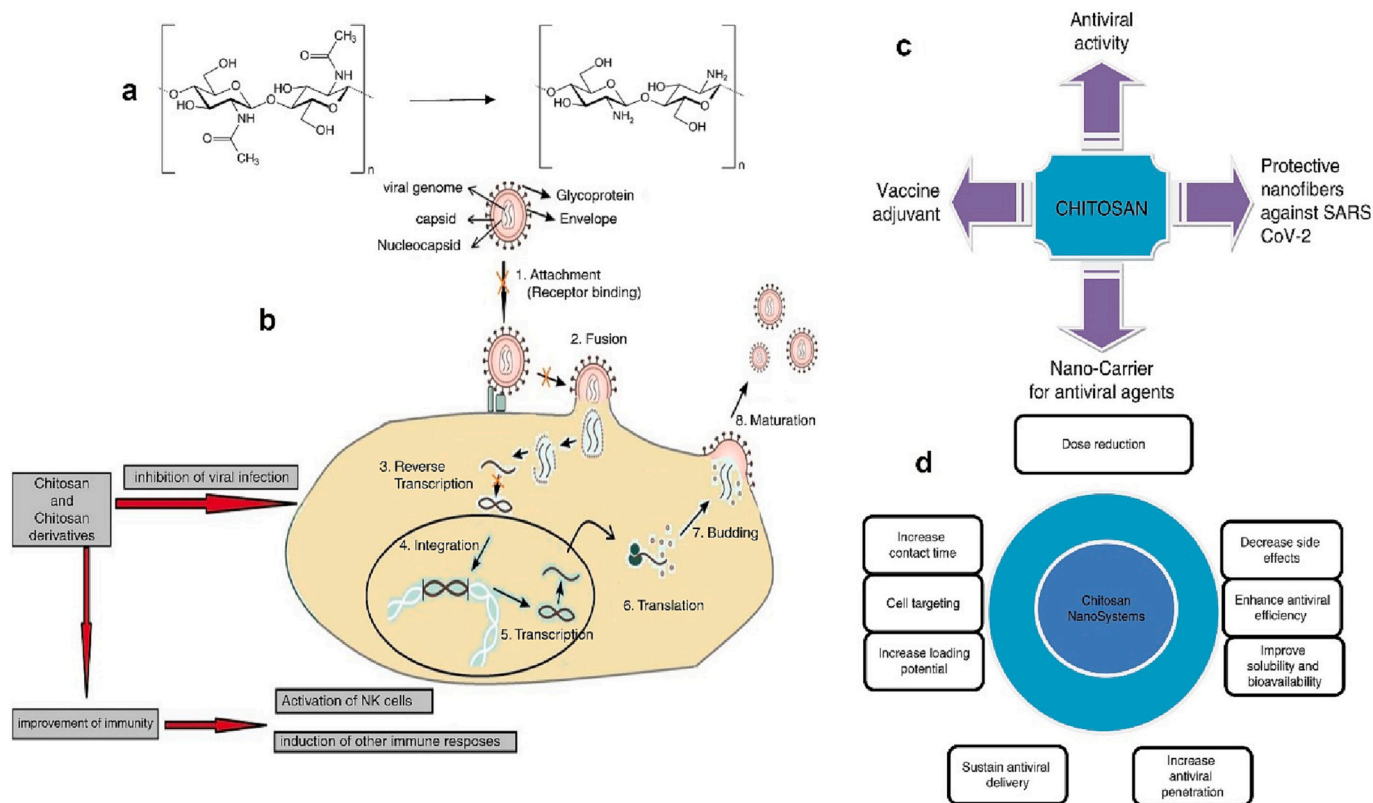


Fig. 7. a) Schematic illustration of the conversion process of chitin to CS via partial deacetylation. Reproduced under terms of the CC license. [159] Copyright 2019, MDPI. b) Antiviral mechanisms of CS depending on the different stages of the life course of a virus. c) Potential contributions of CS to antiviral preventive/therapeutic treatments. d) Various benefits of CS NPs as drug delivery nanocarriers. Reproduced with permission. [167] Copyright 2021, John Wiley and Sons.

coating for various surfaces such as masks, protective clothing, and medical devices [113]. Additionally, HP nanoassemblies have been synthesized to inhibit the activities of HS-dependent viruses such as RSV, HPV-16, HSV-1, and HSV-2 [180]. Such hexagonal nanoassemblies can be obtained via auto-association of *O*-palmitoyl-heparin and α -cyclodextrin within water. Tu et al. [181] also developed inhalable HP NPs that could block the interaction pathway between HS and Spike protein and thereby prevent the infection of SARS-CoV-2 pseudovirus and its variants.

In general, polysaccharides have many desirable features such as antiviral activity, biocompatibility, low toxicity, biodegradability, renewability, and safety [115]. As a result, these natural compounds have been widely used to produce unique antiviral nanomaterials and delivery nanoplateforms for the purpose of preventing, diagnosing, and treating viral diseases especially those related to SARS-CoV-2 [125,182]. Additionally, polysaccharide adjuvants can enhance the antiviral effect and immunity of vaccines [125]. A COVID-19 vaccine combining polysaccharides and nanotechnology could be suggested for future development. However, polysaccharides have several drawbacks that limit their growth, such as their toxicity and anticoagulant effects [115]. Hence, there is still a need to more systematic and analytical studies,

especially a comprehensive analysis of safety, biocompatibility, efficacy, and cytotoxicity for clinical applications [115]. Table 4 tabulates some examples of antiviral polysaccharide nanosystems.

4. Nanocarriers of antiviral peptides and antiviral polysaccharides

There are several challenges ahead of efficient in vivo delivery of antiviral peptides and antiviral polysaccharides. These therapeutic agents can readily be degraded, promptly cleared, or lose their bioavailability. Nanocarriers can address these issues and provide multiple promising solutions. In fact, nanocarriers provide a platform to enhance therapeutic efficacy, to minimize side effects, and to allow for specific targeting of the cargo to assure the targeted effects at cellular scale [15]. Moreover, nanocarriers are meant to (a) raise the solubility of a number of therapeutic agents, (b) allow for steady release of therapeutic agents in a controlled manner, thereby offering a long-term therapy or excessive exposure to the agent (cargo), (c) protect therapeutic agents against in vivo degradation or clearance by the immune system, (d) improve internalization of therapeutic agents by cells [197]. In this regard, biocompatible inorganic and organic (polymeric and

Table 4
Some examples for antiviral polysaccharide delivering nanosystems.

Polysaccharide	Nanocarrier	Cargo	Size (nm)	Application	Synthesis	Ref.
Isatis indigotica Fort. root	–	–	57 to 300	Antiviral activity against influenza virus H1N1	Decoction	[183]
CS	Lecithin/Miglyol® 812	TLR7 agonist, imiquimod, and the recombinant HB surface antigen	200	Nasal vaccination (delivery of TLR7 agonist, imiquimod, and the recombinant HB surface antigen to elicit specific humoral and cellular immune responses)	Solvent displacement technique involving mixing lecithin/Miglyol® 812 in ethanol/acetone solution and an aqueous solution of CS	[184]
Acacia gum	Ag NP	–	10–80	Antiviral activity against MPV	–	[185]
CS and HA	–	PCS peptide (PCS5)	119–211	HIV vaccine to elicit specific humoral and cellular immune responses	PCS5 was first conjugated to CS and HA and then bound with an oppositely charged polymer (DXS and CS) and poly(I:C) to form the NPs.	[186]
Starch, oxidized cellulose and ethyl cellulose	Ag NP	–	<100	Antiviral activity against Herpes simplex virus, Adenovirus and Coxsackie B virus	Addition of biosynthesized Ag NPs to aqueous dispersion of starch, oxidized cellulose, and later mixing with ethyl cellulose/ ethanol solution	[187]
Angelica sinensis	PEI coated PLGA NPs	–	286.3 ± 2.45	As an adjuvant for H9N2 vaccine to improve immune response	A double emulsion solvent evaporation method	[188]
PPS14 derived from <i>S. pneumoniae</i> lysates	–	Recombinant RBD protein of SARS-CoV-2	8–23	Vaccine against SARS-CoV-2	Reductive amination method	[189]
EPS	ZnO NPs	–	10–100	Antibiofilm activity and larvicidal toxicity against malaria and Zika virus vectors	Biosynthesis of ZnO NPs using EPS derived from the probiotic strain <i>Bacillus licheniformis</i> Dahb1	[190]
CYP	PEI coated PLGA NPs	PCV-2 antigen	236.6 to 256.9 depending on the PLGA/PEI weight ratio	Vaccine adjuvant to enhance the immune efficacy of PCV-2 vaccine	W/O/W double emulsion solvent evaporation method	[191]
AHP	PEI coated PLGA NPs	H5N1 antigen	200	As an adjuvant to induce strong and long-lasting Th1 and Th2 mixed immune responses	A double emulsion solvent evaporation method	[192]
GXM	Au NP as filler	–	–	Antiviral activity against TMV	Biosynthesis of Au NPs within GXM aqueous solution	[193]
ABP	Oil emulsion	–	109.37	As an adjuvant to induce strong immune response against FMD virus	Span80 and Tween80 as surfactants, and anhydrous ethanol as a co-surfactant. Isopropyl myristate as the oil phase. ABP aqueous solution was added to the reaction mixture.	[194]
PSP	Spiky TiO ₂ NPs	–	976.11	As an adjuvant to induce a strong immune response against FMD virus	Addition of spiky TiO ₂ NPs to PSP solution	[195]
<i>Salmonella typhi</i> Vi polysaccharide conjugated with r-flagellin	PLA NPs	–	284.2	To raise the immunogenicity of T cell independent antigens	A double emulsion solvent evaporation method	[196]

ABP: *Achyranthes bidentata* polysaccharide, AHP: Alhagi honey polysaccharide, CYP: Chinese yam polysaccharide, EPS: Bacterial exopolysaccharide, DXS: dextran sulfate, FMD: Foot-and-mouth disease, GXM: Glucuronoxylomannan, HB: Hepatitis B, HA: hyaluronic acid, MPV: monkeypox virus, Nanoparticle: NP, PEI: polyethyleneimine, PSP: Plantaginis Semen polysaccharide, PLGA: poly (lactic-co-glycolic acid), RBD: receptor-binding domain, TMV: tobacco mosaic virus, TLR7: Toll-like receptor 7, W/O/W: water-oil-water.

lipid-based) NPs can be customized in terms of physicochemical properties to hold the mentioned cargos with acceptable loading efficiency, thereby optimizing delivery of the conjugated therapeutic agent and pharmacokinetics compared to conventional methods [198].

4.1. Polymeric nanocarriers

Numerous polymeric systems have been investigated over the past decade for development of nanocarriers (Fig. 8a) to deliver drugs and natural antiviral materials. Typically, they include polymeric NPs, dendritic macromolecules, polymeric micelles, vesicles, gels, capsules, and composites with a wide range of submicron diameter (Fig. 8b&c) [199,200]. Polymeric nanocarriers are made of either natural or

synthetic polymers and are selected primarily based on their biodegradability, biocompatibility, and surface properties. As explained earlier, natural polymers are mostly composed of polysaccharides and proteins and are readily derived from a variety of natural sources, including animals, plants, sea creatures, and fungi. They are inexpensive, non-toxic, highly stable, safe, and biodegradable [201]. In addition, some of natural polymers that can be used as nanocarriers show antiviral activity, thus notably promote the synergistic antiviral effect of the nanoformulation. Among synthetic polymers, the most widely used ones are polystyrene (PS), polyvinyl alcohol (PVA), polyglycolic acid (PGA), poly (alkyl cyanoacrylate) (PACA), polymethacrylate (PMMA), poly (isobutyl cyanoacrylate) (PICA), and PLGA [5,201].

As an example for natural polymer nanocarriers, CS and Alg have

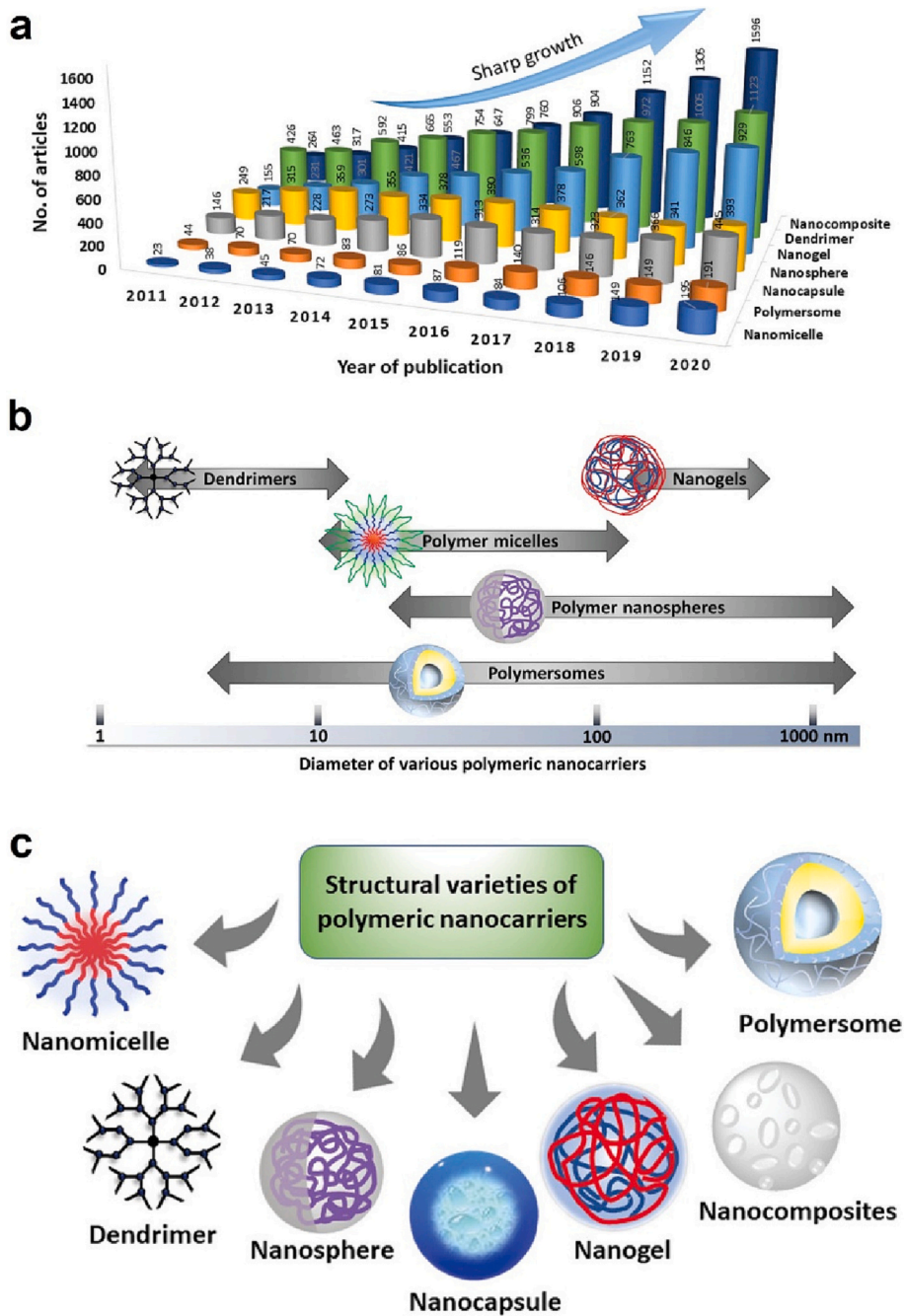


Fig. 8. a) The chart demonstrates the number of publications per year over the past decade on different polymeric nanocarriers. b) The size range of different polymeric nano (submicron) carriers. c) The molecular structure of polymeric nanocarriers for different kinds of therapeutics including antiviral natural polymers. Reproduced under terms of the CC-BY license. [200] Copyright 2022, John Wiley and Sons.

been combined to carry and deliver natural antiviral agents. Such a formulation can cooperatively improve the antiviral efficacy. In this regard, Li et al. [202] prepared CS/Alg NPs incorporating bee venom (BV) and employed them for the suppression of PRRSV. These NPs can adhere to nasal mucosa of pig and slowly release BV, thereby effectively enhancing the systemic immune response and clearing PRRSV. The NP-administered group of animals with PRRSV vaccination were shown to have a notably improved Th1-based response including a large density of CD4+ T lymphocyte and upregulated mRNA levels of cytokines such as interleukin (IL)-12 and interferon-gamma (IFN- γ) and PRRSV-specific IgG levels. Additionally, the animal group treated with the NPs contained a lower viral density in bronchial lymph node and lung and showed insignificant interstitial pneumonia signs. On the other hand, a high level of viral neutralizing antibody and PRRSV-specific IgG was recorded. Alg-coated CS NPs have also shown a promising potential for oral mucosal immunization. The CS NPs encapsulating hepatitis B surface antigen (HBsAg) have been synthesized and coated with Alg to protect them against the aggressive environment of stomach [203]. The NPs (650 nm in diameter) were further loaded with lipopolysaccharide as an adjuvant. These NPs provoked a notable amount of secretory IgA (sIgA) in the mucosal (intestinal (3.32 mIU/ml), vaginal (2.61 mIU/ml), and salivary (2.85 mIU/ml)) secretions and IgG antibodies.

Alongside natural polymers, synthetic, biodegradable polymers have been also employed for construction of nanocarriers to maintain the biofunctionality of the incorporated therapeutic materials including polysaccharides. In this regard, PLA or PLGA NPs have been largely studied for construction of single dose vaccines [204,205]. In addition to steadily delivering antigen, such vaccine delivery nanosystems enable adjuvant activity through provoking the antigen-releasing cells [206]. In contrast to protein antigens, majority of polysaccharide antigens (e.g., Vi capsular polysaccharide antigen) induce antibody response independent to T-cell assistance. They directly affect the polysaccharide-specific B-cells and differentiate them into plasma cells that generate antibodies [207]. The immunogenicity of Vi polysaccharide can be

improved in case of immobilization on a polymer nanocarrier. To achieve this objective, Anish et al. [207] incorporated Vi polysaccharides into PLA nanoparticles to raise IgG titer compared to soluble Vi immunization. Meena et al. [196] also conjugated Vi polysaccharide and r-flagellin of *Salmonella typhi* onto PLA nanoparticles. The resulting nanoglycoconjugate not only provoked the immune response but also caused antibody class switching (from IgG3 to IgG2) and induced memory antibody response against Vi polysaccharide. This strategy also modulated the anti-inflammatory activity of Vi polysaccharide through promoted secretion of IL-6 and TNF- α (i.e., pro-inflammatory cytokine) and decreased the production of IFN- γ .

4.2. Lipid nanocarriers

Lipid nanocarriers are mainly spherical nanostructures, constituting of one lipid bilayer encompassing one aqueous core [208]. A variety of lipids have been explored as nanocarriers for natural antiviral products. Lipid-based nanoformulations offer many advantages over polymers, including biodegradability, biocompatibility, simplicity of formulation, self-assembly, non-toxicity, ease of access, and lower cost [209]. For such reasons, lipids are known as the most common United States Food and Drug Administration (FDA)-approved nanoformulations [208]. Through various processes, lipid nanocarriers may enhance bioavailability of the medications loaded therein, alter their pharmacokinetic characteristics, minimize toxicity, and target drug delivery to the locations that are inaccessible to traditional pharmaceuticals [210]. The commonly used lipid nanomedicines are mainly based on natural glycerides, glycerol palm stearate, and waxes or long-chain fatty acids (beeswax, Brazilian palm wax, etc.) [211]. These formulations also include surfactants and co-solvents from natural lecithin or synthetic sources [211]. Lipid-based nanoformulations mainly include liposomes, lipid NPs (LNPs), and nanostructured lipid carriers (Fig. 9a) [212,213].

Liposomes are the most well-known, largely employed, and simple to fabricate lipid based nanoformulations developed for drug delivery. The

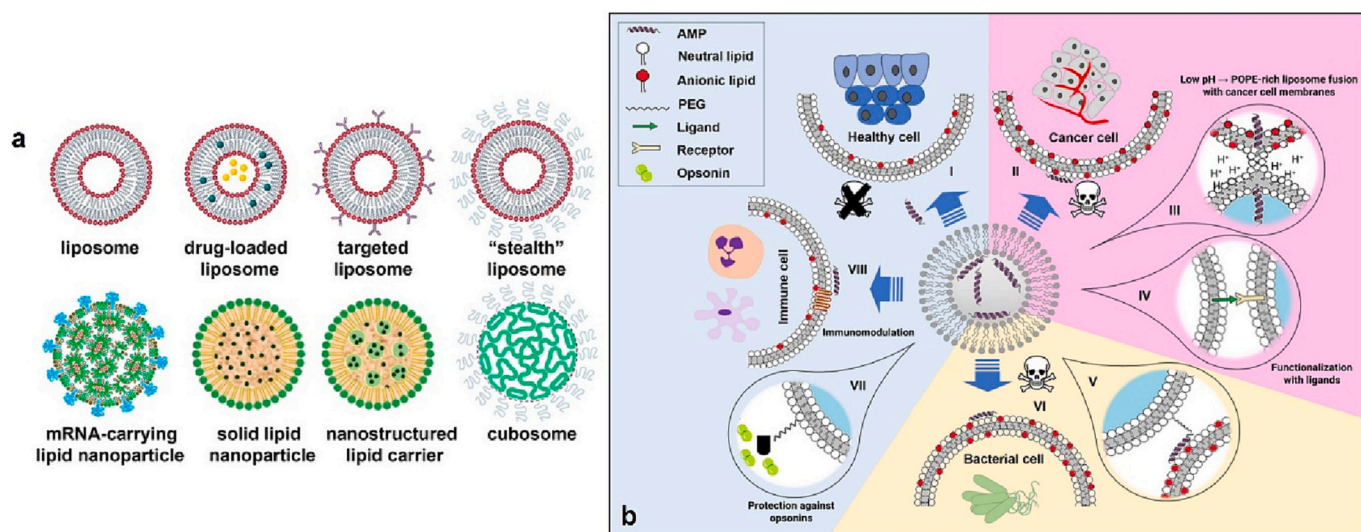


Fig. 9. a) Schematic illustration of various lipid nanocarriers. Reproduced under terms of the CC license. [213] Copyright 2021, ACS. b) Different options to deliver AMPs using liposomes. To improve the diffusion-based delivery of liposomes, their surface can be decorated or their lipid composition be modified. (I) The surface of healthy host cells is almost zwitterionic, thus shows no particular affinity to cationic (positively charged) AMPs. (II) The inherent phospholipid asymmetry available between the two leaflets of the membrane of normal cells is not found in cancer cells' plasma membrane. As a result, anionic phospholipids, typically present on the internal monolayer of the membrane, get exposed on the external leaflet, thereby enhancing the electrostatic interaction between cationic AMPs and the anionic surface of cancer cells. (III) Cancer cells feature an acidic extracellular medium. Lipid NPs rich of POPE tend to create non-lamellar phases under an acidic condition, driving their fusion to cells, thereby delivering AMPs. (IV) Lipid NPs can be surface decorated with the ligands that attach to the receptors expressed by cancer cells. (V) The lipid NP surface can be functionalized with PEGylated AMPs to enable the peptide to directly affect the host cell's membrane. (VI) The anionic phospholipids and/or other anionic biomolecules present on the surface of bacteria facilitate their interaction with AMPs. (VII) The opsonization and protein corona formation are avoided by surface decoration of lipid NPs with specific polymers. (VIII) A number of AMPs show immunomodulatory effects to inhibit adverse inflammatory responses. Reproduced under terms of the CC-BY license. [220] Copyright 2019, MDPI.

liposome based Doxil® was the first nanomedicine approved by regulatory agencies [214]. Liposomes are individual spherical lipid bilayers that can be instantly created within an aqueous medium. The basic constituents of liposomes are phospholipids. Besides, cholesterol has been also frequently added to the formulations of liposomes. They are biocompatible and biodegradable, and induce negligible toxicity and immunogenicity [215]. For the first time, liposomes were proposed as drug delivery systems in the 1970s [216]. After two decades, the PEGylated liposomal doxorubicin (Doxil®) was the first nanomedicine for cancer therapy that was approved by the FDA [214]. Liposome based nanocarriers are nowadays the most used delivery platform for therapeutic purposes [217]. For instance, they can optimally deliver AMPs, while protecting them against proteolytic degradation by their phospholipid bilayer. In this regard, Ron-Doitch et al. [99] developed PEG coated LL-37 and indolicidin liposomes and characterized their antiviral efficiency against HSV-1. According to this study, such a delivery nanosystem was less toxic and caused improved antiviral activity compared with free AMP and indolicidin liposomes. Fig. 9b schematically demonstrates several delivery approaches for AMPs by liposomes.

The capacity of polysaccharide delivering liposomes as an adjuvant for cell mediated immunity has been studied as well. Toda et al. [218] developed mannan-coated liposomes and investigated its adjuvant effect on HIV-1 DNA vaccine. The presence of mannan coating on cationic liposomes notably allowed the vaccine to cause an HIV-specific delayed-type hypersensitivity (DTH) effect. Additionally, the HIV-specific cytotoxic T-cell (CTL) effect emerged by DNA vaccination was also largely promoted in the presence of mannan-liposome conjugate. Wachsmann et al. [219] synthesized Streptococcus mutans vaccine comprised of a purified polysaccharide antigen-a 74 K cell wall protein (able to interact with saliva proteins) conjugate linked to liposomes, which could produce a local immunoglobulin A response (secretory IgA). Therefore, the conjugate incorporated in liposome can be considered as a potential vaccine adjuvant against *S. mutans* vis a vis dental caries.

4.3. Cell penetrating peptides (CPPs)

Therapeutics are generally blocked by the tissue and cell barriers featuring a poor biomembrane permeability [221]. This challenge inhibits proper systemic distribution of the therapeutic and lowers its therapeutic efficacy. To address such a concern, CPPs have been developed to raise the local concentration of therapeutics in hardly

accessible areas. CPPs can carry a plethora of bioactive cargos such as small drugs, siRNAs, DNAs, peptides, and proteins into cells efficiently [221,222]. Depending on chemistry, cargos are conjugated onto CPPs through covalent bonds, e.g., disulfide or thioester bonds, or non-covalent complexation via hydrophobic and/or electrostatic interactions between the positively charged CPP and a negatively charged cargo (e.g., oligonucleotides) (Fig. 10a). The former approach is typically applied for delivering small drug molecules, proteins, peptides, peptide nucleic acids (PNAs), and phosphorodiamidate morpholino oligomers (PMOs) [221]. As a result of CPP conjugation, the bioactive cargo-CPP conjugate is protected against nuclease or protease degradation and the serum half-life of cargo increases [223,224]. Thanks to such a possibility, CPPs have been employed in nanomedicine as a delivery platform for diverse therapeutics such as neuroprotective and antineoplastic agents, and anti-inflammatory and antimicrobial drugs [225].

In terms of cellular internalization mechanisms, a CPP can follow two main pathways for crossing the cell membrane and entering the cell (Fig. 10b). These pathways include endocytosis and direct penetration into the cell plasma membrane that are energy-dependent and energy-independent, respectively. The majority of CPP-cargo conjugates undergo endocytosis to get into cells [226], though at high amounts of CPPs, direct penetration can also take place [227].

With respect to antiviral peptide delivery, a number of CPPs have been shown to offer a promising potential for intracellular delivery of peptide nucleic acids (PNAs) that can hamper hepadnaviral replication [228]. According to Ndeboko et al. [228], the (D-Arg)₈ CPP- PNA conjugate (targeting viral epsilon (ε)) can properly hamper viral replication in the ducklings infected with duck HBV (DHBV). It is worthy to note that (D-Arg)₈ CPP and Decanoyl-(D-Arg)₈ CPP *per se* can show an antiviral effect, thereby affecting the late stages of HBV and DHBV morphogenesis. These antiviral activities of CPPs, however, alters the sequence-specificity of the CPP-PNA conjugates. To maintain sequence specificity while inhibiting hepadnaviral replication, PNA can be conjugated to (D-Lys)₄ CPP instead. As another example, lactose-treated CPP can also effectively deliver anti-HBV PNA to human hepatoma cells (HepaRG), thereby enhancing the antiviral effect of PNA.

4.4. Inorganic nanocarriers

Metal NPs can inhibit viral activities either alone or as coupled with

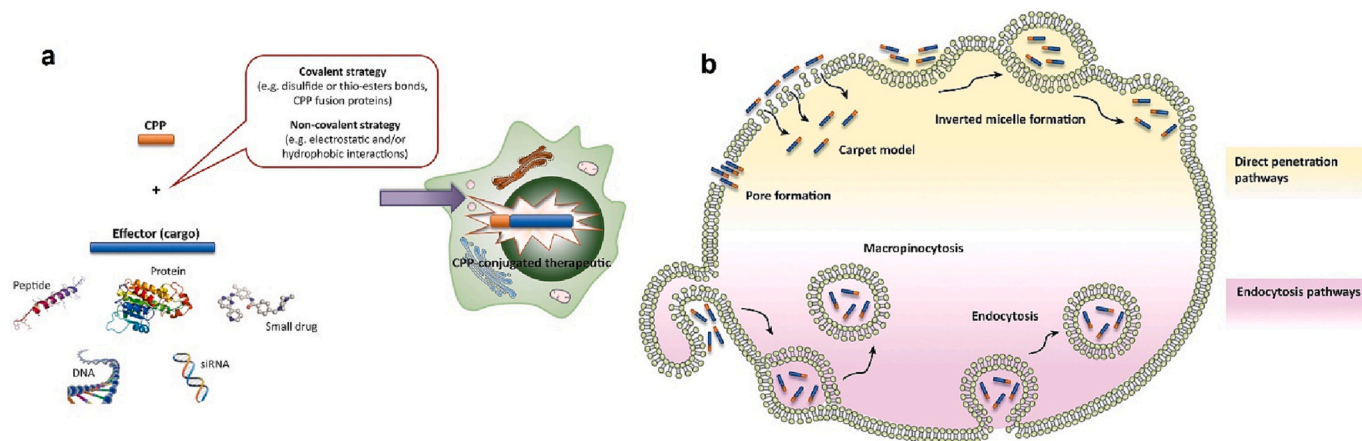


Fig. 10. a) Schematic illustration of CPP-based delivery systems. Hydrophilicity of various cargoes (e.g., small drug molecules, siRNA, DNA, and peptides) can hamper their effective transport into cells. Through covalent/non-covalent conjugation of CPP with a cargo, the CPP–cargo assembly can pass through the cell membrane and get access to hardly accessible intracellular areas. b) Schematic illustration of the mechanisms of action for CPP internalization through direct penetration into the cell plasma membrane (upper half) or endocytic pathways (lower half). The former mode includes multiple energy-independent processes such as CPP insertion into the cell membrane via pore formation and destabilization of the cell membrane (realized as carpet model or inverted micelle formation). The second mode which is endocytic internalization of CPP includes endocytosis and micropinocytosis and is an energy-consuming process. Reproduced with permission [221]. Copyright 2017, Elsevier.

antiviral compounds. Through their unique dimension, morphology, and plasmonic effect, they can affect viral surface proteins via van der Waals forces and Kazimir interactions [229]. The interaction with biomolecules can be further promoted after surface functionalization of metal NPs using thiol or silane groups, thereby altering viral internalization in cells and drug delivery mode [5]. It has been shown that Au NPs can enter brain microendothelial cells, macrophages, and lymphocytes, in which HIV can potentially replicate [5]. Ag is well-known for its intrinsic antimicrobial properties, originating from its potential to interact with bacterial DNA, electron transport chain enzymes, and respiratory chain. Thanks to their small size and extensive surface area, Ag NPs undergo fast dissolution and thereby are extremely active against a broad range of viruses [230]. Ag NPs could actively hamper the interaction between gp120 and CD4. In addition, they could bind to O and S of phosphate and thiol groups of nucleic acid and amino acids, thereby inhibiting the post-entry steps of infection or directly attach to DNA or RNA, thus lowering the reverse transcription rate. Au and Ag NPs have been proven to be promising delivery nanosystems for antiviral peptide (FluPep) [231]. Conjugation of FluPep with Au and Ag NPs improved its solubility and antiviral activity. Niikura et al. [152] synthesized Au NPs in various shapes (cubic, rod, and spherical) and sizes and loaded them with West Nile virus envelope protein (E) to develop vaccine adjuvants. According to their study, Au NP-Es perform in a size or shape-dependent manner and induce the immune response to generate antibody and cytokines. With respect to polysaccharide conjugated metal NPs with antiviral activity, Dhanasezian et al. [232] biosynthesized Au and Ag NPs using seaweed *Sargassum wightii* (Sw). Both Sw-Ag and Sw-Au NPs were shown to be virucidal against HSV. While only 2.5 μL of Sw-Ag NPs could reduce 70% of cytopathic effect (CPE) of both HSV-1 and HSV-2, Sw-Au NPs caused this CPE reduction percentage at much higher dosages of 10 μL and 25 μL for HSV-1 and HSV-2, respectively.

Metal oxide NPs could be also a proper candidate for carrying natural antiviral agents and inhibiting viral activities. For instance, TiO_2 NPs have been used as a carrier for peptide analogues of nucleic acids (PNA). In PNA, there is a neutral peptide-like N-(2-aminoethyl) glycine backbone rather than the normal phosphate linkage of RNA and DNA. As a result of this specific structure, viral gene expression is inhibited, while the combination of PNA/ TiO_2 preserves PNA in physiological conditions and against cellular enzymes [233]. Amirkhanov et al. [234] developed the complex of DNA-PNA, stabilized it via electrostatic interactions, and loaded it on TiO_2 NPs. The 3'-end of the noncoding region of segment 5 of viral RNA (influenza A virus H3N2) was targeted by DNA-PNA/ TiO_2 nanocomposite. This treatment led to 99.8% reduction in virus reproduction. ZnO NPs have been shown to carry antiviral polysaccharides and to induce a reliable antiviral effect. In this regard, Kothai et al. [235] biosynthesized ZnO NPs with crude Fucoidan from brown seaweed *S. marginatum*. The fucoidan/ZnO NPs were shown to be an effective antiviral agent (99.09% antiviral efficiency) for the treatment of dengue fever. Despite various merits of inorganic nanocarriers, their use has been restricted due to their likely toxicity. A number of studies have validated the toxicity of inorganic nanomaterials as a result of their uncontrolled administration [236–238].

4.5. Carbonaceous nanocarriers

Carbon nanotubes (CNTs) can be also decorated with antiviral agents and be employed for targeted therapy. For instance, lentinan, a high-molecular-weight polysaccharide, was covalently attached to CNTs to synthesize a novel adjuvant [239]. This formulation benefits from superhydrophobicity of CNTs and promising immunological activity of lentinan. Lentinan is a β -1,3-glucohexaose with β -1,6-branches, that is derived from the mushroom *Lentinus edodes*. As a strong immunostimulatory drug, lentinan is clinically utilized in east Asia [239]. According to *In vitro* testing data, CNTs could promptly diffuse into dendritic cells and deliver a large amount of antigen, thereby notably

upregulating maturation markers. Synergistically, lentinan/CNTs were shown to act as potent intracellular antigen depots and as catalysts that could provoke functional and phenotypic maturation of dendritic cells [239].

5. Virus-nanocarrier interactions

Apart from the antiviral effect of peptide and polysaccharide cargos, nanocarriers can also damage and inactivate viruses, depending on their shape, size, surface ionic composition, and equilibrium distance [240]. Quantum dots (QDs), i.e., the NPs whose size lies in the range of 1–10 nm, can physically attach to viruses through van der Waals forces (Fig. 11a). This mode of interaction engenders electrodynamic, medium and thermal fluctuation, leading to dispersion forces [241]. NPs/QDs induce the local field enhancement effect on the receptor of viruses and as a result inhibit the entry of the virus into a host cell by impairing the available chemical bonds [240]. The emergence of resonance is associated to the local field enhancement and most likely to occurrence of the “collective” mode, and is witnessed by appearance of an intensive, sharp absorption line in the J-aggregate [242–245]. Additionally, the vacuum field fluctuation existing between virus and NPs restricts the virus infectious activity [240]. Regardless of the type of virus (RNA and DNA virus, or enveloped and non-enveloped virus), the antiviral mechanism of action of NPs is analogous and mainly deals with alteration of virus' receptor geometry, challenging the attachment of the virus to a host cell [246–248]. On the other hand, lipid envelope antiviral disruption (LEAD) is a novel approach that can selectively damage the virus envelope of HSV, HIV, SARS-CoV-2, Ebola, Zika, influenza, for instance, and affect amyloid fibrils, responsible for viral infection, and thereby reduces the infectivity of the virus particle [240,249–251]. Fig. 11b shows the broad-spectrum antiviral agents that specifically deteriorate viral membrane [252]. In general, main classes of antiviral agents that adversely affect the lipid membrane of enveloped viruses include amphipathic peptides, rigid amphipathic fusion inhibitors, photosensitizers, and molecular tweezers [249,250,252]. A photosensitizer acts through oxidizing the unsaturated phospholipids. The amphipathic antiviral peptides (AVPs) either permeabilize the lipid membrane with a large partition coefficient and destabilize the lipid membrane irrespective of membrane curvature or lyse the cell membrane upon formation of a critical density of pores [240]. The rigid amphipathic fusion inhibitors hinder the fusion of virus to host cells via the positive curvature effect. They can also oxidize the unsaturated phospholipids, thereby altering the membrane fluidity [249,250]. There are other mechanisms of action for antiviral activity of nanocarriers, particularly QDs. For instance, in the case of SARS-CoV-2, the 1–10 nm size of QD allows for its efficient penetration into virus [245]. The positively charged QDs such as carbon-made QDs can disperse or sequester CoV's spike protein [253]. As shown in Fig. 11a, positively charged QDs also electrostatically interact with SARS-CoV-2's genome, thereby triggering the release of ROS inside a virion. The as-generated ROS inhibits the replication of negative-strand RNA [245,254,255]. QDs can also induce the production of interferon- α gene and hinder the replication of virus (Fig. 11a). The cationic surface of QDs provokes virus aggregation electrostatically and minimizes viral infection [245,256].

6. Conclusion and future outlooks

Antiviral peptides and antiviral polysaccharides are biocompatible, nature-derived compounds with a plethora of health and economical merits. Till now, many natural polymers, mainly polysaccharides, have been proven to induce antiviral effects and over last decades their antiviral mechanisms of action dealing with the life cycle of viruses (entry, replication, assembly, and spread) and virus-host cell specific interplays have been uncovered. The number of polysaccharides studied for the purpose of prevention and treatment of viral diseases prevails over that of AMPs. Therefore, it is necessary to synthesize and develop

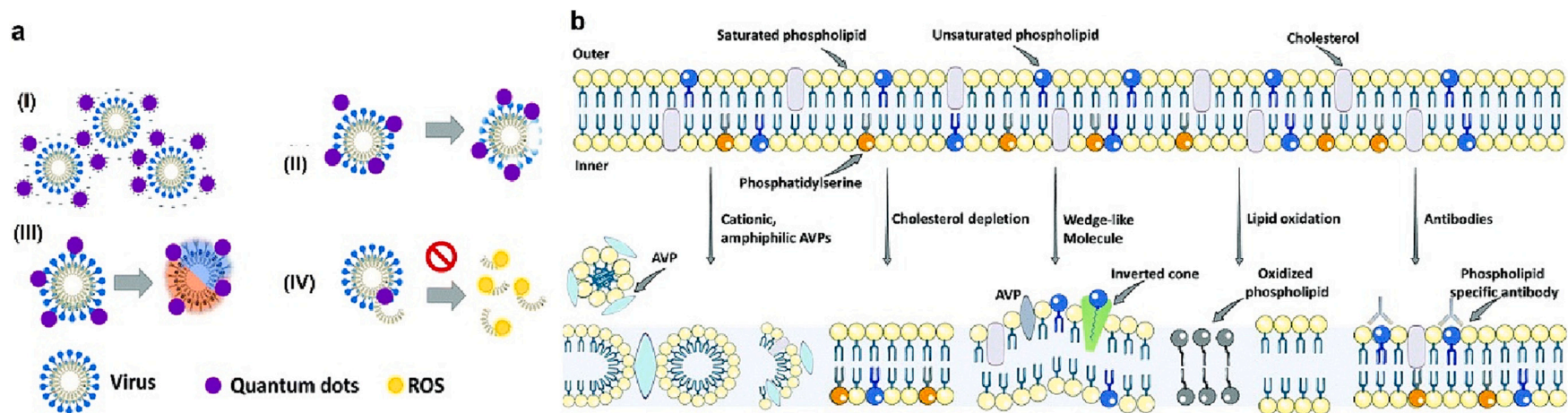


Fig. 11. a) The antiviral mechanism of action of NPs and quantum dots (QDs; NPs with a size ranging from 1 to 10 nm in diameter) against SARS-CoV-2: (I) electrostatic force induced aggregation of viruses, (II) local field effect alters the receptors and inhibits the entry of virus into a host cell, (III) physical (van der Waals) bonding between virus and QDs causes electrodynamic and thermal fluctuations that drive dispersion forces, (IV) ROS generation by QDs and NPs leads to activation of the production of interferon- α gene and inhibition of genome replication. b) The separation or fusion of lipid components from/to the lipid structure of viral membrane deteriorates the curvature of the membrane and reduces its fluidity, thereby inactivating the virus. As an example, cationic amphiphilic antiviral peptides (AVPs) show detergent-like characteristics, particularly at a high concentration and can form pores and lead to micellization of the viral membrane. To be more specific, polyunsaturated endoplasmic reticulum-targeting liposomes have been shown to properly act as broad-spectrum antiviral agents that deplete cholesterol of cellular and/or viral membranes, thereby decreasing membrane fluidity and reducing negative-curvature transitions that play a major role in fusion of virus with the cell membrane. The molecules with wedge-like and inverted-cone shape and several amphiphilic AVPs can promote the spontaneous positive curvature of the lipid bilayer of the viral membrane. As a result, they raise the energy barrier necessary to drive the membrane fusion governed by viral fusion proteins. In an analogous way, membrane-targeting type II photosensitizers release singlet oxygen radicals inside the viral membrane, leading to oxidation of unsaturated phospholipids and thus alteration of nanoarchitecture of the viral membrane that challenges the membrane fusion. The aggregation of oxidized phospholipids results in a decreased membrane thickness, raised area per lipid molecule, increased positive curvature, reduced fluidity, and differential lipid packing. Phospholipid-specific antibodies can attach to the specific phospholipid moieties that are abundantly available in some viral membranes (including phosphatidylserine) and thereby inhibit viral attachment and entry. Reproduced under terms of the CC-BY-NC license. [240] Copyright 2021, Royal Society of Chemistry.

AMP based virucidal nanocompounds in the future in a scalable, cost-effective manner. On the other hand, despite numerous merits of antiviral peptides/polysaccharides with respect to inhibition of viral activities, they are typically vulnerable to hostile intercellular microenvironment. To maintain optimum antiviral efficiency, such materials need to be either conjugated onto or encapsulated within nanocarriers.

Nanomaterials as a delivery means for antiviral peptides/polysaccharides preserve and even promote the therapeutic efficacy of these bioactive agents by addressing the likely physicochemical or biological challenges, such as poor solubility, instability, matrix interference, insufficient bioavailability, non-controlled release, unwanted side effects, and antiviral resistance. Nanomaterials offer a variety of physicochemical and biological merits including [257–259]: a) small particle size, thereby easing the delivery of antiviral peptides/polysaccharides through biological membranes, b) extensive specific surface area to assure high cargo contents, c) adjustable surface polarity (charge) to allow for cellular entry through the negatively charged cell membrane, d) biomimicry, leading to intrinsic antiviral properties, e) possibility of anchorage of targeting moieties, thereby raising specificity towards given cell or tissue types, f) optimized solubility and pharmacodynamic and/or pharmacokinetic properties leading to slower dissolution, thereby enabling larger accumulation, tailored and steady release, g) improved therapeutic efficiency via capturing an antiviral peptide/polysaccharide for the purpose of its protection against physiologically aggressive media, or via surface conjugation to deliver the compound to given tissues, h) lower toxicity, and i) multifunctionality, reflected in concurrent stimulation of the replication of latent virus and delivery of an antiviral peptide/polysaccharide to the activated cell [260]. Despite such advantages, there are several bottlenecks that might hinder wide applicability of nanomaterials as a delivery tool for antiviral peptides/polysaccharides. For instance, NPs are degraded within gut after being orally administered, or cannot pass through the mucus barrier and thus are poorly absorbed [261]. They can also interact with biomolecules, leading to opsonization, or can be taken up by macrophages [262], or even be absorbed non-specifically, causing apoptosis, cell membrane disruption, and unfavourable immunological consequences [263]. Moreover, their size could be too large for renal clearance and if not degraded in vivo, they will be accumulated and engender toxicity [264]. Ultimately, scalability of their production and high involved costs are challenging. As a result, sustainable, advanced, yet economical synthesis strategies are demanded to circumvent the mentioned challenges. It is crucial to develop the techniques that enable precise tuning of surface chemistry and dimensionality of nanocarriers. In this regard, novel characterizations are highly necessary to assure effectiveness of the developed nanosystems. Moreover, mathematical modelling is indeed an attractive means that can raise the success possibility of viral therapeutics. The model can reveal exciting facts about dynamics of viral infection spread and the factors relating to the treatment of viral diseases [265]. Considering that currently there is almost no particular medicine that can absolutely treat viral diseases, a mathematical, predictive model can assist in development of new therapeutic formulations and in engineering advanced therapies and can potentially anticipate the outcomes of the treatment approach. Additionally, this perspective can assure low cost strategies through minimizing experimental costs and likely wastes and/or addressing the drug resistance, etc. [266]. For instance, considering the characteristics of Ebola, cost and time optimization, and dynamic factors, Jiang et al. [267] succeeded to devise a mathematical model for the control of Ebola virus.

Stimuli-responsive nanocarriers, i.e., those that respond to physicochemical conditions of surrounding media and cells would be highly interesting. Additionally, a new generation of nanocarriers of antiviral agents including nanorobots, nanotraps, nanobubbles, nanodiamonds, and nanofibers is emerging. Such nanocarriers that are beyond the state of the art would hold great promise for antiviral treatments. Such nanosystems would broaden the relevant research vision and open up a

totally new field of research towards antiviral therapeutics. Among these advanced nanotechnologies, nanofibers, nanotraps, and nanodiamonds have already been applied in antiviral strategies against HIV-1 and influenza viruses and are expected to be employed for other viral diseases [5].

Future innovations would be aimed at development of multifunctional nanocarriers that can be site-specific, simultaneously deliver several drugs and multiplex to treat a wide range of diseases and comorbidities in a diverse population. The creation of theranostic nanotools that can assure precise diagnosis, proper treatment, and instantaneous monitoring will be another necessity to address viral challenges. There is a need also to other studies to further immune response and benefit from nanomaterial-based adjuvants to support antiviral vaccines for the purpose of inhibition and control of various viral infections.

CRedit authorship contribution statement

Shahin Homaeigohar: Conceptualization, Formal analysis, Investigation, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing. **Xuan Liu:** Investigation, Writing – original draft. **Mady Elbahri:** Formal analysis, Investigation, Validation.

Data availability

No data was used for the research described in the article.

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