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Human Respiratory Viral Infections: Current Status And Future Prospects Of Nanotechnology-Based Approaches For Prophylaxis And Treatment

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Title: HUMAN RESPIRATORY VIRAL INFECTIONS: CURRENT STATUS AND FUTURE PROSPECTS OF NANOTECHNOLOGY-BASED APPROACHES FOR PROPHYLAXIS AND TREATMENT

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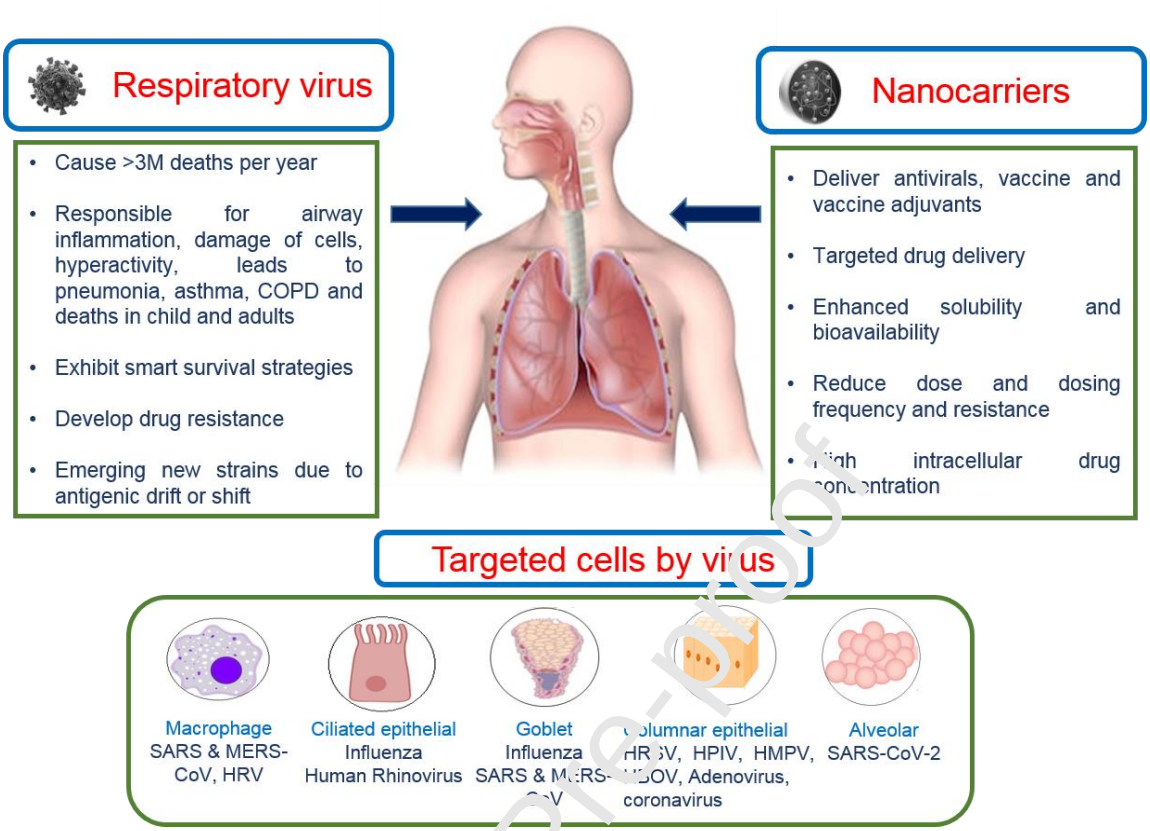
Abstract

Respiratory viral infections are major cause of highly mortal pandemics. They are impacting socioeconomic development and healthcare system globally. These emerging deadly respiratory viruses develop newer survival strategies to live inside host cells and tricking the immune system of host. Currently, medical facilities, therapies and research –development teams of every country kneel down before novel corona virus (SARS-CoV-2) which claimed ~2,828,629 lives till date. Thus, there is urgent requirement of novel treatment strategies to combat against these emerging respiratory viral infections. Nanocarriers comes under the umbrella of nanotechnology and offer numerous benefits compared to traditional dosage forms. Further, unique physicochemical properties (size, shape and surface charge) of nanocarriers provide additional advantage for targeted delivery. This review discusses in detail about the respiratory viruses, their transmission mode and cell invasion pathways, survival strategies, available therapies, and nanocarriers for the delivery of therapeutics. Further, the role of nanocarriers in the development of treatment therapy against SARS-CoV-2 is also overviewed.

Graphical Abstract



Key words: Respiratory viruses, escape mechanisms, invasion mechanisms, treatment therapies of respiratory viruses, nanocarriers, SARS CoV-2.

1. Introduction

Infectious diseases are caused by many pathogens as viruses, bacteria, parasite and fungi, reason for over 17M mortalities worldwide [1]. In current times, several outbreaks are caused by viruses (Fig. 1)[2]. Among them respiratory viral respiratory viruses, influenza, rhinovirus, human respiratory syncytial virus (HRSV), human parainfluenza virus (HPIV), human Metaneumovirus, respiratory adenovirus, human Bacovirus, Middle East respiratory syndrome virus (MERS), and Severe acute respiratory syndrome virus (SARS) accountable for 3M deaths and are the major cause of respiratory infections. Currently, novel coronavirus held responsible for terrible pandemic situation and claimed around 2.82 M deaths worldwide to date [3]. In last ten decades, respiratory viral infections pose major global health problems by affecting millions of people and creating acute socioeconomic crisis worldwide. Thus, it is need of time to review over such respiratory infections in detail, to frame a proper strategy for future drug discovery and development to deal with such situations.

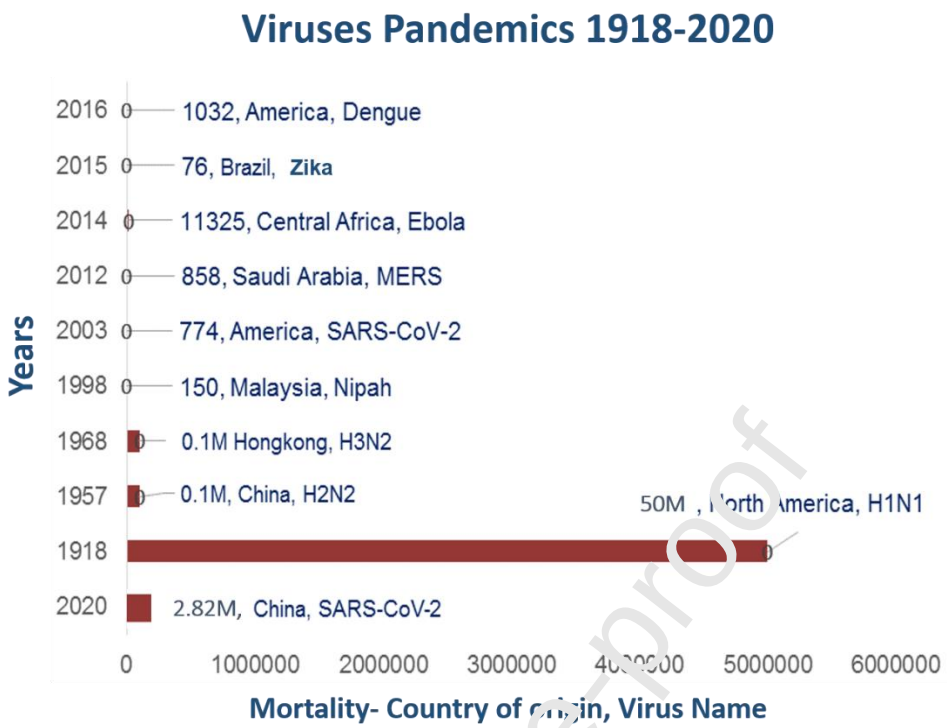


Fig. 1 Viruses associated Pandemics in last century [4]**,** [5], [6], [7], [8], [9], [10], [11]

The continuous emergence of newer respiratory virus species, diverse strategies to survive and multiply in host, emergence of resistance to anti-viral drug, and new-fangled respiratory viral infections cause challenges to the existing anti-viral therapy. For instance, novel corona virus and drug resistant species of influenza viruses proved that there is a need of new antiviral therapies [12]. Furthermore, most of the antiviral agents exhibit low solubility, less stability, high potential of drug-drug interaction, high frequency of adverse effects or toxicity lower concentration at the site of infection, short half-life, [13] and development of drug resistance. Therefore, there is an urgent need to develop more efficient novel drug delivery systems to treat respiratory viral infections.

The advent of novel drug delivery systems (NDDS) including nanomedicine have overcome most of the limitations of conventional dosage forms. As compared to traditional drug delivery systems, NDDS offers numerous advantages viz. high drug loading or encapsulation, delivery of insoluble drugs, targeted delivery, and tunable surface charge (enhanced entry inside cells). Furthermore, they possess biomimetic properties, resulting inherent antiviral property (dendrimers, carbon nanotubes and silver nanoparticles) [14]. Functionalization or modification

of nanoparticles is also possible by decorating with polyethylene glycol (PEG) to enhance the circulation time and to avoid uptake by reticuloendothelial system. The nanocarriers can easily be tailored by attaching ligands to site specific delivery resulting higher drug concentration at the site of action. Recently, novel drug delivery systems have gained considerable attention and many nano-formulations launched in the market successfully for treatment of few infectious diseases as well as cancers. Many nano-formulations are under clinical trials at various stages for delivery of antivirals compounds, biologics (ribonucleic acid, deoxyribonucleic acid), vaccine and vaccine adjuvants [15].

The current review will provide an overview on respiratory viruses, specifically, their mode of transmission & cell invasion mechanisms, survival strategies inside host cell, and novel drug delivery systems for treatment through antiviral agents. Furthermore, it outlines recent nano-technological advancements made to deliver therapeutics as well as vaccine development to prevent infection, specifically of SARS-CoV-2.

2. Viruses causing respiratory infections

2.1. Influenza virus

Influenza virus is member of the family of viruses *Orthomyxoviridae*. The four genera of influenza virus are influenza virus A, B, C, and D. The natural reservoir of influenza virus A (IAV) is a marine bird whereas influenza B virus (IBV) is mainly human pathogen. Influenza virus C and D exhibit property of zoonosis, however, responsible for minor respiratory infections. Influenza infection, commonly known as flu is a communicable viral infection mostly caused by influenza virus A and influenza B virus. It largely influences the upper respiratory tract (i.e., throat, nose, bronchi, and lungs) consequently affecting other organs such as the heart, brain, and muscles. The severe complications of influenza lead to pneumonia, myocarditis, and pericarditis.

The influenza virus is enveloped, pleomorphic, or spherical virion (80–120 nm in diameter) enclosing single-stranded RNA (ssRNA) and glycoproteins. The outer layer of the virus is covered with two important glycoproteins i.e. hemagglutinin (HA) and neuraminidase (NA) that encodes antigenicity. The hemagglutinin is responsible for host receptor binding and cell invasion while neuraminidase is accountable for breaking the hemagglutinin receptor complex and release of new particles. The pandemics of influenza are mostly caused due to transformations in the regions of the neuraminidase of influenza A virus and influenza B virus.

In 2009, a new species of H1N1 influenza A virus appeared probably from pigs. This was the reason of global contagion [16].

2.2. Human Rhinovirus

Human Rhinovirus (HRVs) is a member of the virus family *Picornaviridae*. The two strains of HRVs are A, B, and the new strain C was discovered. Mostly they cause respiratory infection in humans, and responsible for common cold [17]. Human rhinovirus are also associated with exacerbations of chronic obstructive pulmonary disease (COPD), chronic bronchitis, asthma, and infant respiratory infections and immunocompromised hosts. The virus are non-enveloped and icosahedral virion (~30nm in diameter) containing single-stranded RNA. It translates proteins 2A-C and 3A-D and capsid protein VP1. It is the major pathogen of acute respiratory infection globally. It has been a reason of approximately 50% respiratory infections in children in tropical area and 80% in grown person in United States [18].

2.3. Human respiratory syncytial virus

Human respiratory syncytial virus (HRSV) belongs to the family of virus *Paramyxoviridae* and the genus *Pneumovirus*. It is one of the commonest pathogens to cause infection in children globally and progressively more recognized as a vital pathogen in adults, particularly the old aged. It is responsible for upper respiratory infections, usually cause infection in children, a lower respiratory area infection with airway blockade, bronchiolitis, and can seldom lead to apnea, respiratory failure, pneumonia, and demise.

Human respiratory syncytial virus is enveloped, spherical or filamentous virion with diametric size 100–200 nm, consisting of a RNA. This RNA is attached with lipid bilayer containing the glycoproteins G (receptor binding) and F (membrane fusion). Besides, it consists of nonstructural proteins (NS1, NS2, and M2), a phosphoprotein (P) and a RNA-dependent RNA polymerase (L) [19]. The HRSV virus has two lineages (A and B) based on attachment glycoprotein G. It has been reported that HRSV is accountable for 33M respiratory infection cases, 3M hospitalizations, and reason of 199,000 infant mortalities [20].

2.4. Human Parainfluenza Virus

Human para influenza viruses (HPIVs) are a member *Paramyxoviridae* family. They are classified into four strains 1, 2, 3, and 4 based on antigenicity. Further, HPIV-4 has subspecies A and B and causes repeated lower respiratory tract infections in children and infants worldwide. They have enveloped, pleomorphic and spherical virion (300–500 nm diameters), enclosing a

single-stranded RNA genome in a helical nucleocapsid. This virus fuse with cell by interaction between sialic acid present on cell surface and glycoproteins neuraminidase, hemagglutinin esterase and hemagglutinin [21]. Further, the glycosylated receptor-binding protein (RBP) and the glycosylated fusion (F) protein is also present. The HPIV 1 is a common cause of laryngotracheobronchitis, mostly in infants (0.5 to 3 years). The symptoms are common cold following fever, cough, and hoarseness. Respiratory failure due to upper airway obstruction is not a usual but possibly a serious complication. However, the HPIV-2 can cause similar infections but complications are less severe and HPIV -3 may cause bronchiolitis and pneumonia in infants and immunocompromised host.

2.5. Human Metaneumovirus

Human Metaneumovirus (HMPV) belongs to the family of viruses *Paramyxoviridae* and genus *Metapneumovirus*. The HMPV is classified into two lineages, A and B, and each group consists of no less than two subspecies (A1, A2, B1, and B2) [22]. It is enveloped, filamentous particles or spherical, pleomorphic (~209nm diameter) with a single-stranded RNA genome. It is the common cause of community spread of respiratory infection in adults and youngsters. The HMPV is responsible for shortness of breath, nasal congestion, cough, and fever and clinically infection leads to pneumonia and bronchitis.

2.6. Respiratory Adenovirus

Respiratory Adenovirus belongs to the genus *Mastadenovirus*, family *Adenoviridae*. They are categorized into six groups (A, B, C, D, E, F, and G) with an additional 100 types identified to date. The indications of infection are of various type ranging from respiratory illness to diarrhea. Adenoviruses are non-enveloped, icosahedral virions (70 to 90 nm in diameter) containing double-stranded DNA (dsDNA). This icosahedral virion covered with fibers spread from each of the 12-penton base capsomers. These fibers have knobs which assist virus to attach on the host cells, cofactor proteins and monocyte chemoattractant protein (CD46 and MCP) and coxsackie and adenovirus receptor (CAR receptors) [23]. Mostly respiratory adenovirus utilizes only one type of receptors; however, subspecies D type of virus's usage both receptors concurrently. Adenoviruses most commonly cause cold that leads to croup, bronchitis, and pneumonia.

2.7. Human Bacovirus

Human Bacovirus (HBOV) belongs to the family *Parvoviridae*, genus *Bocavirus* and

subfamily *Parvovirinae*, The HBOV virions are non-enveloped and icosahedral particles (~25 nm diameter). The capsid includes a single-stranded DNA (ssDNA) genome and exhibit two capsid proteins (VP1 and VP2) with two nonstructural proteins (NP1 and NS1) [24]. The prevalence of HBOV was found globally and causes infections of the respiratory, intestinal epithelium, and lymphoid organs of children as well as adults in Asia, the Americas, Europe, Australia, and Africa [25].

2.8. Middle East respiratory syndrome and Severe acure respiratory virus coronavirus

Middle East respiratory syndrome (MERS) coronavirus and severe acute respiratory syndrome (SARS) coronavirus are members of the family of *Coronaviridae*. They are enveloped spherical virions in size range of 120–160 nm consisting of single-stranded RNA. Further, the presence of the long protrusions made of trimeric glycosylated spike protein that promotes fusion with membrane and receptor binding. All coronaviruses exhibit commonalities that is envelope (E) glycoproteins, the nucleocapsid and the membrane (M) protein. SARS-COV causes a global outbreak of 2003. The infection spread to more than two dozen countries in Asia, North America, Europe, and South America. The outbreak of MERS-COV occurred in Saudi Arabia, 2012, and in the Republic of Korea, 2015 [26].

2.9. Novel Coronavirus

Novel coronavirus (SARS-CoV-2) also belongs to the family *Coronaviridae*. The SARS-CoV-2 is enveloped, spherical or pleomorphic virion enclosing single-stranded RNA with spike glycoproteins on its surface. Coronaviruses have four subspecies such as alpha, beta, gamma, and delta coronavirus. It exhibits several proteins viz. spike protein (S), membrane protein (M), envelope protein (E), nucleocapsid protein (N). Further, polyproteins PP1a, PP1ab proteases and nonstructural proteins (NSP1-NSP16) also present. Coronavirus is zoonotic and found in cats, pigs, dogs, and birds [27]. First SARS-CoV-2 positive case was identified and virus was isolated from a pneumonia patient from Wuhan, China in November, 2019. The clinical symptoms of SARS-CoV-2 are diverse, and from asymptomatic to symptomatic state including acute respiratory distress syndrome and multi-organ failure. Currently, WHO reported ~129,619,536 confirmed cases of COVID-19 including 2,827,610 deaths [28].

The genome, family, subtypes, and structural features of respiratory viruses illustrated in Table 1.

Table 1: Respiratory viruses & their genome, family, and structural features

Genome	family	virus	subtypes	Envelope	Shape and size (nm)
Single stranded RNA	*Orthomyxoviridae*	Influenza	A, B, C and D	Enveloped	Spherical (80-120 nm)
	Picornaviridae	Human Rhinovirus	A, B and C with 100 stereotypes	Non-Enveloped	Icosahedral (~30)
	Paramyxoviridae	Human respiratory syncytial virus	Group A and B	Enveloped	Spherical or Filamentous (100-200)
		Human Parainfluenza Virus	1,2,3, and 4	Enveloped	Spherical. Pleomorphic (300-500 nm)
		Human Metaneumovirus	Group A and B	Enveloped	Spherical or Filamentous (209)
	Coronaviridae	SARS & MERS Coronavirus	1 type	Enveloped	Spherical (120-160)
		SARS-CoV-2	Types OC43, 229E,NL(NH), HKU1	Enveloped	Spherical (120-140)
Double stranded DNA	*Adenoviridae*	Respiratory Adenovirus	51 stereotypes	Non-enveloped	Icosahedral (70-90)
Single stranded DNA	*Parvoviridae*	Human Bocavirus	2 lineages	Non-enveloped	Icosahedral (25)

3. Transmission mode and cell invasion pathways of the respiratory virus

In general, respiratory viruses among humans transmit by three modes; indirect or direct interaction to diseased persons, via aerosols or droplets. Direct transmission takes place by straight contact from an infected person to a vulnerable individual (e.g. via contaminated hands) or indirect virus spreads through fomites. Respiratory viruses can also be transmitted through the air via aerosols and droplets. Droplets produced during sneezing, talking, or coughing do not linger in the air and move less than 1m before inhabiting the mucosa of close contacts or environmental surfaces. However, aerosols remain suspended in the air for a longer time and travel more due to slow settling velocity [29]. The accepted cut-off size amid the small aerosols

and large droplets is 5 mm, while this varies significantly up to 12 mm between studies [30]. Nevertheless, in the case of zoonotic viral infection e.g. SARS-CoV-2 and MERS-CoV, the ingestion of uncooked meat and milk or direct touch to carrier animals are additional doubted sources [31].

Viruses are the smart and obligatory parasites. The cell invasion of the virus involves five steps; attachment or binding to cell-surface receptors, signaling, endocytosis, penetration, and loading of their genome (RNA or DNA) in the host cytoplasm [32]. Subsequently, attachment with receptors that could be lipids, proteins, or carbohydrates; viruses can exploit two major pathways to make an entry inside the cell i.e. the endocytic and non-endocytic pathways (Fig. 2). In general, viruses utilize endocytic pathways for internalization is clathrin-coated pits; whereas macropinocytosis, caveolae/ raft dependent endocytosis, and novel/unusual endocytic pathways are also involved [33]. The non-endocytic pathway for cell invasion involves direct passage across the plasma membrane at neutral pH. A fundamental cellular process i.e. membrane fusion is vital for pinocytosis, phagocytosis, and vesicular trafficking [34]. Membrane fusion is essential for enveloped viruses because they use non-endocytic or endocytic pathways. When the membranes are close to each other, the entry scheme is mediated and regulated by membrane proteins. The structural or conformational modifications of host-cell receptors or these entry proteins play important role in avidity, tropism, and invasion of both non-enveloped and enveloped viruses into the cell. In case of enveloped viruses' entry takes place by fusion while non-enveloped viruses infiltrate. Some virus exploits novel pathways to enter inside the cell.

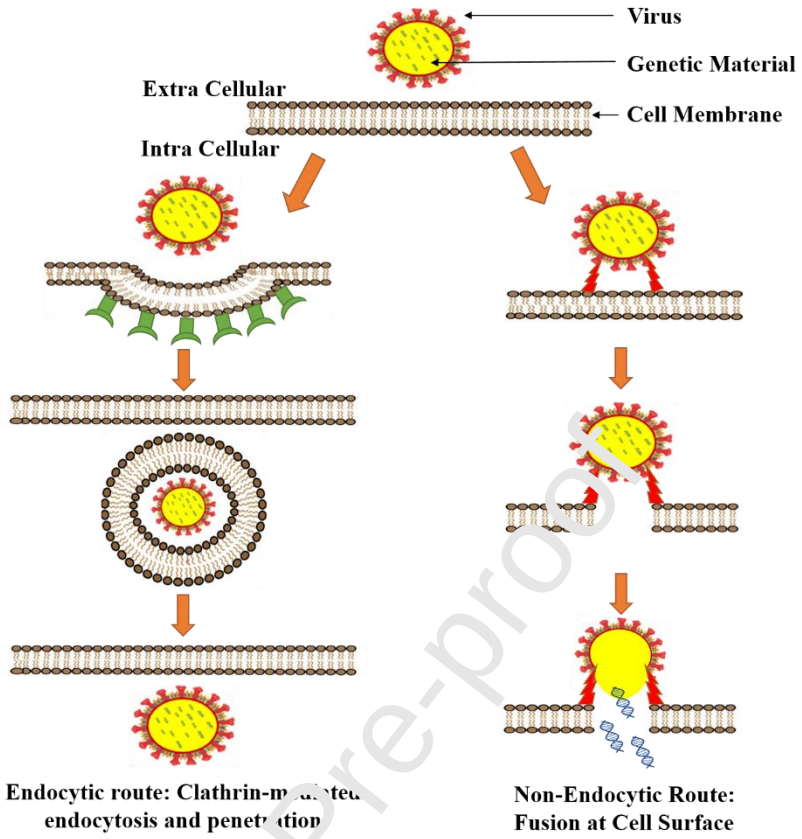


Fig. 2 Virus uptake pathways; Clathrin mediated endocytosis; Non-endocytic route.[35]

3.1. Endocytic pathways

3.1.1. Clathrin-mediated endocytosis

Clathrin mediated endocytosis (CME) is the preferred and most studied route for internalization by viruses and is the key process for vesicular trafficking. This endocytosis process creates minute (60-200 nm) membrane vesicles that internalize a variety of cargo molecules from the plasma membrane of cells into the cytoplasm. The size and shape of viruses play a predominant role in entry through Clathrin mediated endocytosis. The viruses which infect animals mostly in the size ranging from 30 nm (parvoviruses) to 400 nm (poxviruses), with the majority of respiratory viruses in the range of 60–200 nm [36]. Many viruses pretend as endocytic cargoes to get an entry inside the cell. Following the attachment to cells, viruses are not distorted; though the plasma membrane shows inversion to harbor virion. In many cases, such retraction of plasma membrane is imperative for endocytic uptake. The formation of Clathrin mediated endocytosis can also be triggered by a virus [33].

The mechanism of CME involves several sequential steps, which consist of: (1) the creation of a clathrin-coated pit (CCP); (2) cargo capturing and sorting; (3) initiation of membrane invagination; and (4) vesicle separation and unloading the cargo. The process of Clathrin mediated endocytosis includes several cellular factors and proteins such as clathrin light and heavy chain, actin, Rab molecules, AP2, epsin 15, actin, microtubules, phospho inositol phosphate, P2, cholesterol, cortactin, Arp2/3, GTPase dynamin, synaptojanin, auxilin, and HSC70, etc [33].

The important organelles occupied in Clathrin mediated endocytosis is lysosomes, recycling endosomes (REs), early endosomes (EEs) and late endosomes (LEs). In between EEs and LEs, there are transitional organelles, known as maturing endosomes (MEs) which are originators for LEs. They have the possibility to show an essential role in the internalization of many viruses. The movement of endosomes and vesicular trafficking takes place with microtubules. Further, the endosome is associated with the Golgi apparatus and plasma membrane for the trafficking or recycling of apoptotic or digested materials. During the Clathrin mediated endocytosis process internalized cargo is transferred to early endosomes within 2 to 5 min, then reach to LE after 10 to 15 min and finally processed by lysosomes in 30 to 60 min [37]. The first virus studied to incursion the cell through clathrin-coated pits was Semliki Forest Virus. Most respiratory viruses including Influenza virus, rhinovirus, HRSV, HPIV, HMNV, adenovirus, HBOV, SARS, MERS, and SARS-CoV -2 use CME for internalization and trafficking inside the host cell.

3.1.2. Caveolae/ raft dependent endocytosis

Caveolae are flask-shaped small (50-80 nm) invaginations of the plasma membrane. They are composed of small dimeric proteins caveolin and lipids (cholesterol and sphingolipids). The mechanism is to some extent analogous to Clathrin mediated endocytosis involving different sets of molecular factors. The various cellular factors involve in caveolae-mediated endocytosis are caveolin-1, dynamin-2, RhoA, cholesterol, tyrosine kinases, phosphatases, actin, microtubules, and Rab5. Previously scientist predicted that a new organelle, the caveosome was involved and act as a station for transition in intracellular trafficking, whereas Helenius and group revealed that this organelle exhibit commonality with late endosomes [33].

Several viruses that enter by this route exploit glycosphingolipid as their receptors. The known viruses that preferred caveolar/raft-dependent endocytosis belong to the family

polyomavirus [38]. The viruses from this family are SV40, mouse polyomavirus and two human infectious agents, JK and BC viruses. Among respiratory viruses, coronavirus (HCoV-229E and HCoV-OC43), influenza virus, and human respiratory syncytial virus exploit caveolae-mediated endocytosis and lipid rafts to commute across the cell and transfer virions into another cell [39].

3.2. Non-endocytic pathways

3.2.1. Macropinocytosis

The macropinocytosis is described as actin and growth factor induced transitory endocytic pathway that causes engulfment of a large amount of fluid with membrane into the vacuole. The process involves the development of macropinosomes when rearrangements of plasma membrane extensions occurred in outward-direction known as ruffles, while in other invasion pathways the membrane is invaginated and forms a bud or pit into the cell [34]. The ruffle structure can be circular ruffles, blebs (large plasma membrane extrusions), or lamellipodia (planar folds). The formation of macropinosomes is not directed by any cytoplasmic coat/proteins, thus resulting in irregular size ruffles in size range of 0.5–10 μm. The mechanism involves various cellular components such as tyrosine kinases, cholesterol, serine/threonine-protein kinase PAK1, myosins, Ras-related C3 botulinum toxin substrate 1 (Rac1), cell division control protein 42 (Cdc42), Na+/H+ exchange, Ras-related protein Rab-3 (Rab3), C-terminal-binding protein 1, phosphatidylinositol 3-kinase, protein kinase C, actin, microtubules, Ras-related protein 5 (Rab5), Ras-related protein Rab-7 (Rab7), and ADP-ribosylation factor 6 (Arf6) [40].

Numerous viruses from diverse families take advantage of this macropinocytosis route either for direct entry or through an indirect pathway to support the infiltration of virions that may take entry by another endocytic pathway. Among the viruses that use this entry, the mechanism is the vaccinia virus, HIV type 1, rubella virus, and echovirus type 1. Amid respiratory viruses, human respiratory syncytial virus, respiratory adenovirus, and influenza virus make use of macropinocytosis for the cell infiltration [34,41]. Besides, it was further observed that viruses use additional endocytic pathways to enter the cell but need macropinocytosis to support infiltration. The viruses which require macropinocytosis assistance for internalization are adenovirus 2/5 and SARS-CoV-2 [42], [43].

3.2.2. Phagocytosis

Phagocytosis (cell eating) is a mechanism of endocytosis different from

macropinocytosis. The phagocytosis is used by particular cell types, as monocytes, dendritic cells, and macrophages for the engulfment of big size foreign particles example bacteria. It exhibits properties similar to macropinocytosis, comprising regulatory components, big vacuole size, actin dependency, cellular factors, and transient activation [44]. However, the molecular process is dissimilar; since attachment of foreign particle at the plasma membrane not only activates the phagocytosis process but also triggers the covering of particles by vacuoles formed by actin. Factors normally involved incorporating RhoA, actin, dynamin-2, tyrosine kinases, and cholesterol, Cdc42, AP2, Arf6, and Rac1. Phagocytosis is not a commonly used pathway for virus internalization. However, few viruses like herpes simplex virus 1, amoebal pathogen mimivirus, influenza virus, and RSV have reported entry by using phagocytosis mechanism [45].

3.3. Novel/Unusual entry routes

Along with the well-studied endocytic pathways discussed above, there is an indication of contribution of alternate or unusual pathway for the internalization of viruses. Internalization by these routes is independent of dynamin, actin, lipid rafts, clathrin, and caveolin, but necessitates cholesterol. Thus far, the viruses reported that use unusual or novel routes are lymphocytic choriomeningitis virus [46], influenza A virus, human papillomavirus 16, and rotavirus. For instance, the influenza virus uses the novel entry routes corresponding with CME that provides supportive entry route; however, there is little information available.

Although understanding the unusual pathways of internalization is still not clear and incomplete. Cell biology literature still not describe how the viruses have been evolved to exploit novel endocytosis pathways. It will be very exciting to study these pathways and to recognize their functions and ligands. However, studies reported that there are mechanisms with which no virus entry has so far connected. These incorporate the flotillin pathway, the ADP-ribosylation factor 6 (Arf6) pathway, the glycosylphosphotidylinositol- anchored protein (GPI-AP) enriched compartments (GEEC) pathway, and the interleukin (IL-2) pathway [47]. The respiratory viruses' transmission mode, target cell, receptors of host cells, entry pathways, virus and host cell expressed proteins, pathogenesis, and symptoms are disclosed in Table 2.

Table 2: Transmission mode, entry mechanism, attached cells, expressed proteins, receptors, and symptoms

Respiratory Viruses	Transmission mode	Attached Cell	Cellular receptor	Entry pathway	Viral Expressed protein	Infected cells expressed proteins or cytokine	Pathogenesis	Symptoms	Reference
Influenza	Contact, droplet, aerosol	Ciliated epithelial and goblet cells,	Sialic acid	CME, caveolae mediated, Clathrin or caveolae independent, macropinocytosis, Phagocytosis	Polymerase basic protein 1 -2, Polymerase acidic protein, nucleoprotein, Hemagglutinin, neuraminidase, matrix protein 1-2 and nuclear export protein	Inflammatory proteins mediated by nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) activation,of Interleukin 1 beta (IL-1β), Interleukin-6 (IL-6), Interleukin – 8 (IL-8), Tumor necrosis factor alpha (TNFα), C-C Motif Chemokine Ligand 2 (CCL2), monocyt	Airway inflammation, alveolitis damage of epithelial cells, Hyperactivity	shortness of breath, asthma, COPD, acute respiratory distress syndrome (ARDS), and pneumonia	[48], [49], [50]

						e chemoattractant protein 1 (MCP-1), CD200, and PB1-F2, Macrophage inflamratory protein 1α (MIP-1α), C-C motif chemokine Ligand 5 (CCL5) (RANTES), and C-X-C motif chemokine ligand 10 (CXCL10)			
Human Rhinovirus	Contact, droplet, aerosol	ciliated cells	Intercellular Adhesion Molecule 1,sialic acid	CME	Viral protein 1 (VP1) capsid proteins	Interferon gamma and interferon alpha, RANTES, IP-10, IL-6, IL-8, and epithelial cell-derived neutroph	Airway inflammation, mucus hypersecretion, rhinosinusitis,	Acute respiratory infections, COPD, chest tightness, wheezing asthma and pneumonia	[18], [30], [51]

						ilactivating peptide 78			
Human respiratory syncytial virus	Contact droplet, aerosol	Respiratory epithelial cells, macrophages	Sialyl glycoproteins, glycolipids	CME, caveolae mediated endocytosis, micropinocytosis	Glycoprotein G, H and SH, NS1, NS2, M2-2,M2-1, phosphoprotein	RSV F protein and Toll like receptor 4 (TLR4), Increase p38 and heat shock protein-27 activation, decrease surfactant Proteins A and D increase the expression of matrix metalloproteinase-9	Fluid extravasation into the lung air spaces, inflammation ,hypersensitivity, alter shape of infected cells, increase virulence, epithelial cell death and decrease immune cell response	Acute respiratory infections, croup, COPD bronchiolitis bronchitis and pneumonia	[52]
Human Parainfluenza Virus	Contact, droplet,	Epithelial cells	Sialyl glycoproteins, glycolip	Fusion, CME	Glycoprotein HN. Hema	Proinflammatory (IL-1β, IL-6 and	airway inflammation and	acute respiratory infections	[53], [54], [21]

(HPIV)	aerosol		ids	gglutinin, Neuramidase	TNF-α) and tissue remodelling-related cytokines (platelet-derived growth factor and vascular endothelial growth factor (VEGF), Interferon gamma-induced protein 10	airway structural changes	, bronchiolitis, croup bronchitis, pneumonia	
Human Metapneumovirus	Contact, droplet	Epithelial cells	Sialyl glycoproteins, glycolipids	G, F and SH	Glycoprotein-gamma (IFN-γ), interleukin (IL)-2 and IL-4, IFN-γ against HBoV VP2 VLPs, IL-10 and IL-13 (Th2 cells) in CD4+ T cells	Allergic reactions, disrupt membrane architecture, inflammation	acute respiratory infections pneumonia and bronchitis	[55], [56]

Respiratory Adenovirus	Contact, droplet, aerosol	epithelial cells	chimeric antigen receptor (CAR), integrins	CME, macropinocytosis, penetration in EE	CAR, CD46	Adenoviral gene E1A, increased expression of Interferon gamma-induced protein 10 (IP-10) and T-cell alpha chemoattractant (I-TAC)	Inflammation, allergic reactions	Pharyngoconjunctival fever (PCF), bronchitis, pneumonia	[57], [58]
Human Bacovirus		Bronchial epithelial cells,	Sialylglycoproteins	CME	VP1, VP2 and VP3, nonstructural proteins1-4	Interferon-gamma (IFN-γ), interleukin (IL)-2 and IL-4, FN-γ against HBoV VP2 VLPs, IL-10 and IL-13 (Th2 cells) in CD4+ T cells	Mucus secretion, inflammation, allergic reaction	acute respiratory infections, bronchiolitis, bronchitis, asthma exacerbation, and pneumonia	[25], [59]
SARS & MERS Coronavirus	Contact, droplet, aerosol Contact,	Epithelial cells, mucosal cells and immu	Nucleocapsid Protein 63 (NL63), CD209L, CD26	CME, non-clathrin-mediated endocytosis	Protein S, M,E, N, and HE, polyproteins PP1a,	IL-1, IL-6, IL-8, IL-12, IFNγ, monocyte chemotactic	Lung injury, inflammation, allergy	acute respiratory infections, bronchitis, pneumoni	[60], [61]

	droplet	ne cells			PP1ab proteases, NSP1-NSP16	protein (MCP)-1 (or CC-motif ligand 2, CCL2), monokine induced by IFNγ, IFN-inducible protein (IP-10, or CXCL10), and transforming growth factor (TGF)β		a & ARDS	
SARS-CoV-2	Contact, droplet, aerosol	alveolar cells (AT2) of the lungs, upper esophagus and stratified epithelial cells	CD13, 229E, Angiotensin-converting enzyme (ACE2) receptors CD209L, Toll receptors, heat shock protein 90 (HSP90)/HSP 70, cell surface serine protease Transme	CME, caveolae mediated, non-clathrin mediated endocytosis, fusion pathway	Spike (S), Nucleocapsid (Nc), Envelope (E), SARS polymerase (RdRp), SARS protease (3CL), and membrane (M)	IL1-β, IL1RA, IL-6 IL7, IL8, IL9, IL10, basic fibroblast growth factors 2 (FGF2), Granulocyte colony-stimulating factor (GCSF), Granulocyte-macrophage colony-stimulating factor	Inflammation, alveolar damage, mucus plugs, damage lung parenchyma, septic shock and multi-organ dysfunction	Chronic obstructive pulmonary disease (COPD), ARDS, Shortness of breath or difficulty breathing, Chest pain, runny nose	[62], [63], [64]

	mbrane protease serine 2 (TMPRSS2), ER chaperonin GRP78 TIM/TAM macrophages	(GMCSF), IFNγ, IP10, monocyte chemoattractant protein-1 (MCP1), Macrophage Inflammatory Protein 1α, MIP and 1β, PDGFB, TNFα, Vascular Endothelial Growth Factor A VEGFA

4. Virus survival strategies inside the host cell

The viruses are opportunistic pathogens; they can evolve several strategies to escape two barriers of a host that is the endosomal barrier and immune barrier [65]. They exhibit the inherent ability to adopt strategies under stress conditions to combat for their survival. These adaptive strategies facilitate them to impart superior protection against the host immune system and there by prolonging survival. Both enveloped and non-enveloped viruses develop several survival tactics; membrane fusion and pore formation are predominant [66], [67]. In the following subsections, several strategies developed by respiratory viruses to survive and escape endosomal uptake or immune system are illustrated. The survival strategies, molecules involved in the process, and antiviral agents for treatment therapy act on specific survival pathway are enlisted in Table 3.

4.1. Fusion with endosomal membrane

The viruses evolved with fusion peptides, which attach to the endosomal membrane

causes their destabilization. The fusogenic peptides constitute of short peptide domain of 20–30 amino acids [67]. Membrane fusion is a crucial process in cellular endocytosis and trafficking. The majority of enveloped viruses exhibit single fundamental membrane peptides, which undergo conformational changes upon a trigger such as a change in pH. At acidic pH, fusogenic peptide undergoes structural changes from a hydrophilic coil to a hydrophobic helical [50]. This new-fangled α-helical conformation guides to the fusion of the viral membrane into the cellular membrane, resulting in disruption of the membrane and trafficking its genome into the cytoplasm. For example, Haemagglutinin is a peptide of the influenza virus coat, exhibits fusogenic activity [63].

4.2. ***Pore formation***

The other approach use by viruses to escape the endosomal barrier is pore formation. The formation of a pore is by the interrelationship between a line tension that seals the pore and membrane tension that broadens the pore. Some virus peptides have a high affinity for the edge of the pore. Attaching the peptide to the rim reduces the line tension resulting in instability in the pore radius and does not permit to seal it again. In an acidic environment, the protonation of the amino acid group of fusogenic peptide brings conformational changes [66]. As a result, the peptides adhere and self-assemble inside the phospholipid membrane in upright orientation to the plane of the membrane, hence creating pores. The 'Barrel-stave' model demonstrated the attachment of peptides with the membranes of endosomes and slowly their diffusion into the phospholipid layer. The respiratory viruses which use this strategy to invade the cells are human rhinoviruses [68]. Other viruses that use this mechanism are the vp1-Coxsackie virus and poliovirus [67].

4.3. Enzymatic modifications

Viruses have developed a tactic to transform the membrane of endosomes by the enzymatic actions of either virus or host-encoded enzymes to ease escape. The influenza A virus exhibit neuraminidase protein, which directly attaches to the lysosome-associated membrane proteins (LAMPs), resulting in the glycosylation of LAMPs, interruption lysosome integrity, and ultimately cause cell death [69]. The SARS-CoV-2 virus also uses enzymes of the host as a receptor for internalization; example angiotensin-converting enzyme 2 (ACE2) and aminopeptidase N (APN). The ACE-2 is a mono-carboxypeptidase, which hydrolyses angiotensin II, in large quantities present on the lung surface. The substitution of an amino acid

sequence of residues between 505 and 323 with a chain of SARS-CoV receptor-binding domain allocates human ACE2 receptor utilization [69]. Several coronavirus species like CCoV, FCoV, and HCoV-229E all make use of the protein aminopeptidase N of the host as a receptor [70].

4.4. Proteolytic cleavage induced by endosomal enzymes

Moreover, some respiratory viruses adopt other strategies to enter the host cell. A low acidic pH is not enough to make an entry inside the cell membrane. However, the endosomal proteases trigger the fusion of the virus with the membrane is also essential [71]. For instance, coronavirus relies on proteases (cathepsin B and L) to invade the cell. Studies also reported that other proteases elastase, trypsin, and thermolysin enhance productive entry in vitro. The exogenous proteases transmembrane protease serine 2 (TMPRSS2), transmembrane Serine Protease 11A (TMPRSS11a), and histone acetyltransferases (HAT) also trigger the fusion of SARS-CoV-2 to the cell membrane. The study also illustrated that MERS- COV tropism increased by proteolytic processing and resulting in an increase in the trafficking of the virus across the cell membrane. In the case of influenza A virus proteolytic cleavage by proteases (TMPRSS2 & HAT) activates the fusion glycoprotein HA and triggers membrane fusion [72].

4.5. Antigenic drift and shift

To escape from recognition by host immune system virus develop another strategy that is by continuous mutation of surface glycoprotein known as antigenic drift or by creation of new subtypes of these glycoprotein termed as antigenic shift [72]. For instance, influenza A virus evolved with antigenic glycoproteins hemagglutinin (HA) and neuraminidase (NA) (antigenic drift) whereas evolution of novel subtypes of hemagglutinin is also reported (antigenic shift). Moreover, the newly emerged SARS-CoV-2 also displayed modified spike proteins on its surface and notable deviation in receptor binding domain of S-glycoprotein. Both antigenic shift and drift are major cause of epidemic outbreaks and also is the biggest hurdle in vaccination development against these viruses [73].

Table 3: Survival strategies, molecules involved, and antiviral agents acting on specific strategy of respiratory viruses

Survival strategy	Respiratory Viruses	Molecules involved	Antiviral agents	References
Fusion in the endosomal	Influenza A virus	HA	Lj001, Arbidol	[67], [74]

membrane				
Pore formation	Rhinovirus	Capsid protein VP4, ICAM-1	Pleconaril, Vapendavir	[75], [76]
Enzymatic modifications	Influenza, SARS-CoV-2	Neuraminidase, ACE-2, APN	Neuraminidase inhibitors , N-(2-aminoethyl)-1aziridine ethanamine (NAAE)	[69], [77]
Proteolytic cleavage induced by endosomal enzymes	Influenza, SARS-CoV-2, SARS-Cov & MERS-Cov	Cathepsin B and L, elastase, trypsin, and thermolysin, TMPRSS2, TMPRSS11a, and HAT	-	[78]
Antigenic drift and shift	Influenza, SARS-CoV-2, HPIV	HA & NA, spike glycoprotein	NAAE	[73], [79]

5. Treatment therapies for respiratory viral infections

These emerging and reemerging respiratory viruses pose the biggest challenge in the development of treatment therapies due to these survival strategies and continuous antigenic shift or antigenic drift. The plethora of antivirals developed and discovered as a treatment therapy for respiratory virus infections. Several antiviral agents are going through clinical trials in the pipeline. However, enormous bulk is still not approved for clinical use. These developed or developing antiviral agents act by several mechanisms viz. attacking on target proteins, act as ligand analogues, and disturb viral replication cycle. The significant events of viral infection are fusion, attachment, internalization, replication, virion release, and pinching off/budding. The antiviral agents directly act on the virus or intracellular trails for viral replication (Fig. 3). This section illustrated a few antiviral therapies with their potential target stage of the virus replication mechanism.

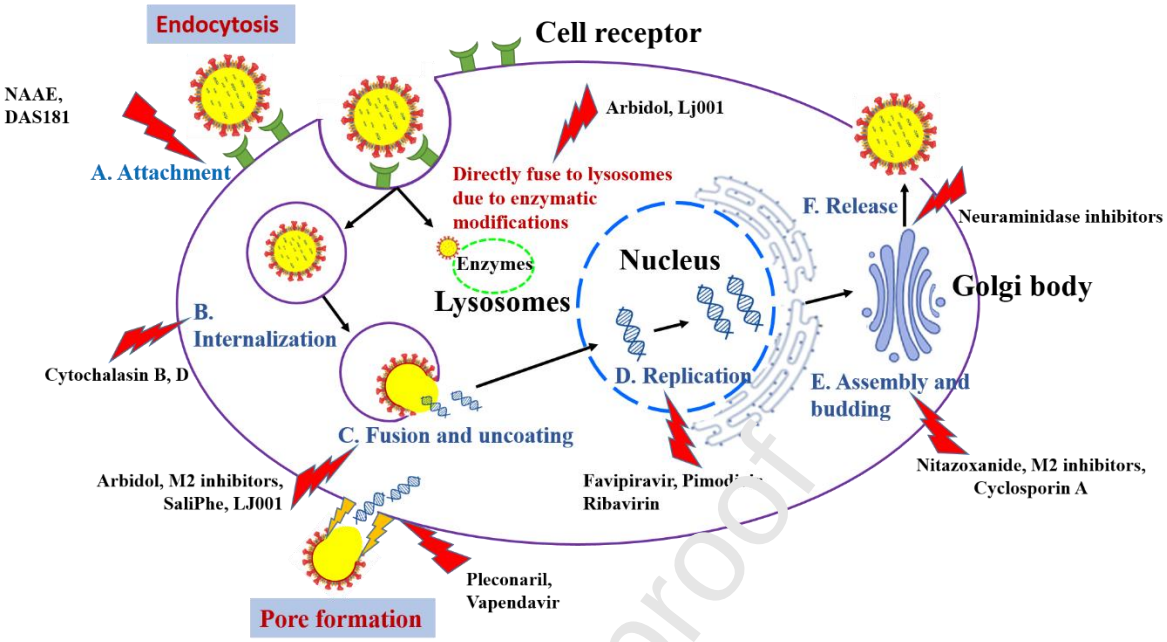


Fig. 3 Virus replication cycle and target sites of antiviral drugs [74]

5.1. Inhibitors of virion formation, release, and assembly

Several antiviral agents restrain the budding event and release of virion of many respiratory viruses. For instance, for the treatment of influenza A virus inhibitors developed are M2 inhibitors and neuraminidase inhibitors (NAIs). The M2 inhibitors hinder the budding event of the influenza A virus and it is a matrix protein that mediates ion channel responsible for uncoating, acidification of vacuoles, and assembly of the virus [74]. Further, the M2 proteins modify the membrane bending at the neckline of the budding virus to brace the pinching off from the membrane and begin the release of the new virion [80]. The M2 inhibitors approved for the treatment of influenza are rimantadine and amantadine. Cyclosporin A also inhibits the proliferation of the influenza virus by impeding the budding or assembly of the virus [81].

Another treatment therapy for influenza is NAIs, which block the active site of neuraminidase; consequences are residues of non-cleaved sialic acid present on virus envelope and the host cell. This uncleaved sialic acid attaches to the HA resulting in its aggregation on the host cell membrane and decrease the quantity of virion release. These drugs are approved for human use is peramivir, laninamivir, oseltamivir, and zanamivir [82]. Oseltamivir can be administered orally, whereas zanamivir is a dry powder administered by oral inhalers. However, peramivir approved by FDA as NAIs in 2014 and the only drug administered by I.V. route.

Laninamivir is recently approved, long-circulating NAI, and given by dry powder inhaler. The emergence of influenza strains resistant to these NAIs can be a significant confront to antiviral treatment in the future [83]. The assembly of viral protein inhibited by verdinexor, nitazoxanide, and leptomycin B. Verdinexor is a new antiviral agent selectively inhibits virus ribonucleoprotein (vRNPs) transporation by binding with Crm-1 homolog exportin-1. The studies suggest that verdinexor exhibit high efficacy and decrease the replication of many strains of influenza. Nitazoxanide is an antiparasitic drug and repurposes for the treatment of infections caused by the influenza virus. It acts by inhibiting transport of HA from the endoplasmic reticulum to the Golgi complex resulting in restrain the entry of viruses inside the cell. Furthermore, nitazoxanide is a broad-spectrum antiviral and in vitro found active against both DNA and RNA viruses [84]. Leptomycin-B is a potent inhibitor of Crm1- dependent export, which regulates the event of trafficking of vRNPs to the cytoplasm and their assembly resulting in inhibition of virion replication [85].

5.2. Inhibitor of virus genome replication

The replication of viruses depends on the enzyme RNA polymerase. The specific inhibition of this enzyme DNA-dependent RNA-polymerase enzyme controls the viral replication and does not impact protein translation or mRNA synthesis of the host cells**.** One of the antiviral agents that specifically inhibit DNA-dependent RNA-polymerase is favipiravir (T-705), approved in Japan for the treatment of influenza strains resistant to M2 inhibitors and NAIs. Favipiravir is a broad-spectrum antiviral drug currently repurposed and approved for the treatment of Covid-19 [86]. Pimodivir is also an inhibitor of non-nucleoside polymerase and in the phase-III stage of a clinical trial against the influenza virus. Another molecule ALS-008176 and PC 876 is in the phase-II clinical trials that inhibits polymerase enzyme of human respiratory syncytial virus [82].

Ribavirin is a potential inhibitor of inosine 5’-monophosphate dehydrogenase. This enzyme plays an essential role in the synthesis of viral RNA and the biosynthesis of guanosine-5'-triphosphate. The previous studies proved that aerosolized ribavirin shows good inhibitory activity against influenza virus and RSV as compared to orally administered drugs. However, the utility of ribavirin is holding back due to the toxicity of the drug [87].

A few novel drugs, which are in the pipeline specifically, inhibit viral capsid protein resulting in inhibition of virus replication. Pleconaril is an anti-human rhinovirus drug

exclusively binds to the viral capsid [88]. Vapendavir is another oral antiviral agent that attaches to the HRV VP1 capsid protein and stops the release of the genome of the virus into the host cell. Rupintrivir is another molecule, which is a protease inhibitor and exhibit in vitro efficacy against HRVs.

5.3. Inhibitors of virus internalization/ endocytosis

The inhibition of viral internalization shows potential approach to form new antiviral. The endocytosis event of respiratory viruses involves several steps: fusion, internalization, and unloading. The inhibition of endocytosis can be achieved by one of the mechanism; 1. Diminish membrane fluidity and curvature; 2. Obstruct the routes that assist viral internalization; 3. Hinder viral uncoating; 4. Control the decrease of endosomal pH; 5. Hamper the conformational changes of fusion proteins. Several antiviral agents develop for these functions. For example, Lj001 is a lipophilic broad-spectrum antiviral drug that inhibits the membrane fluidity and curvature by O_2 triggered lipid oxidation. Arbidol is also a broad-spectrum antiviral agent; it exhibits anti-fusion activity by affecting the stability of the HA of the influenza virus at low pH [89].

For many enveloped respiratory viruses, the low pH triggers fusion between virus membrane and endosomes. Further, promote dissociation of viral ribonucleoprotein complexes (vRNPs) from the capsid. The transportation of these vRNPs to the nucleus initiates the viral replication. Hence, the suppression of endosomal acidification can also hamper the virus replication. The drugs which suppress the endosomal acidification are archazolid B, saliphenyihalamide, bafilomycin A1, and concanamycin A [90]. The pathways for influenza internalization are both dynamin-independent and dynamin-dependent. Blockers of these pathways which exclusively inhibit the entry of the influenza virus are jasplakinolide, cytochalasin B and D, and latruncul A [91].

5.4. Inhibitor of viral fusion and attachment

The viral fusion and attachment method is an essential step for the invasion of the virus inside the cell. Fusogenic peptides, specific viral proteins, and surface receptors support the mechanism of fusion and attachment. The blocking of the interactions of all these proteins and receptors with the cell membrane stops the viruses' entry into the cell and can be a hopeful scheme to develop new antivirals [92]. Several drugs have been studied for this purpose and are under clinical investigation. For instance, fludase (DAS181) is a modified fusion protein that breaks the sialic acid receptor present on the respiratory epithelium hence, averting the

infiltration of the virus into the airway epithelium. In preclinical studies, fludase revealed activity against respiratory viruses, influenza strains, and parainfluenza virus.

The entry of HRSV into the cell inhibited by targeting F protein. Antivirals studied that precisely inhibits F-protein are JNJ-53718678, AK-0529, GS-5806, RV521, and BTA-C585 [93]. They are all in phase II of clinical trials. The small molecule N-(2-aminoethyl)-1aziridine ethanamine (NAAE) reduces the contact between spike proteins of SARS-CoV and their surface receptor, angiotensin-converting enzyme 2.

In addition to that, various monoclonal antibodies also developed and studied for the inhibition of viral attachment to cells. Palivizumab and motavizumab have been protecting participants from infection caused by HRSV. However, the incoherent clinical data and the sky-scraping price of these biologics can also be difficult for the treatment of these infections.

5.5. Inhibitors of Signal-Transduction

An additional potential approach to reduce viral replication is by focusing on the intracellular pathways instead of directly aiming at viral proteins. Several signaling pathways Protein Kinase C (PKC) or phosphatidylinositol 3-kinase (PI3K)/ protein kinase B (Akt), Rapidly Accelerated Fibrosarcoma (Raf)/ mitogen-activated protein kinase MEK/ extracellular-signal-regulated kinase (ERK), and NF-κB may be a prospective target to develop antiviral therapies.

6. Nanocarriers for delivery of antiviral agents

The antiviral treatment therapy discussed in the above section exhibit several challenges like targeting specifically to the virus life cycle, the short half-life of drugs, less solubility or permeability, and low bioavailability, and drug-related toxicity or adverse drug reactions [94]. The main confront is the emergence of drug resistance viral species. Currently, due to all these challenges, the world is facing a pandemic situation caused by a novel coronavirus and claimed numerous lives. Nanomedicine becomes apparent as one of the most promising technologies because of its ability to combat against these viral infections efficiently, tackling the limits of conventional therapies [94]. Various nanoformulations for antiviral drugs, including solid lipid nanoparticles, polymeric nanoparticles, liposomes, dendrimers, micelles, self-assembled nanoemulsions, and cyclodextrins have been studied (Fig. 4)[95]. Nanoformulations have been explored for delivery of antiviral agents for various viral infections, however few studies reported against respiratory viral infections. This section systematically presented nanocarriers studied so far for delivery of antiviral therapy for respiratory infection. Table 4 showed

nanocarriers developed for the delivery of antiviral compounds, or as a vaccine adjuvant against respiratory viral infections.

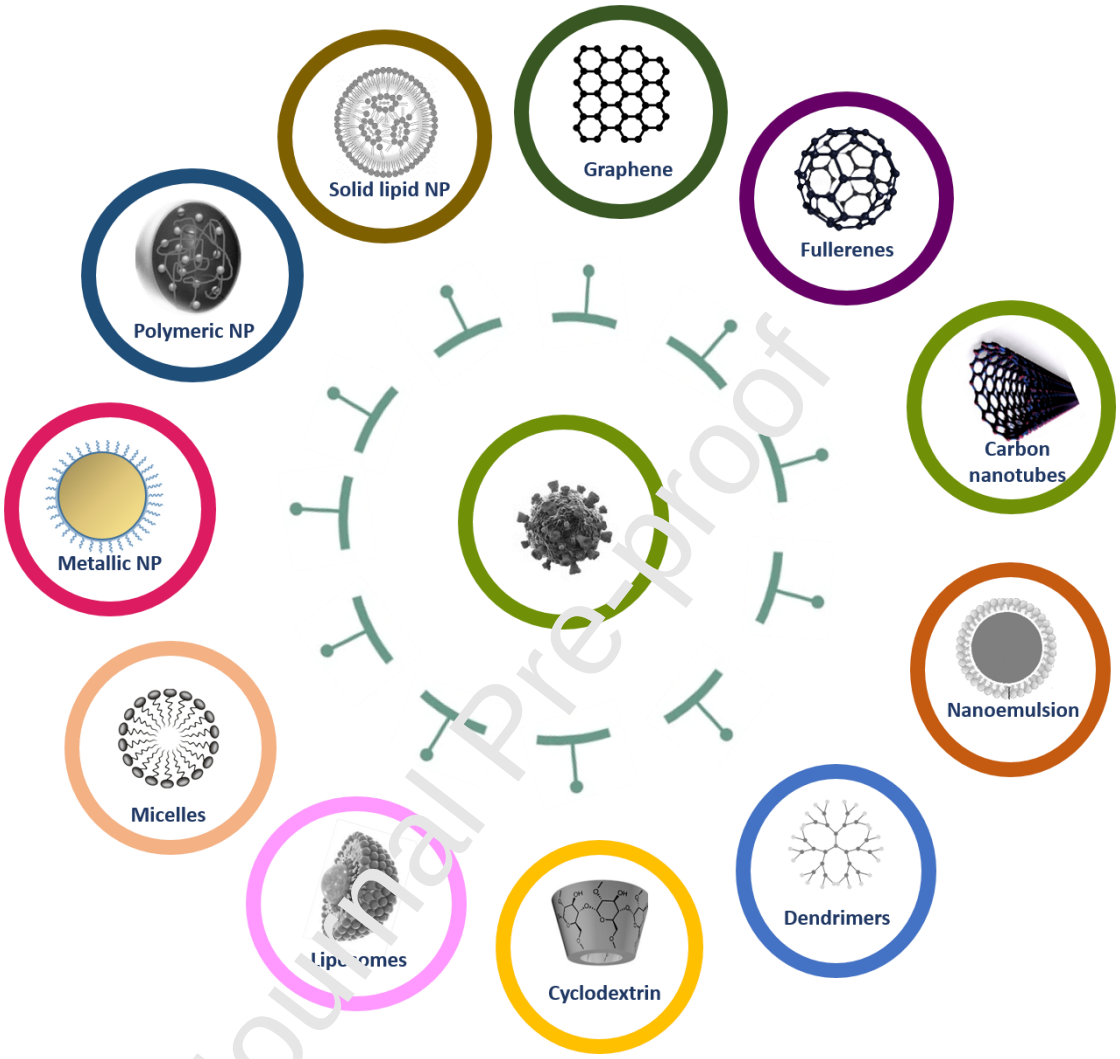


Fig. 4 Nanocarriers for targeting respiratory viruses [96], [97], [98], [99], [100], [101], [102]

6.1. Nanoparticles

Nanoparticles (NPs) are colloidal particles that exhibit size <1 micron in diameter and can be generated by using inorganic materials, lipids, proteins, and polymers. It can be fabricated in two types i.e. matrix-like and capsule-like known as nanospheres and nanocapsules, respectively. In matrix type, the drug is uniformly dispersed or physically attaches within the nanospheres of size range 100-200 nm whereas in nanocapsules, active agents are encapsulated in the inner cavity, surrounded by the polymeric membrane. They are classified into following types based on the materials used for preparation.

Inorganic nanoparticles are smaller as compared to organic nanoparticles in the size range of 1 nm to 100 nm; however, they exhibit high loading efficiency. There are two strategies for the manufacturing of metal oxide or metallic nanoparticles i.e. top-down approach and bottom-down approach. Metallic nanoparticles exhibit inherent antiviral activity and explored widely for this purpose [103]. Amongst them silver and gold nanoparticles showed high efficacy, and among metallic oxides Titanium dioxide (Tio2), copper oxide (CuO), Zinc oxide (ZnO) and silicon dioxide (SiO_2) revealed greater efficacy. These nanoparticles have been found efficacious against broad spectrum of viruses including respiratory infection causing viruses. Metallic nanoparticles due to their exclusive size, shape, configuration, and local-field improvement action can attach with the viral proteins via Van der Waals forces responsible for their inactivation. A small number of researchers have furthermore investigated grafting as functionalized metal nanoparticles for the purpose to augment their selectivity and efficacy.

The selenium nanoparticles (SeNps) due to their intrinsic antiviral activity are gaining attention for development of therapies for the treatment of viral infections [104]. The arbidol decorated selenium nanoparticles were developed against influenza virus infection. This drug loaded selenium nanoparticles interact with of hemagglutinin and neuraminidase of influenza virus and suppress their activity. The developed nanoparticles illustrated promising antiviral therapy against H1N1 influenza virus [105]. In another reported studies SeNPs decorated with other antiviral agents like oseltamivir, ribavirin, zanamivir, amantadine, and arbidol were studied against H1N1 infection and revealed less toxicity in association with good activity [105], [106], [107].

Silver nanoparticles (AgNPs) loaded with oseltamivir revealed remarkable inhibition against H1N1 infection and less toxicity [108]. Similar group developed zanamivir loaded AgNPs against H1N1 influenza virus infection. Curcumin loaded AgNPs were studied and found efficacious against respiratory syncytial virus infection [109]. PEGylated zinc oxide nanoparticles were studied and indicated against H1N1 influenza virus infection [110].

Polymeric nanoparticles are colloidal particles, in general less than 500 nm in size, and are fabricated by using biodegradable and biocompatible polymers may be natural or synthetic origin. The antiviral drugs are adsorbed, entrapped or covalently adhered. The polymeric nanoparticles are prepared by several reported techniques and based on properties of drugs, size and shape of nanoparticles required these methods were used [111]. Polymeric NPs can be easily

surface modified and decorated with the ligands to enhance uptake by the receptor mediated endocytosis that resulted in high drug concentration to targeting cells. The polymeric nanoparticles have been extensively investigated for the delivery and enhancement of anti-HIV drugs for targeting to specific cells or organs. However, few studies reported for delivery of therapeutic molecules against respiratory viral infections [112].

Solid lipid nanoparticles (SLNs) are another category of nanoparticles; they are distinct from polymeric nanoparticles as they are made up of lipids that are solid at body temperature. The solid lipids which can be used for construction of SLNs are fatty acids, triglycerides, waxes, and steroids. They exhibit size ranging from 10-1000nm and more stable than polymeric nanoparticles as well as scalable. The other advantages of SLNs are sustained release, decreased in P-gp efflux, less cytochrome P 450 metabolism, enhanced permeability & bioavailability, superior tissue distribution and high lymphatic system uptake and reduced first-pass metabolism. Solid lipid nanoparticles have been exploited for various antiviral agents. The zanamivir loaded SLNs were investigated against influenza viral infection [113]. Another group also reported SLNs of zanamivir which revealed good entrapment efficiency [114].

6.2.Carbon-based nanocarriers

Carbon-based nanocarriers present graphene, fullerenes, and carbon nanotubes for the delivery of antiviral drugs.

Graphene is the most versatile and promising carbon-based nanocarriers investigated as antiviral therapy. Chemically it is made up of 3-D material graphite and a two-dimensional solo atomic layer of sp2-hybridized carbon atoms that arrange in a honeycomb lattice. Graphene demonstrates amazing physicochemical properties like superior biocompatibility, high drug incorporation ability, and high surface area, flexible surface modification, and greater mechanical strength. These properties make graphene a striking molecule for loading antiviral agent. In drug delivery systems, graphene has been utilized in two forms first functionalized graphene (GO), and second, the graphene quantum dots (GQDs) to transfer antivirals to virally infected cells. The GO exhibit oxygen carrying functional groups therefore, an excellent candidate for surface modification, reduction of toxicity, enhancement of dispersibility, and biocompatibility. The graphene oxide is an amphiphile that makes it feasible to entrap both hydrophobic and hydrophilic molecules. Furthermore, these functional groups offer attachment positions for the several biomolecules enzymes, DNA or RNA, and proteins [115].

Yang et al. reported β-cyclodextrin (CD) conjugated graphene oxide (GO) nanostructure loaded with curcumin. These nanostructures revealed excellent antiviral activity against respiratory syncytial virus infection [116]. Further, copper-graphene nanocomposite was developed and showed antiviral activity against the influenza virus. This copper-graphene nanocomposite inactivates the virion particles only within 30 minutes of pre-incubation. Hence, interfere with the entry of these virion particles into the host cell [117]. Graphene silver nanoparticles nanocomposites were developed and assessed against non-enveloped viruses, feline coronavirus (FCoV), and infectious bursal disease virus. The results showed that this nanocomposite inhibits 25% of infection by coronavirus [118].

Fullerenes are one of the allotropes of carbon nanostructures and also known as a buckyball. They are first invented highly symmetric carbon-based nanostructures and gained attention for the delivery of antiviral molecules [119]. Fullerenes are consisting of carbon atoms figuring a spherical hollow cage of nanosize. They have distinct physicochemical features like less toxicity, free radical scavenging, and the enormous capacity of derivatization due to their unique structure. It has been extensively utilized for the delivery of drugs as well as their inherent antimicrobial and antiviral activity.

Some studies intended to screen these fullerene derivatives against respiratory viral infections. Fullerene derivate tested in vitro for inhibition of acid polymerase (PA) endonuclease. The PA stands for the subunit of influenza A RNA polymerase that shows endonuclease action. The study revealed eight fullerene derivatives that illustrated endonuclease inhibition action. These fullerene derivatives showed good potential against influenza A virus infection and in the Madin-Darby Canine Kidney cell culture [120]. Du et al. developed fullerene-liposome and studied its antiviral activity on influenza virus infection in a mouse model. The results demonstrated that fullerene-liposome decrease the lung index, reduce mean pulmonary virus loads, and decrease mortality of H1N1 virus-infected mice. The study confirmed that fullerene-liposome has the anti-influenza activity in vivo at much lower concentrations in comparison to the rimantadine [121].

Fullerene-(tris-aminocaproic acid) hydrate was designed, and their activity against the respiratory syncytial virus was studied [122]. Fullerene modified with thiosialosyl-a (2,6)-galactose disaccharide was synthesized and investigated for interaction with influenza viral proteins HA and NA. Results of this study, revealed that these fullerene derivatives target NA to

some extent, but did not aim HA [123].

Carbon nanotubes (CNTs) are cylindrical hollow tubes in the nanometers range, constructed by allotropes of carbon, prepared of graphite. They classified into two type's single-walled carbon nanotubes (SWCNTs) and multi-walled carbon nanotubes (MWCNTs) based on the number of layers. Single-walled carbon nanotubes are a single hexagonal close-packed graphene cylinder with a size ranging from 0.4 and 2 nm. However, MWCNTs are consisting of numerous coaxial cylinders, all prepared of a single graphene sheet surrounded by a hollow center. The external diameter of MWCNTs is 100 nm, though the internal diameter ranges from 1–3 nm, and their length is 0.2 to several microns [124]. The carbon nanotubes contain unique features like remarkable structure, ultralight weight, cell penetration capacity, high electronic thermal and electrical conductivity, high surface area, and mechanical strength. As a result, CNTs can deliver or conjugated with a variety of therapeutic agents (DNA, RNA, proteins, antibodies, enzymes, drugs, etc.) [125].

MWNTs tagged with Protoporphyrin IX (PPIX) were developed as a potent antiviral to combat the influenza A virus [117]. During this photodynamic therapy, in which Influenza A/X-31 (H3N2) become inactivated after exposure to visible light. The inactivation process includes fissure of RNA and RNA-protein bond and protein oxidation due to reactive oxygen species generated by PPIX. In another study, SWCTs explored for modulating pulmonary immune responses and enhance influenza A virus titer in mice. The study confirmed that SWCNT increases influenza A virus titers in vivo with exacerbation of inflammation in lung tissues and mechanisms pointing towards modulation of key antiviral and inflammatory markers [126]. These nanostructures also showed antiviral activity against the respiratory syncytial virus.

6.3. Micelles

Micelles are colloidal structures (usually 5 nm to 100 nm) generated by amphiphilic molecules or copolymers, consist of hydrophobic and hydrophilic regions. They interact with water and instinctively form micelles at certain temperatures and concentrations. These amphiphilic molecules at low concentrations exist as individual molecules and as the concentration increases they initiate to form aggregates. Further increase in concentration results in the appearance of micelles, known as critical micelle concentration. Micelles contain a hydrophobic core and a hydrophilic shell. The hydrophobic core incorporates lipophilic drugs, and the hydrophilic shell is a carrier of polar groups, acts as a protective layer for the cargo, and

diminishes nonspecific contact with cells, proteins, and enzymes. Thus, it assists in circumventing the clearance by the reticuloendothelial system (RES) and increase in circulation time that enhances efficacy and accumulation. Further, micelles conjugated with monoclonal antibodies and specific ligands that offer targeted drug delivery potential [127]. Reported investigations revealed the utilization of these micelles for the delivery of various antiviral drugs. Micelles loaded with amantadine were developed, and sialic acid interacts with the HA of influenza that results in inhibition of the virus triggered infection [Ahn Y. et al., 2010]. Prabakaran et al. entrap baculovirus inside reverse micelles of phosphatidylcholine. Studied efficacy as an oral vaccine in mice infected with cross-clade H5N1 infection [128].

6.4. Liposomes

Liposomes are small lipidic vesicles, 20 nm -1000 nm in diametric range composed of cholesterol and phospholipids. The aqueous core entrapped by the phospholipid bilayer into which entrapment of drugs is feasible. Based on their configuration, they classified as small unilamellar vesicles and multilamellar vesicles. Liposomes exhibit the capacity to entrap both lipophilic and hydrophilic molecules. For enhancement of their specificity, several targeting moieties attach to the surface of liposomes. Further, its surface can be modified with polyethylene glycol molecules that decrease the protein interaction, low uptake by RES, and increases the circulation time. Due to their lipophilic nature, they were capture by the reticuloendothelial system. In some infection conditions, it is advantageous; for example, HIV resides inside the macrophages. However, liposomes utilization is very limited due to instability in vitro (storage and administration) as well as in vivo (protein interaction), less drug loading efficiency, and high development cost [129].

Interestingly, some lipids have the potential to act against the respiratory syncytial virus. Therefore, few studies illustrate the formation of liposomes by using these lipids and exploring them for drug delivery or vaccine development against RSV. Numata et al. cited inactivation of RSV is achievable by the surfactant lipid phosphoinositol (PI) [130]. Furthermore, they explained that PI lipids prevent the RSV attachment with cell but do not act as virucidal. In earlier findings, researchers have described the anti –RSV activity of fatty acids and glycerides as well. One review article also discussed the potential of liposomes as a carrier or nanovaccine against RSV [131]. Inhalable aerosolized liposomes are attached to α-gal/sialic acid design. The influenza virus attaches to sialic acid epitopes on α-gal/SA liposomes. Results trigger innate

anti-Gal antibody binding to α-gal epitopes on α-gal/sialic acid liposomes and stimulate the complement system resulting in the triggering of macrophages. The macrophages engulf the influenza virus bound to α-gal/SA liposomes after contacting between anti-Gal antibody and Fc-receptors on macrophages [132]. Liposomes of phosphatidylserine species, 1-stearoyl-2-arachidonoyl-sn-glycero-3-phospho-L-serine were fabricated and targeted to toll-like receptors of human rhinoviruses [133].

6.5. Cyclodextrin- based drug delivery systems

Cyclodextrins (CDs) are cyclic oligosaccharide derivative of starch, in which six to twelve α-D-glucopyranose molecules are bonded by α1–4 linkages. They are bucket-shaped due to the arrangement of glucopyranose molecules. This bucket-shaped structure represents hydrophobic core, hydrophilic edges with –OH functional groups. The commonly used CDs are α-CDs, β-CDs, and γ-CDs, holding 6, 7, and 8 glucopyranose units, respectively. These CDs possess unique features to form complexes with inorganic and organic lipophilic molecules. Cyclodextrins are chiefly used in the pharmaceutical region to improve aqueous solubility, protect the drugs, increase bioavailability and stability of antiviral agents. Modified CD derivatives prepared by enzymatic and chemical treatment of macrocycle 1 of CDs. These CD derivatives self-assemble in the aqueous phase and offer a variety of shapes like nanorods, nanospheres, micelles, vesicles, liquid-crystalline arrangement, and nanoparticles ranging 30–500 nm for drug delivery purpose [134].

Currently, there is an urgent need to search for efficient therapy for the covid-19. Many antivirals repurposed (remdesivir, lopinavir + ritonavir, oseltamivir, and nitazoxanide) to combat against novel coronavirus. These antiviral agents encounter a common problem of low aqueous solubility. Hence, hydroxypropyl beta-cyclodextrins (HPβCD) that entraps remdesivir and lopinavir were tested against novel coronavirus. In another study, modified CDs with mercaptoundecane sulfonic acids were developed and studied against many viruses like respiratory syncytial virus. Results revealed that these modified CDs are effective in vitro against RSV in respiratory culture models [135]. Kusakabe et al. reported usage of HPβCD as an adjuvant with hemagglutinin and inactivated whole-virion influenza for influenza vaccine in mice. They found that immunization resulted in secretion of antigen-specific IgA and IgGs in the airway mucosa and the serum as well. Hence it was showed that HPβCD might be a promising mucosal adjuvant for influenza vaccine [136]. In another study, CDs derivatives were generated

and screened for anti-influenza action. Cell-based assay revealed that they exhibit inhibition activity against the influenza virus and block the entry of the virus into the host cell [137]. Recently, the combination of ritonavir with lopinavir repurposed and found efficacious for novel coronavirus. These antiviral drugs were loaded inside γ-CD and HPβCD for the enhancement of solubility [138]. Remdesivir is an insoluble drug, therefore, loaded in CDs for improvement of solubility and stability. Nitazoxanide is another repurposed drug against novel coronavirus, entrapped in CDs [139].

6.6. Dendrimers

Dendrimers are highly-branched, symmetrical, monodispersed 3D nanosystems (2-100 nm). They generally have a symmetric interior core, which is created by repetitive building units, whereas the outer core exhibit enormous functionalities. The flexible and empty space inside the dendrimers eases the loading of drugs, and the external functionalities conjugate the molecules/drugs via covalent bonds or electrostatic interaction. Dendrimers purposes several benefits like tremendous uptake by cells, enhance circulation time, improve stability and solubility, and targeted delivery. The functionalization of dendrimers is primarily by conjugation of three types of particle anionic groups, peptides, and carbohydrates. Noteworthy, these dendrimers acquire natural antiviral and antimicrobial properties. Successfully, one dendrimer formulation reached up to phase III clinical trials that are vivaGel. It is a poly-L-lysine dendrimer modified with naphthalene disulfonate groups for a vaginal microbicidal activity [140].

Gunther et al. developed poly(amidoamine) (PAMAM) dendrimers functionalized with 3′-sialyllactose (3SL) or 6′-sialyllactose (6SL) and evaluated their prospective to inhibit avian and human influenza virus strains. Hemagglutination inhibition assay confirmed that human influenza strains are restrained by (6SL) more as compared to 3SL modified dendrimers [141]. The carbosilane dendrimers functionalized with hemagglutinin binding peptide (sialic acid-mimic peptide, Ala-Arg-Leu-Pro-Arg) were designed and assessed for anti-influenza activity [142]. In another study, polyvalent sialic acid -conjugated PAMAM dendrimer was synthesized and assessed against strains of influenza A virus. In vivo results confirmed that these dendrimers prohibited infection by an H3N2 subtype in a murine influenza pneumonitis model [143]. Carbosilane dendrimers functionalized with sialyl lactose moieties (Neu5Acα2→3Galβ1→4Glc) were synthesized and evaluated for anti-influenza virus activity. Dendrimers also studied in

nanovaccine formulation; adjuvant free, single-dose dendrimer nanoparticle incorporating mRNA replicons evaluated to produce protective immunity against *Toxoplasma gondii*, Ebola virus, and H1N1 influenza. The results suggest that they have a high potential to develop an adjuvant free vaccine [144].

6.7. Nanoemulsions

Nanoemulsions mainly comprise of oil, water, co-surfactants, and surfactants. They are thermodynamically single-phase systems with the globule size of 20-200 nm. Nanoemulsions exhibit advantages like greater drug loading capacity, improve solubility, enhanced absorption, and bioavailability, higher lymphatic uptake, and increase residence time in gastrointestinal tract. Therefore, nanoemulsion loaded with antiviral agents enhances the solubility of these drugs. Self-nano emulsifying drug delivery systems (SNEDDS) are a different category of lipidic systems [145]. They form instantaneous emulsions of oil or lipid in water with the aid of cosurfactants, surfactants, cosolvents, and solvents upon moderate stirring. They are thermodynamically stable systems and can be used to load lipophilic drugs. Several antiretroviral drugs deliver with lipid-like Labrafil, Capmul MCM, and Capryol 90 [146].

Several studies reported on the usage of these nanoemulsions for adjuvant delivery and to develop a vaccine against respiratory viral infections. Other group developed intranasal nanoemulsions based adjuvanted vaccine against the respiratory syncytial virus. They confirmed that these NEs based vaccines induce high antibody titers and a robust Th1-skewed cellular response against RSV in an animal model. In another reported study, the group established the anti-influenzal activity of non-ionic nanoemulsions in vivo in mice infected with influenza [147]. Nanoemulsion was developed that target cellular immunity, induce protective immunity response, and avoiding vaccine-induced adverse effects [US 2013/0064867 A1]. It consists of surface proteins, fusion proteins, and glycoproteins of RSV. Bielinska et al. developed nanoemulsion based vaccine adjuvant by intranasal route to induce IgG and IgA antibody responses and TH1/TH17 cellular immunity consequential to protect against a range of respiratory viral infections [148]. Nanoemulsion enclosing the recombinant H5 adjuvant was administered intranasally in mice against the avian influenza virus [14].

Table 4: Nanocarriers for respiratory antiviral agents

Nanocarriers	Antiviral agent	Size	Disease	References

Nanoparticles				
Selenium nanoparticles	Arbidol, Oseltamivir, Ribavirin, Zanamivir, Amantadine	65 nm and 100 nm (ribavirin), 200 nm (amantadine), 80-90 nm (Zanamivir), 100-200 nm (oseltamivir),	Influenza	[149], [150], [107], [105]
Silver nanoparticles	Oseltamivir, Zanamivir, Curcumin	2nm -2.3 nm (Zanamivir), 11.95 ± 0.23 nm (RSV)	Influenza, RSV	[108], [106], [109]
Zinc oxide nanoparticles	PEGlyated ZNO-NPs	20-50 nm	Influenza	[110]
Solid lipid nanoparticles	Zanamivir	324.2 and 224.9 nm	Influenza	[113]
Lipid Nanoparticles	mRNA	-	H7N9 influenza	[151]
Carbon-based nanocarriers				
Graphene				
β-cyclodextrin functionalized graphene oxide nanostructure	Curcumin	10[illegible]6 127.7 nm	Respiratory syncytial virus	[116]
Copper-graphene nanocomposite	-	Nanometer	Influenza	[117]
Graphene silver nanoparticles nanocomposite	-	7.5 nm	Feline coronavirus	[152]
Fullerenes				
Fullerene derivatives		-	Influenza A virus	[120]
Fullerene-liposome		28.7 to 100 nm	Influenza	[121]
Fullerene-(tris-aminocaproic acid) hydrate		-	RSV	[122]
Fullerene modified with thiosialosyl-a (2,6)-galactose disaccharide		-	Influenza virus proteins	[123]
Carbon nanotubes				
Multi wall carbon nanotubes	Protoporphyrin IX		Influenza A virus	[117]
Single wall carbon nanotubes	As a vaccine	0.78 nm	Influenza A virus	[153]
Micelles				

Micelles	Amantadine	-		[154]
Reverse micelles	Baculovirus as a vaccine	-	Influenza	[128]
Liposomes				
Liposomes	Carrying antiviral lipids	Nanometer to microns	HRSV	[155]
Liposomes	Tagged with α-gal /SA	-	Influenza	[132]
Liposomes	Phosphotidylserine	-	HRV	[130]
Cyclodextrins				
Hydroxypropyl beta-cyclodextrins	Remdesivir, Lopinavir		Novel coronavirus	[138]
CDs modified by mercaptoundecane sulfonic acids		-	RSV	[135]
Hydroxypropyl beta-cyclodextrins	Influenza virion	-	Influenza vaccine adjuvant	[136]
Dendrimers				
Modified PAMAM dendrimers	3′-sialyllactose- and 6′-sialyllactose-conjugated dendritic polymers	-	Influenza virus	[136]
carbosilane dendrimers			Influenza virus	[142]
Sialic acid – conjugated PAMAM dendrimer		-	Influenza virus	[156]
Dendrimer nanoparticle		200 nm	Influenza virus adjuvant	[144]
Nanoemulsion				
Non-ionic nanoemulsion			Influenza	[147]
Nanolifeemulsions	Surface proteins, fusion proteins, and glycoproteins	350–400 nm	RSV	[148]
Nanoemulsion	Recombinant H5 (rH5) adjuvant		Influenza	[157]

7. Nanocarriers intervention for treatment of Covid-19

Currently, we all are in the middle of a pandemic situation due to novel coronavirus -2 officially named severe-respiratory syndrome coronavirus-2 (SARS-Cov-2). Wuhan (China) was the epicenter of this pandemic, and now more than 129 M cases reported with 2.82 M deceased

condition and, it is believed the most terrible disaster since World War II. This worldwide crisis needs a response to the covid-19 pandemic with the knowledge of technology and science. Nanotechnology strategies can also contribute by providing more advanced resolutions for this emergency. The nanotechnology strategies are under investigation against covid-19 for varied purposes like to develop nanotechnology-enabled PPE kits and masks, filter systems, diagnostic kits development, and delivery of antiviral drugs and vaccines [158],[159],[160], [161]. In this section, nanocarriers under investigation for vaccine development and antiviral compounds delivery against SARS-CoV-2 were discussed.

7.1. Vaccine development

The covid-19 pandemic has severely affected human lives and desperate attempts are going on to develop a vaccine for Covid-19. Several big pharmaceutical organizations are under race to develop a vaccine for covid-19. However, few nanocarriers based vaccines are already reached in clinical trials phase I/II. One of the preliminary report published by Moderna/NIAID disclosed that they developed cationic lipid nanoparticle (LNP) that are virus sized (80-200 nm) and self-assembled formulated of four types of lipids enclosing mRNA-1273. Results suggest that the messenger RNA (mRNA) -1273 vaccine stimulate anti–SARS-CoV-2 immune responses in each candidate, and no side effects or safety issues were observed [162]. Otherwise, unprotected m-RNA is very susceptible and undergoes degradation by RNases. Thus, forming nano vehicles is crucial. Another company Arcturus Therapeutics, a leading company focused on vaccine development for infectious diseases claimed that they developed a lipid nanoparticulate-based vaccine named

LUNAR®-COV19 encapsulating m-RNA. In vivo studies in human ACE2 transgenic mice revealed that a single shot of vaccine in mice at 2μg and 10μg doses produces both cellular and humoral immune responses. Besides, in mice, mortality was not there, and neutralizing antibody titers enhanced up to day 60. Further, they designed a STARR™ technology platform that coalesces self-replicating RNA with LUNAR®-COV19. This blend of the STARR™ and LUNAR® technology offers lesser dose requirements due to prolonged protein expression as compared to non-self-replicating RNA-based vaccines, higher immune response, and prospectively facilitating to develop vaccines rapidly [163].

BioNTech collaboration with Pfizer developed lipid nanoparticles (LNP) containing the mRNA vaccine (BNT162b1) expressing the SARS-CoV-2 receptor-binding domain currently in

phase I/II clinical trials studies. Novavax formulated Covid -19 vaccine presently in phase III clinical and they planned to enhance vaccine manufacturing capacity to over 2 billion annualized doses in collaboration with Serum Institute of India. This developed vaccine is a nanotechnology-based comprised of recombinant SARS- CoV-2 glycoprotein encapsulated in nanoparticle with matrix M adjuvant. Furthermore, Alnylam Pharmaceuticals Inc. jointly with Vir Biotechnology Inc. proposed stable nucleic acid-lipid particles (SNALP) technology. The SNALP is a lipid nanoparticle-based siRNA activated formulation comprising of cholesterol, shielding lipids, ionizable lipids, and exogenous or endogenous targeting ligands. In another study, McKay and colleagues presented SARS-CoV-2 spike protein encapsulated within a lipid nanoparticle (LNP) as an intranasal vaccine. Results confirmed that specific antibody titers for SARS-CoV-2 were observed and this vaccine is harmless [159], [164]. On the other hand, some adjuvants specifically developed and licensed for vaccine development for covid -19 example cytosine and guanine with phosphodi-ester backbone (CpG 1018,Dynavax), adjuvant system 03 (ASO3, GSK), and MF59 (Sequirus) [164]. Table 5 explained several covid-19 vaccine under clinical trial, nanotechnology used for fabrication, and major key findings of vaccine.

Table 5: Covid-19 vaccine based on nanotechnology under clinical trials

Company	Nanotechnology platform		Clinical trial status	Key findings	Reference
Moderna/NIAID	Lipid nanoparticles (LNP) encapsulating m-RNA	RNA	Phase III	mRNA-1273 vaccine stimulate specific anti–SARS-CoV-2 immune responses	[94]
Arcturus Therapeutics	Lipid nanoparticles LUNAR®-COV19 encapsulating m-RNA	RNA	Preclinical	single shot of vaccine in mice at 2 μg and 10 μg doses produces both cellular and humoral immunity response	[163]
Arcturus Therapeutics	STARR™ technology that is	RNA	Preclinical	lesser dose requirements as	[94]

	in combination with self-replicating RNA with LUNAR®-COV19			compared to LUNAR alone and sustained action	
BioNTech/ Pfizer	Lipid nanoparticles encapsulating m-RNA	RNA	Phase I/II	Elevation of RBD-binding IgG concentrations and neutralizing antibody with no adverse side effects	[159]
Novavax	SARS-CoV-2 glycoprotein encapsulated in nanoparticle with matrix M adjuvant	Protein subunit	Phase III	High antibody titer with matrix M adjuvant	[94]
Alnylam Pharmaceuticals Inc./Vir Biotechnology Inc.	SNALP technology (lipid nanoparticles containing SiRNA)	RNA	Preclinical	Functionalized siRNAs are then into different types of nanoscale capsules, including lipids, liposomes, cyclodextrins, etc., so as to easily reach and enter the targeted cells.	(164)
Imperial College London	Lipid nanoparticles	RNA	Phase I	Specific antibody titers for SARS-CoV-2 with no side effects	[165]

7.2. Delivery of therapeutics

To combat against this coronavirus infection several prophylactic and therapeutic drugs are under trials or development. Many drugs like hydroxychloroquine, including antivirals (lopinavir, remdesivir, tenofovir and other combination therapy) are repurposed for the treatment of SARS-CoV-2 infection [166], [167], [168]. Further many biologics like neutralizing antibodies and sera proposed as a treatment therapy. However, these drugs and biologics could not able to reach at the site of action successfully therefore, to maintain their therapeutic

concentration is difficult. At this point, nanotechnology intervene to develop nano-drug delivery carriers to encapsulate these drugs. Nanocarriers offers numerous advantages like high therapeutic concentration, enhanced solubility and stability, protection of these drugs form enzymatic degradation, modification of release kinetics, multi- drug delivery and co-delivery with adjuvants, maintenance of conformational structures of biologics and site specific delivery (cell, organ and organelles). In France, one study reported and developed multidrug nanoparticulate system to fight against cytokine storm and hyperinflammatory condition of covid-19. Squalene and adenosine (anti-inflammatory agents), and fat entrapped in envelope made of vitamin E (tocopherol) and form nanoparticulate system. The formulation was investigated in mice suffered from hyper inflammation and cytokine storm to mimic the situation of covid-19. Results shown that there was considerable decrease in TNF-alpha laterally increase in anti-inflammatory cytokines interleukin -10 [165].

Nanodiscs carrying sialic acid acts a decoy molecules were developed and tested against influenza virus [169]. This could also act a treatment therapy of covid-19. Lima et al. developed Chloroquine nanoparticles which are anti-HSV-1 [170]. Liu et al. manufactured cholesterol-modified hydroxychloroquine loaded liposomes that could be effective for inflammation associated with pulmonary fibrosis. It also reduces dose and toxicity associated with hydroxychloroquine. This formulation strategy could also be advantageous for SARS-CoV-2 treatment, and act dually o viral load and pulmonary fibrosis [126]. Another study presented development of poly (lactic-co-glycolic acid) and polyethylene copolymer nanoparticles for encapsulation of combination antiretroviral therapy that is ribavirin and DX600 (specific, potent and novel peptide inhibitor of ACE2) could be promising treatment therapy for SARS-CoV-2. However, metallic nanoparticles (silver, zinc, and copper) also revealed antiviral activity against coronaviruses, which exhibit alike characteristics with SARS-CoV-2.

8. Natural products with antiviral activity

The toxicity and inability to treat viral/resistant viral infection, there is an increasing need of new antiviral molecule. Natural resources have potential to cater the need due presence of plethora of structurally diverse and complex chemicals with broad-spectrum bioactivity in it. Nature is continually under extensive exploration in search of new chemical entity with antiviral activity. Number of herbal, microbial and marine origin natural products have been reported to possess antiviral activity. Various chemical classes of plant secondary metabolites including,

flavonoids, terpenes, alakloids, lignans, glycosides, polysaccharides, polyphenols, saponins, quinones, proanthocyanidins, nucleoside analogs, phenolics, tannins, steroids, thiosulfonates, and coumarins have been reported to possess antiviral compounds [171][172][173]. Many immunemodulatory also been utilized for their indirect antiviral activity with certain exception of immune-compromised patients due to disease (HIV etc.) or drug therapy (post organ transplant etc.) [172]. In post COVID 19 time, a surge of preclinical and clinical studies has been initiated with natural products in search of new molecules/combination with treatment, prophylaxis and adjuvant therapy potential.

There are number of natural products under clinical trial for viral disease treatment like a combination of essential oil containing plants *Thymbra capitata* (L.) Cav., *Salvia fruticosa* Mill and *Origanum dictamnus* L have been reported to inhibit influenza A/H1N1 virus strains, influenza B and human rhinovirus 14 (HRV14), by significantly inhibiting replication cycle, progeny virus production and by inducing defects in trafficking of influenza A Nucleoprotein [174][175]. Many compounds, isolated from plants found to inhibit respiratory viruses like Amentoflavon (*Torreya nucifera*) inhibit SARS CoV by inhibiting SARS-CoV 3CL Protease, Lycorine (Lycoris squamigera) & Digoxin (*Digitalis purpurea*) inhibited MERS-CoV, SARS-CoV by CPE inhibition [173], Xanthones (*Polygala karensium*) inhibited Influenza A virus by inhibiting Influenza A neuraminidase, Cimicifugin (*Cimicifuga foetida* L.) inihibited Respiratory Syncytial Virus by inhibiting viral attachment, internalization and stimulate INF-beta secretion [176].

However, many studies are of preliminary level, thus further studies with isolated compounds responsible for activity, study of interplay of additional compounds (present in same extract or other natural product) for presence of any synergy, characterization of mechanism and toxicity, and co-activity with the currently available promising drugs/therapy. Furthermore, it is largely believed in scientific community and proved that natural products have potential to be explored further and may certainly produce more precise and specific molecules to be used as antiviral therapeutics.

9. Conclusion and future directions

The alarming rise of respiratory viral infections, drug-resistant strains of viruses, and high zoonosis posing need of newer technological solutions in the field of medicine and presently, the covid-19 pandemic had proven that. These respiratory viral infections impacting socioeconomic

and major health crisis globally. The industry and academia all over the world at present working very furiously to find solution of these respiratory viral diseases. Nanotechnology has transformed whole world by proposing several innovative approaches to address many problems, specifically in healthcare sector. The application of nanocarriers or nanotechnological tools to deal with these emerging respiratory viral infections is currently a good strategy. We have summarized in this review the respiratory viruses, their tactics to survive inside cells, transmission mode, and nanocarriers under the umbrella of nanotechnology. Further, the few nanocarriers under trials for SARS-CoV-2 treatment is also overviewed.

Future demands the development of novel antiviral therapeutics, theranostics, and nanocarriers to combat against these deadly viruses. Further, basic research by using computer aided drug discovery to find new drugs and computational simulation to study interaction between virus and nanoparticles is necessary. As discussed above, many nanotechnological approaches to deal with SARS-CoV-2 are also under progress like vaccine development, and therapeutic delivery. However, nanotechnological strategies also applied for diagnostics, PPE kits, and mask development against covid-19. Several new approaches nanodiamonds, nanotraps, nanofibers, nanoherbal formulations, and nanorobots are also under investigation against HIV and influenza, and may be extended to other viruses. It can be endorsed to enlarge research on this theme to improve the current knowledge, therapy and to avoid resistance of these viruses.

However, major barriers in advancement of these nanocarriers are complication in characterization, construction, large-scale production, and lack of regulatory guidelines. Further, the nanotoxicity study of these carriers is supreme requirement to prove safety. However, the continuous emergence of these respiratory viruses need prompt advancements to control and manage viral infections more efficiently.

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