



Mechanistic insight into anti-COVID-19 drugs: recent trends and advancements

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Abstract

The Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2) has been established now to be a deadly disease afflicting the whole world with worst consequences on healthcare, economy and day-to-day life activities. Being a communicable disease, which is highly pathogenic in humans, causing cough, throat infection, breathing problems, high fever, muscle pain, and may lead to death in some cases especially those having other comorbid conditions such as heart or kidney problems, and diabetes. Finding an appropriate drug and vaccine candidate against coronavirus disease (COVID-19) remains an ultimate and immediate goal for the global scientific community. Based on previous studies in the literature on SARS-CoV infection, there are a number of drugs that may inhibit the replication of SARS-CoV-2 and its infection. Such drugs comprise of inhibitors of Angiotensin-Converting Enzyme 2 (ACE2), transmembrane Serine Protease 2 (TMPRSS2), nonstructural protein 3C-like protease, nonstructural RNA-dependent RNA polymerase (RdRp) and many more. The antiviral drugs such as chloroquine and hydroxychloroquine, lopinavir and ritonavir as inhibitors for HIV protease, nucleotide analogue remdesivir, and broad-spectrum antiviral drugs are available to treat the SARS-CoV-2-infected patients. Therefore, this review article is planned to gain insight into the mechanism for blocking the entry of SARS-CoV-2, its validation, other inhibition mechanisms, and development of therapeutic drugs and vaccines against SARS-CoV-2.

Keywords SARS-CoV-2 · COVID-19 · Inhibitors · Vaccines · Therapeutic drugs · Mechanism

Introduction

The year 2020 witnessed an outbreak of devastating and pandemic coronavirus disease, COVID-19 which is caused by SARS-CoV-2. The very first case of mortality due to COVID-19 was reported in late December 2019 in the Wuhan city of China (Saxena 2020; Singh and Florez 2020). Coronavirus has the largest single-stranded positive RNA genome which is packed in the enveloped nucleocapsid protein. It is spherical or pleomorphic in structure with spike- or crown-like projections of glycoproteins with 80–120 nm in diameter on its surface, 6–10 open-reading frames, and 26.2–31.7 kb in size (Yang et al. 2006; Guo et al. 2008; Prajapat et al. 2020; Sood et al. 2020). Till now, there are seven important strains of human coronavirus (Chang et al. 2016), whose conserved genes (McBride et al. 2014) and structural components (Hilgenfeld 2014) have been depicted in Fig. 1. The main hypothesized reservoir of SARS-CoV-2 are considered to be bats which transmit the virus to human beings with symptoms such as common cold, respiratory tract infections, cough,

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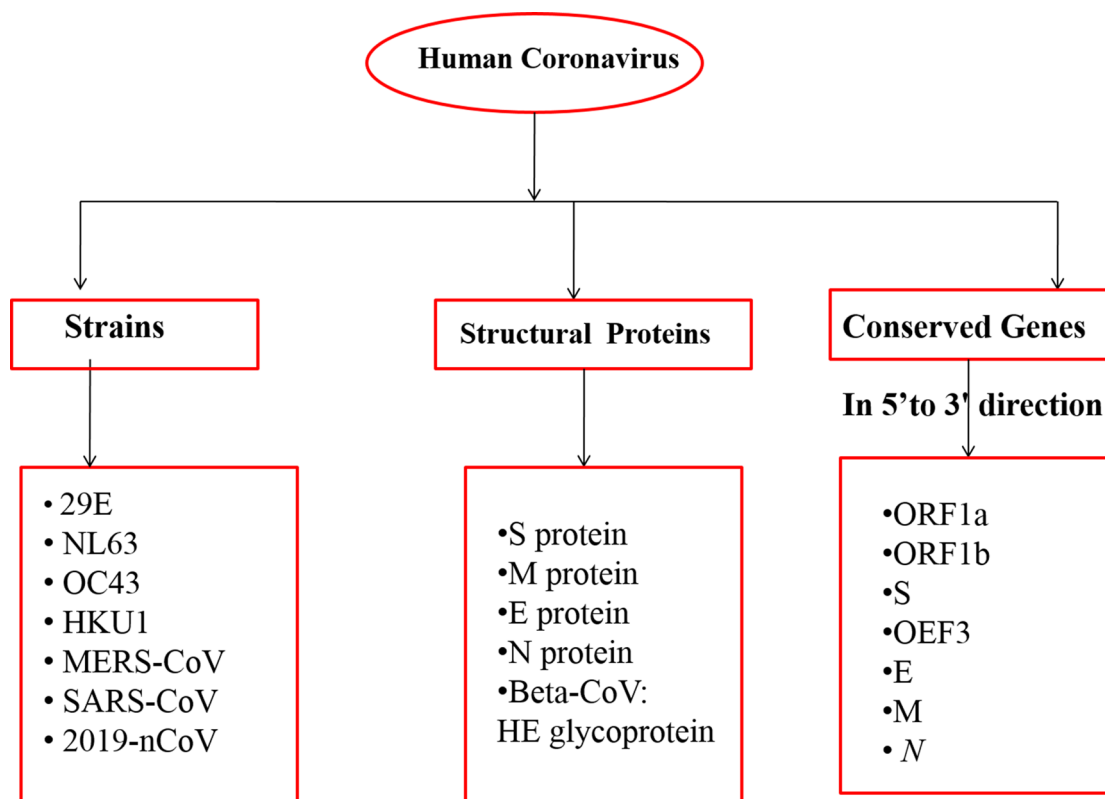


Fig. 1 Conserved genes and structural components of seven strains of human CoVs responsible for infection

fever bronchiolitis and many more (Saif 2004). During the emergence of Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) in Guangdong province of China in 2003 (http://www.who.int/csr/sars/country/table2004_04_21/en/) and the Middle East respiratory syndrome (MERS-CoV) in the year 2012 in Saudi Arabia, they were declared as emerging viruses because of being adaptive to the changing environments. However, the COVID-19 virus was declared as public emergency on 30 January 2020 by World Health Organization (WHO) because this virus mutated rapidly and its recombination frequency was very high, which further gave rise to newer strains with new virulence characteristics. Therefore, to protect the world, special precautions of social distancing, wearing of masks, sanitization of containment zones, quarantine and lockdowns were adopted by the respective Governments and people (Gennaro et al. 2020; Upadhyay et al. 2020). The onset of SARS-CoV-19 in Wuhan and the status of infected people worldwide have been shown in Fig. 2. The increase in the number of patients in coronavirus with symptomatic and asymptomatic conditions and lack of a proper vaccine or drug available for the treatment of patients, have led to an increase in death rate. Therefore, immediate approaches are required to study and design novel antiviral drugs to combat with COVID-19 (Abdul-Rahman et al. 2020; Down et al. 2020; Jin et al. 2020; Bhatia et al. 2020). To achieve this, various

pharmaceutical companies, researchers, drug discovery labs and organizations have explored the identification and evaluation of the target and along with the underlying mechanism (Alexander et al. 2020a, b; Jeon et al. 2020). Across the world, various therapies, treatments, and clinical trials of vaccines are being carried out by various firms including Moderna and NIAID, BioNTech and Pfizer, Inovio Pharmaceuticals, University of Oxford, AstraZeneca, CanSino Biologics, Wuhan Institute of Biological Products, Beijing Institute of Biological Products, Sinopharm, Sinovac, Institute of Medical Biology and Chinese Academy of Medical Sciences and Novavax. (Talwar et al. 2020; Mullard 2020). In this article herein, we review the potential drug targets and the putative mechanisms thereof against SARS-CoV-2. Moreover, the review also includes the RNA synthesis inhibitors, antiviral therapies, inhibition of viral endocytosis and ACE2 receptors, antibiotics, inhibition of inflammatory mechanisms mediated by different cytokines and phagocytosis mechanism as well.

Chemistry of major anti-COVID-19 drugs

Since the beginning of year 2020, COVID-19 has created havoc in the world. It is of paramount importance to develop a vaccine against this virus which is a

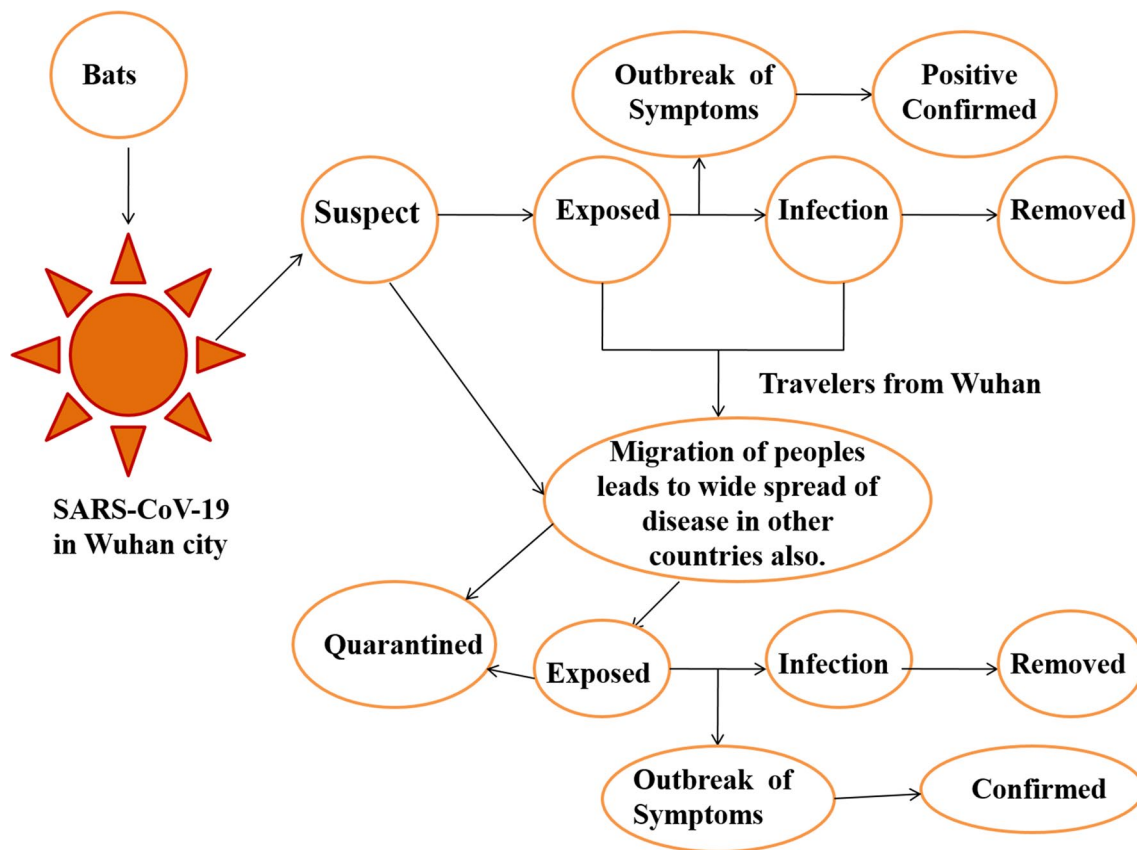


Fig. 2 Schematic representation of SARS-CoV-19 onset in Wuhan and its possible routes transmission, infection and its migration to others

time-consuming process and need clinical trials (Jiang et al. 2020). In 2020, Chang et al. recommended drugs which have been used against viral infections which were already approved by US Food and Drug Administration (FDA). Various investigations have been carried out for the treatment of COVID-19 with antiviral compounds which have been proven to inhibit the COVID-19 infection. The proposed drugs which are reported to work against the virus infection with their molecular formula and mechanism of action, have been tabulated in Table 1. The innate immune system of humans plays an important role in defense against SARS-CoV-19 replication. With the help of interferons, the immune response and the binding of virus to the Angiotensin-Converting Enzyme 2 (ACE2) increase (Omrani et al. 2014). Coronavirus can be blocked by inhibiting the virus self-assembly through structural proteins, virus association with human cells, inhibiting the replication process of virus by blocking several enzymes and the viral transcription factors (Saikatendu et al. 2005). There were three main criteria and strategies based on antiviral compounds which were adopted by scientists and researchers to treat COVID-19 (Huang et al. 2019). The first input was to use the drugs associated with cyclophilin

inhibitors, interferons and ribavirin which are associated with pneumonia-like symptoms, hence approved for the virus treatment. The major disadvantage of these drugs is that they are broad spectrum and killing the virus in a targeted manner still requires a more in-depth research. The second input was to use the existing literature, molecular databases and to find the new molecules with therapeutic potential which are useful and effective against COVID-19 or coronavirus. The anti-HIV drugs such as ritonavir and lopinavir were discovered as potential therapeutics with high-throughput techniques which further help in the effective functioning of the new molecules (Chen et al. 2014; Mummmed 2020). The last input was based on the coronavirus genetic and pathological features. The 3-D structures of drugs used for the treatment of the Coronavirus-19 have been shown in Fig. 3 which are retrieved from PubChem database (Kim et al. 2016). It was supposed that development of drugs through this method will be more efficient and powerful against the virus. But the method was found to be time consuming which could take even more than 10 years to develop the drug after passing all phases of the clinical trials (Omrani et al. 2014; Mummmed 2020).

Table 1 Bird-eye view of anti-SARS-CoV-2 drugs with their molecular and chemical formula

Drugs	Molecular weight	Category/class	Status	Targets	Side effects	References
Chloroquine $C_{18}H_{26}ClN_3$	319.9	Antimalarial, anti-rheumatic and dermatologic drug, an autophagy inhibitor an anticoronaviral agent	United States Food and Drug Association	Angiotensin-converting enzyme 2 (ACE2)	Nausea, vomiting, gastrointestinal problems	Vincent et al. 2005; Wang et al. 2020
Hydroxychloroquine $C_{18}H_{26}ClN_3O$	335.9	Mild antimalarial and anti-rheumatoid, chronic discoid and systemic lupus erythematosus	United States Food and Drug Association	Angiotensin-converting enzyme 2 (ACE2)	Gastrointestinal reactions, cramps, liver dysfunction, itching, headache, dizziness, insomnia, peripheral neuropathy	Vincent et al. 2005; Wang et al. 2020
Lopinavir $C_{37}H_{48}N_4O_5$	628.8	HIV protease inhibitors	United States Food and Drug Association	Nonstructural protein 3C-like protease	Gastrointestinal problems	Chu et al. 2004; De Wilde et al. 2014
Ritonavir $C_{37}H_{48}N_6O_5S_2$	720.9	HIV protease inhibitors	United States Food and Drug Association	Nonstructural protein 3C-like protease	Hepatic injury, pancreatitis, more severe cutaneous eruptions	Kupferschmidt et al. 2020; ClinicalTrials.gov 2020a, b, c
Remdesivir $C_{27}H_{35}N_6O_8P$	602.6	Antiviral drug, adenine nucleotide analog	Investigational drug, off-label	Non-structural proteins RNA-dependent RNA polymerase (RdRp)	Anaphylactic reactions, transaminase elevations, nausea, headache, renal impairment	Wang et al. 2020; Mulangu et al. 2019; Grein et al. 2020
Favipiravir $C_5H_4FN_3O_2$	157.1	Antiviral drug, pyrazine-carboxamide derivative and guanine analog	Approved as broad-spectrum antiviral drug, off-label	Non-structural proteins RNA-dependent RNA polymerase (RdRp)	Reduced body weight, vomiting, and decreased locomotor activity, decreased red blood cell (RBC) production	Furuta et al. 2017; Jin et al. 2013; Delang et al. 2018; Furuta et al. 2009; Sissoko et al. 2016
Imatinib $C_{29}H_{31}N_7O$	493.6	Anti-inflammatory and antibiotics	United States Food and Drug Association	Bcr-Abl tyrosine kinase inhibitor	Gastrointestinal discomfort due to nausea, vomiting, diarrhea as well as superficial fluid retention and skin rashes	Abruzzese et al. 2020
Disulfiram $C_{10}H_{20}N_2S_4$	296.5	Antiviral activity	United States Food and Drug Association	PL protease	Mild headache, drowsiness, tiredness, impotency	Gil Ayuso-Gontán et al. 2020; Maurya et al. 2020
Nafamostat $C_{19}H_{17}N_5O_2$	347.4	Serine protease inhibitor	Approved in Japan, off-label	Transmembrane serine protease 2 (TMPRSS2)	Cardiac arrest in patients receiving dialysis	Hoffmann et al. 2020; Sai et al. 2010
Camostat $C_{20}H_{22}N_4O_5$	398.4	Serine protease inhibitor	Approved in Japan, off-label	Transmembrane serine protease 2 (TMPRSS2)	Mild And include rash and pruritus nausea or abdominal discomfort and liver enzyme elevation	Hirota et al. 2020; Yamamoto et al. 2016
Cyclosporin A $C_{62}H_{111}N_{11}O_{12}$	1202.6	Antiviral, antifungal, anti-infective, dermatologic, anti-rheumatic	United States Food and Drug Association	Calcineurin phosphorylase	Kidney and liver damage, anemia, anorexia, confusion, muscle pain	Rudnicka et al. 2020; Cour et al. 2020

Table 1 (continued)

Drugs	Molecular weight	Category/class	Status	Targets	Side effects	References
Sarilumab C ₆₃₈₈ H ₉₉₁₈ N ₁₇₁₈ O ₁₉₉₈ S ₄₄	150,000.0 Da	Moderate-to-severe rheumatoid arthritis	United States Food and Drug Association	Cytokine	Sore throat or fever, or have unexplained bruising, bleeding or paleness	Atal and Fatima 2020; Regeneron Pharmaceuticals 2020
Tocilizumab C ₆₄₂₈ H ₉₉₇₆ N ₁₇₂₀ O ₂₀₁₈ S ₄₂	148,000.0 Da	Immuno-modulatory and anti-inflammatory drugs	United States Food and Drug Association	Interleukin 6 receptor	Headaches or dizziness, high blood pressure, hypercholesterolaemia, stomach irritation or abdominal pain	Xu et al. 2020a, b; Scott 2017. Clinicaltrial.gov (2020a, b, c)

Mechanistic insight

The new therapies for treating the coronavirus are known to act by inhibiting the viral targets and by controlling the infection caused by nucleotide analogues (Raj et al. 2020; Chandel et al. 2020a). The surface glycoproteins of viruses (Influenza, Ebola, SARS, and MERS) require proteolytic cleavage by a host cell protease. The coronavirus-2 enters the host cells by ligating the spike proteins of the outer membrane of virus with ACE2 receptor as host cell which is further primed by Transmembrane serine protease 2 (TMPRSS2 protease). The replication of the virus and assembly can be blocked by antiviral drugs which target protease 3-chymotrypsin-like cysteine protease (3Clpro) and RNA-dependent RNA polymerase (RdRp) (Bertram et al. 2012; Zhou et al. 2015; Yamaya et al. 2015).

Inhibition of viral endocytosis

Endocytosis is a fundamental cellular process through which extracellular material is brought into the cell interior. Classically, it occurs via the regulation of two different modules—pinocytosis (cell drinking) and phagocytosis (cell eating) depending upon the type of molecules approaching towards the cell surface. The foreign molecules (viruses, bacteria, etc.) use endocytosis process to enter inside the cell. Nowadays, it is the utmost need of biologists and researchers to understand the endocytosis mechanism to stop the pathogen particles to enter inside the cell. However, it is not clear until date how this process is regulated at the molecular level. Classically, pinocytosis involves the uptake of liquid particles while phagocytosis, an actin-dependent course involves the internalization of viruses or bacterial particles to the cell (Dutta and Donaldson 2012). In addition, pinocytosis can be sub-categorized into clathrin-mediated endocytosis (CME) and clathrin-coated independent endocytosis (CIE).

Cell biologists are now trying to block the entry of SARS-CoV-2 inside the cell via inhibiting the endocytosis process, a novel therapeutic strategy to make the vaccine for curing Covid-19 patients. Endocytosis inhibitors could be chemically and genetically originated consisting of selective pharmacologic agents, molecular agents (inhibitors of selective cell-surface proteins and ribonucleic acid). In the current scenario, therapeutic targets are being tried to design specifically to block the attachment of SARS-CoV-2 with cell-surface protein and endocytosis process (Fig. 4). The proposed drugs for Covid-19 such as Nafamostat and Camostat block the fusion of SARS-CoV-2 to cell-surface protein (TMPRSS2). Chloroquinone blocks the ACE2 protein–SARS-CoV-2 fusion. Similarly,

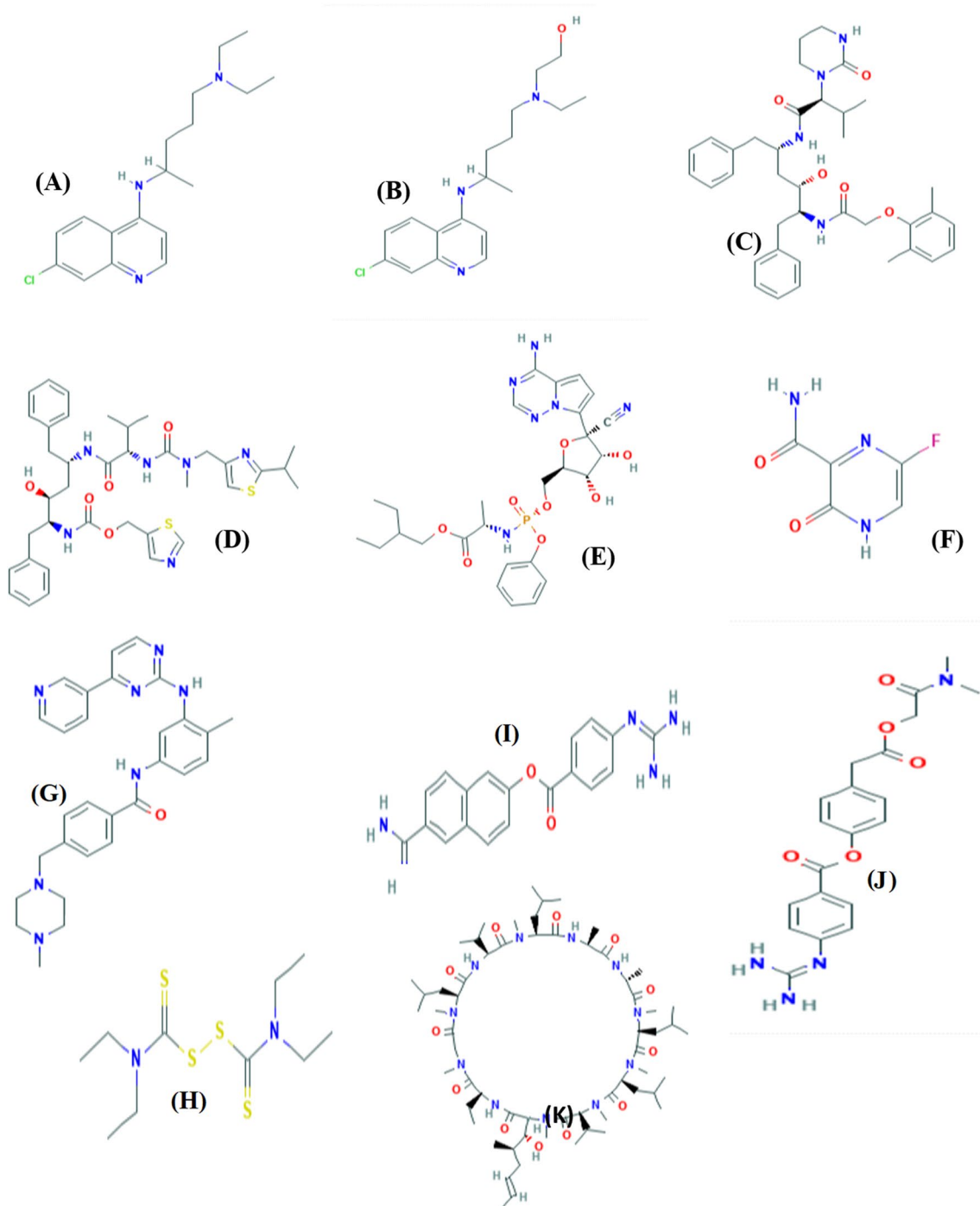


Fig. 3 Chemical structures of anti-COVID drugs 19: (a) chloroquine, (b) hydroxychloroquine, (c) lopinavir, (d) ritonavir, (e) remdesivir, (f) Favipiravir, (g) Imatinib, (h) disulfiram, (i) nafamostat, (j) Camostat, (k) cyclosporin A

the other drug Imatinib inhibits the endocytosis process. Baricitinib drug also inhibits the clathrin-mediated endocytosis by blocking the numb-associated kinase (NAK) particularly AAK1 (Stebbing et al. 2020). As per our best

knowledge, chemically and genetically designed inhibitors have been utilized in the preparation of therapeutic targets against SARS-CoV-2 virus, listed in Table 2 (Stebbing et al. 2020; Yang and Shen 2020).

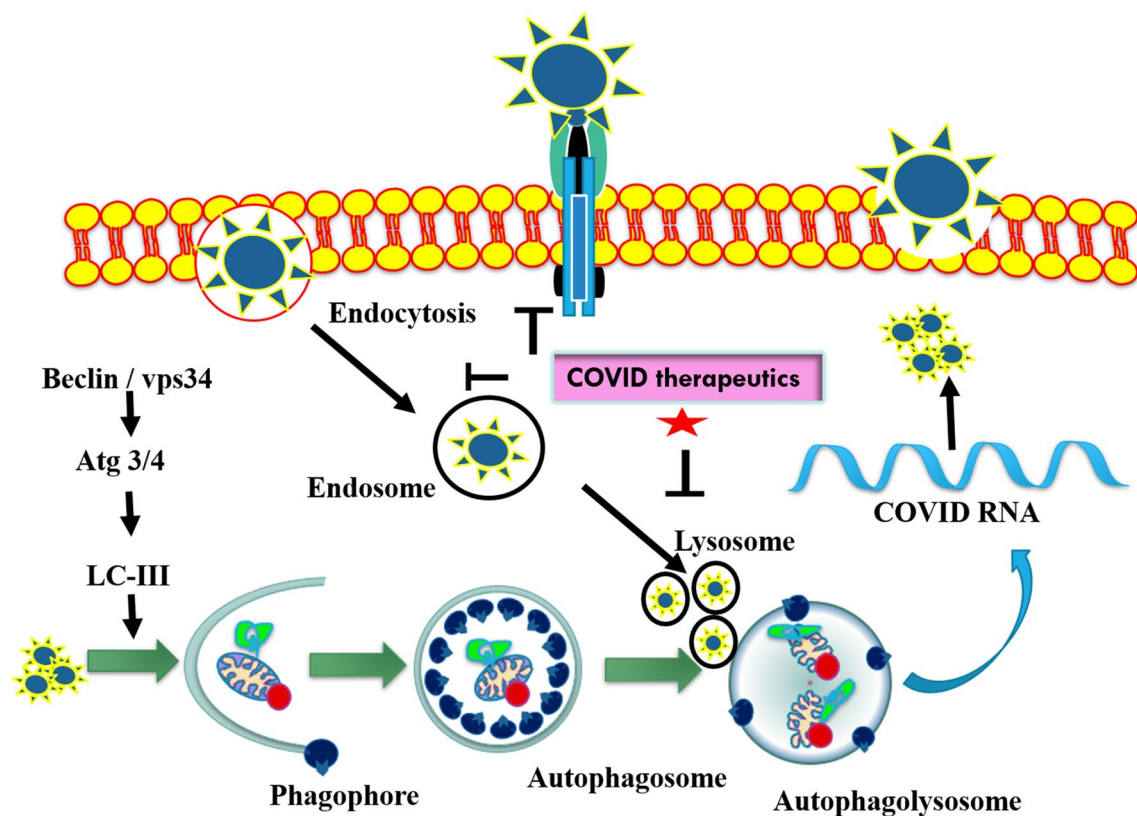


Fig. 4 Schematic representations of viral endocytosis inhibition as promising drug target to block COVID-19 entry. It has been observed that COVID therapeutics inhibit promisingly endosome and lysosome formation, and consequently, it leads to the inhibition of viral replication

Inhibition of ACE2 receptor

ACE2 is mainly present in lungs, kidney, testis, and heart (Donoghue et al. 2009; Ferrario and Varagic 2010; Ohtsuki et al. 2010) and was first discovered in 2000 by Donoghue et al. (2009). It is expressed in non-keratinized squamous epithelium basal layer of nasopharynx, oral and nasal mucosa basal epidermal skin layer with the strongest expression in type II epithelial cells (Cheng et al. 2020). However, ACE2 is not expressed in glomerular endothelial and mesangial cells whereas it is slightly expressed in glomerular tubules. Further B cells, T cells, bone marrow, macrophages, thymus, spleen, Kupffer cells, lymph nodes, and hepatocytes do not depict the presence of ACE2 (Hamming et al. 2004; Santos et al. 2018). ACE2 activity of tissues is higher as compared to its plasma activity (Haber et al. 2014). ACE inhibitors do not inhibit the activity of ACE2 (Donoghue et al. 2009). ACE2 possesses 400 times higher efficiency for angiotensin II (Ang II) than angiotensin I (Ang I) (Vickers et al. 2002) with difference in its activity depending on the sex and age of individuals (Xudong et al. 2006; Soro-Paavonen et al. 2012).

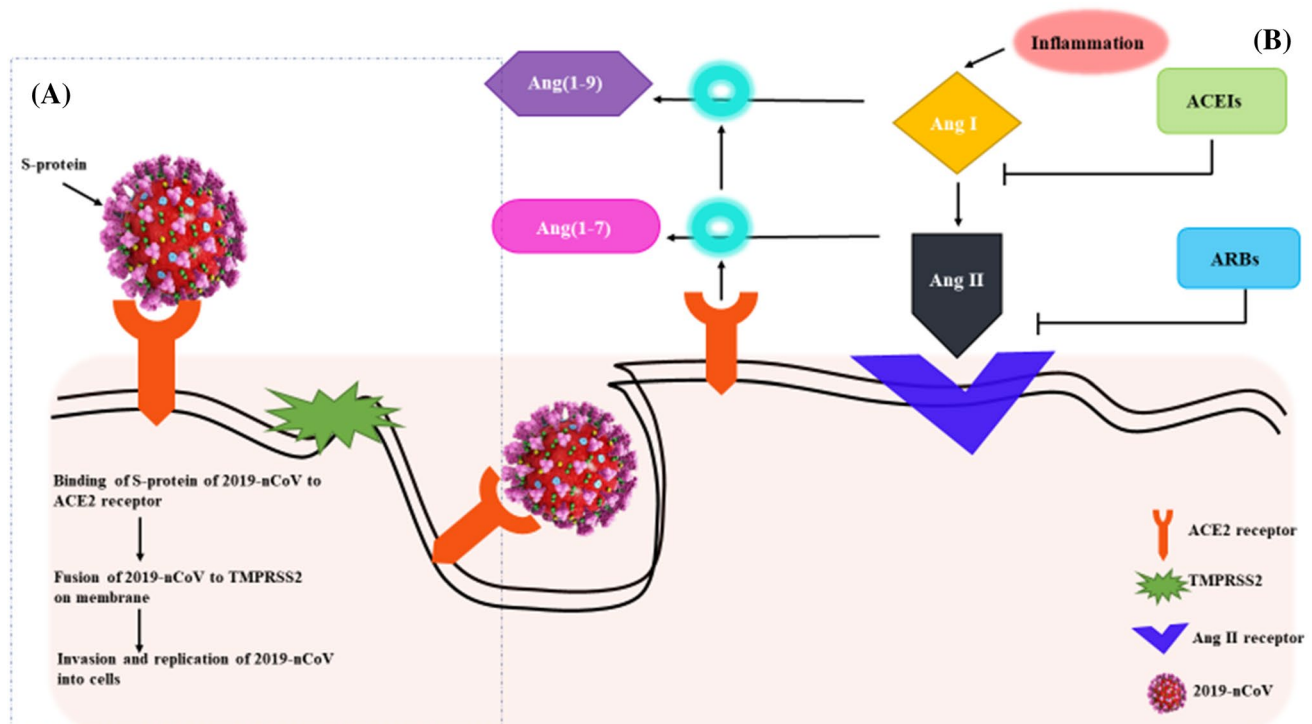
One of the worst symptoms of COVID-19 is acute respiratory distress syndrome (ARDS) which causes increased

pulmonary edema and pulmonary vascular permeability. The novel coronavirus for COVID-19 (SARS-CoV-19) invades the human alveolar epithelial cells through ACE2 (Yang and Shen 2020). ACE2 exhibits a protective role in case of ARDS (Kuba et al. 2005; Xu et al. 2020a, b). When COVID-19 binds to ACE2 receptor it activates the transmembrane serine protease 2 (TMPRSS2), the envelope of the virus fuses with the membrane and thus invades the cells (Fig. 5) (Heurich et al. 2014; Hoffmann et al. 2020). ACE2 generates Ang (1–9) by the cleavage of leucine from Ang I and Ang (1–7) by the cleavage of phenylalanine from Ang II (Rossi et al. 2020). The detrimental effects such as fibrosis, inflammation, and increased vascular permeability, caused by Ang II are counteracted by Ang (1–7). Therefore, ARDS is improved by angiotensin-receptor blockers (ARBs) or ACEIs and Ang (1–7) (Kuba et al. 2005; Wösten-van Asperen et al. 2011; Imai et al. 2005). The COVID-19 entry to the lung cells could be prevented by TMPRSS2 inhibitors such as nafamostat mesylate (Yamamoto et al. 2016) and comstat (Hoffmann et al. 2020) or neutralizing antibodies present in SARS convalescent sera.

Since ACE2 was spotted as the receptor for COVID-19, there were two scientifically unsupported articles which contended that ARB- and ACEI-supplemented treatment for

Table 2 Chemically and genetically designed inhibitors of viral endocytosis as therapeutic targets against SARS-CoV-2 virus

Inhibitors	Targeted pathway	Mode of action	References
Chemical designed inhibitor			
NH ₄ Cl, CQ, Bafilomycin A1	Endo-lysosomal cysteine protease cathepsins	Endosomal proteolysis by cathepsins are required for viral entry	Qiu et al. 2006
Chlorpromazine, MβCD	Clathrin-dependent endocytosis	Virus entry is mediated by clathrin-dependent endocytosis	Inoue et al. 2007
Chlorpromazine, BafilomycinA1, Concanamycin A, NH ₄ Cl, Monensin	Clathrin-dependent endocytosis	Infection by MHV is sensitive to lysosomotropic agents and inhibitors of endocytosis	Eifart et al. 2007
Ouabain, Bufalin	Clathrin-dependent endocytosis	Cardiotonic steroids ouabain and bufalin inhibit infection of cells with MHV and MERS-CoV	Burkard et al. 2015
Phenylarsine oxide	Clathrin-dependent endocytosis	Not known	Gibson et al. 1989
Monodansylcadaverine	Clathrin-dependent endocytosis	Stabilizes CCVs	Schlegel et al. 1982
Dynasore	Clathrin-dependent endocytosis	Blocks GtPase activity of dynamin	Macia et al. 2006
Pitstop 2	Clathrin-dependent endocytosis	Interferes with binding of proteins to the N-terminal domain of clathrin	Von Kleist et al. 2011
Potassium depletion	Clathrin-dependent endocytosis	Aggregates clathrin	Larkin et al. 1983
Cytochalasin D, latrunculin	Phagocytosis macropinocytosis	Depolymerizes F-actin	Fujimoto et al. 2020
Amiloride	Macropinocytosis	Inhibits Na ⁺ /H ⁺ exchange	Lagana et al. 2000
Genetically designed inhibitors			
Clathrin Hub mutant	Clathrin-dependent endocytosis	Dominant negative mutant of clathrin	Liu et al. 1998
Eps15 mutant	Clathrin-dependent endocytosis	Inhibits clathrin pits assembly	Benmerah et al. 1999
AP180C	Clathrin-dependent endocytosis	Clathrin-dependent endocytosis	Zhao et al. 2001
Dynamin mutant, Dyn K44A	Clathrin-dependent endocytosis	Defective in GtP hydrolysis	Van Der Blik et al. 1993

**Fig. 5** Schematic representations of (a) the invasion of 2019-nCoV into cells and its binding to ACE2; (b) mechanism behind the development of anti-COVID-19 drugs based on ACEIs and ARBs to block the binding of 2019-nCoV to ACE2 receptor

COVID-19, was harmful for the patients. This caused distress amongst the public and health officials as more patients began to question the treatment given to them. It was also documented in the *Lancet Respiratory Medicine* journal, that the cardiac (diabetes and/or hypertension) diseased patients developed higher amounts of ACE2 after ARB and ACEI treatments (Fang et al. 2020). However, upon reviewing the literature, it was found that the higher amount of ACE2 secretion was due to conditions like myocardial infarction (Ishiyama et al. 2004; Burrell et al. 2005; Ocaranza et al. 2006) rather than the treatment with drugs for COVID-19 (Rossi et al. 2020). It was found that the increased levels of ACE2 aided the blocking of 2019-nCoV attachment to the lung cells by jamming its S protein (Fig. 5). This strategy was used in the development of anti-COVID-19 drugs to prevent the lung infection caused by 2019-nCoV (Kruse 2020; Zhang et al. 2020). This hypothesis was spread by various scientific societies such as the Italian Society of Arterial Hypertension, the Italian Society of Cardiology and the European Society of Hypertension (ESH) and encouraged the patients to continue their ARB- and ACEI-based treatments (Greene et al. 2013; Danser et al. 2020; Perico et al. 2020). In fact, it was found in a study that adverse health effects and clinical instability were observed in high-risk patients if the ARB and ACEI-based treatments were withdrawn abruptly (Vaduganathan et al. 2020).

Inhibition of proteolysis via 3CLpro and PLpro

The structure of 2019-nCoV consists of six open-reading frames (ORFs) which code for the synthesis of subgenomic mRNAs. The frameshift mutations amongst ORF1a and ORF1b are responsible for coding pp1a (486 kDa) and pp1ab (790 kDa) polyproteins (Muramatsu et al. 2016; Rana et al. 2020). These polyproteins are cleaved into functional proteins by papain-like protease (PLpro) and 3-chymotrypsin-like protease (3CLpro), also known as main protease (Mpro) (Ziebuhr et al. 2000). The main function of PLpro is to defend the coronavirus from immune reaction of the host by removing ubiquitin, whereas 3CLpro aids in the synthesis of functional proteins responsible for translation and replication of the virus. Plant-derived products (Akram et al. 2018) or some other natural products (Aanouz et al. 2020; Borkotoky and Banerjee 2020; Wahedi et al. 2020) that inhibit 3CLpro can be used as anti-COVID-19 drugs (Al-Obaidi et al. 2020; Bhardwaj et al. 2020; Kumar et al. 2020). In a study, 32,297 compounds from medicinal plants known for their antiviral properties were screened and it was found that nine of them (Myricitrin, Methyl rosmarinate, 5,7,3',4'-Tetrahydroxy-2'-(3,3-dimethylallyl) isoflavone, Calceolarioside B, 3,5,7,3',4',5'-hexahydroxy flavanone-3-O-beta-D-glucopyranoside,

Licoleafol, Myricetin 3-O-beta-D-glucopyranoside, Amaranthin, (2S)-Eriodictyol7-O-(6"-Ogalloyl)-beta-D-glucopyranoside) could be used as the anti-COVID-19 drugs. However, these drugs need to be analyzed in vitro and in vivo, before using them as clinical drugs to treat COVID-19 patients (ul Qamar et al. 2020). Chloroquine and formoterol are also known to inhibit the PLpro (Arya et al. 2020).

Proteases have always been a key component in the synthesis of antiviral drugs such as in case of hepatitis C virus and human immunodeficiency virus (HIV) (De Clercq 2002; Turk 2006; Chandel et al. 2020b). Since 3CLpro and PLpro are essential for 2019-nCoV survival, these can be targeted as anti-COVID drugs (Han et al. 2005). PLpro possesses papain-like cysteine protease characteristics, three self-cleaving sites and deubiquitinating activity (Barretto et al. 2005; Han et al. 2005). It is known to hydrolyze synthetic ubiquitin peptide substrate, polyubiquitin and diubiquitin in vitro (Barretto et al. 2005; Lindner et al. 2005). In a study, 6-thioguanine (6TG) and 6-mercaptopurine (6MP) were found to be slow-binding inhibitors of PLpro in 2019-nCoV (Chou et al. 2008) through allosteric inhibition which change the conformation of active site making it unavailable for binding. Like previous antiviral drug formulations (O'Connor and Roth 2005), these compounds can be optimized as anti-COVID-19 drugs. However, these drugs can be cytotoxic to the patients if administered in higher dosages (Chou et al. 2008).

3CLpro possesses a His41 which behaves as a basic acid-base during proteolysis and an active site with Cys145 (Liu and Zhou 2005). TG-0205221 and chloromethyl ketone (CMK) (Anand et al. 2003) were first-generation 3CLpro inhibitors forming a covalent bond between the reactive atom and Cys145 (Anand et al. 2003; Xue et al. 2008) giving rise to a strong protease interaction. However, these drugs exhibit some adverse side effects such as lower potency, toxicity, and off-target reactions (Ghosh et al. 2010; Tuley and Fast 2018). A strong inhibitory interaction was observed with the binding of *Cm*-FF-H, a peptide aldehyde inhibitor, to protease of 2019-nCoV. The ligand bound non-covalently to hydrophilic pocket of protease via its electrophilic P1-phenyl alanine residue (Zhu et al. 2011). This inhibitor explicated its inhibitory activity by catalyzing the conversion of trifluoromethyl-*b*-amino alcohol to four tetra- and triglutamic acid and glutamine peptides (Sydnes et al. 2006). Good to moderate inhibitory activity has been observed using tripeptidic Z-Val-Leu-Ala(pyrrolidone-3-yl)-2-benzothiazole (Hosseini-Zare et al. 2020). As the peptidyl inhibitors possess weaker pharmacokinetics profiles, impermeability to cell membranes and in vivo instability, caution should be taken while considering them as 3CLpro inhibitors.

Inhibition of replication complex via RNA-dependent RNA polymerase

COVID-19 is characterized by a highly conserved genomic organization, unique enzymatic activities, and expression of nonstructural genes by ribosomal frame-shifting (Fehr and Perlman 2015). Mature SARS-CoV-2 virion reproduction depends on the host cellular mechanisms. A plausible therapeutic target to inhibit RNA replication from an RNA template which leads to three potential benefits as depicted in Fig. 6. Even though low-level nonstructural proteins (NSPs) production is still possible inside the cell, but eliminating the viral infection is only possible by targeting the RNA replication of the virus (Astuti and Ysrafil 2020).

The genome of coronavirus includes a 5' cap structure along with a 3' poly (A) tail that serves as a mRNA for translation, and this is responsible for translation of the replicase polyproteins. Two-thirds of the genome is formed by the replicase gene which encodes the NSPs. Several accessory proteins have been shown to play a role in viral pathogenesis, but these are not essential for viral replication but are also included in the genome (Sood et al. 2020).

Once the viral genome enters the cytoplasm, the host ribosomes translate the viral positive-sense RNA into 16 NSPs that may be engaged in making sure that the viral RNA is translated efficiently without interference from the host. Some NSPs are vital for the production of mature virions, while the other NSPs develop the replicase-transcriptase complex (RTC) that consists of proteins needed to replicate both genomic and sub-genomic viral RNA

through anti-sense RNA intermediates (Ziebuhr 2005). The viral structural proteins enter the endoplasmic reticulum (ER) following viral genomic RNA replication and viral protein translation from sub-genomic RNA. The proteins then follow the secretory pathway and develop the endoplasmic reticulum–Golgi intermediate compartment (ERGIC). Following this formation, the N protein encapsulated viral RNA genomes get incorporated into the ERGIC, and then bud into mature virions which eventually exit the cell via exocytosis and infect other cells, thereby spreading the virus load (Choudhury et al. 2020).

Besides treating the various symptoms of COVID-19, clinicians can opt for targeted treatment for the SARS-CoV-2 by targeting viral-specific processes such as viral replication through RdRp inhibition. This is a better approach as it stops the formation of mature virions and stops the virus from spreading and damaging other host cells (Warren et al. 2016; Siegel et al. 2017).

Antiviral drugs that target the RdRp active sites such as the ASP760 and ASP761 may potentially serve as a therapeutic option. Anti-viral drugs such as Favipiravir are viral-specific, and they inhibit the RdRp and result in the inhibition of SARS-CoV-2. Favipiravir structurally has a carboxamide (C–[O]–NH₂) moiety that targets the viral RNA polymerase, and its active form blocks the catalytic domain of the viral RNA-dependent RNA polymerase, and its enzymatic activity. This effectively ends the infectious cycle of SARS-CoV-2. Favipiravir is not toxic to mammalian cells since it does not inhibit RNA or DNA synthesis within mammalian cells (Holshue et al. 2020).

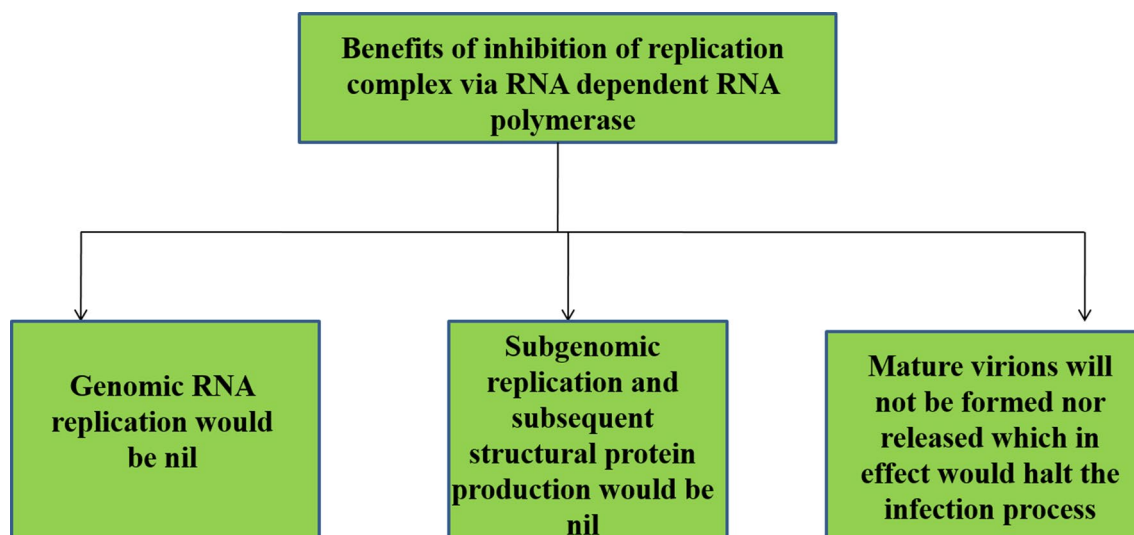


Fig. 6 Diagrammatic representations of Advantages of Inhibition of RNA replication using RNA template via inhibition of genomic RNA, structural proteins, and virions production

Inhibition of calcineurin NEFT pathways

In humans, transplantation of organs such as heart, lungs, liver and kidneys are being performed more frequently. In response to this transplantation, lifelong dual or triple immunosuppressive therapy is needed to prevent the organ rejection. COVID-19 has become a problem in solid-organ transplant (SOT) patients (Willicombe et al. 2020) and there is no clue to deal with immunosuppression in SOT recipients having COVID-19. Immunosuppressive drugs named as calcineurin inhibitors (CNIs), a calcium-calmodulin-activated serine/threonine-specific phosphatase, an immunosuppressive drug, which acts as an important inhibitor in the prevention of rejection. On the other hand, drugs named as cyclosporin and tacrolimus are helpful in transplantation of medicine in CNIs. (Hage et al. 2020). Tanaka et al. (2013) studied that cyclosporin suppressed the replication process of SARS-CoV-1 which is another common virus of Severe Acute Respiratory Syndrome (SARS). Calcineurin inhibitors (CNIs) such as cyclosporin and its derivatives such as cyclosporine A-derivatives inhibit the calcineurin pathway by binding to cellular cyclophilins (Cyps) and NL63 is inhibited by cyclosporine A-derivatives (Carbajo-Lozoya et al. 2014; Sanchez-Pernaute et al. 2020). Tacrolimus, another immunosuppressive drug, inhibits calcineurin by suppressing the early phase activation of T cells and expression of cytokines resulting in the suppression of immune-cellular responses, which lead to the prevention of blizzard of cytokines (IL-2, IL-4, TNF- α and IFN- γ) in COVID-19.

Inhibition of de-regulated proinflammatory response in COVID-19

A cytokine is a signaling molecule responsible for the regulation of distinct biological functions via receptors present on the surface of the cell (Bartee and McFadden 2013) while chemokine is a specific cytokine for attracting the cells to the site of inflammation or infection. Cellular infection followed by viral replication leads to the release of proinflammatory cytokines and death of the cell resulting in an amplified inflammatory response due to release of damage-associated molecular pattern (Tay et al. 2020; Siu et al. 2019; Chen et al. 2019). The exact nature of the inflammatory response depends upon the type of virus and the tissue that has been infected (Thomas et al. 2009; Allen et al. 2009). Cytokine Release Syndrome (CRS) or Cytokine storm is a condition of exaggerated release of cytokines after infection by a virus and it is emerging as a leading cause of Multiple Organ Failure (MOF) and Acute Respiratory Distress Syndrome (ARDS) in COVID-19 (Tay et al. 2020).

Severely affected patients have been found to have raised levels of interleukins (IL): (IL)-1 β , IL-2, IL-6, IL-7, IL-8, IL-9, IL-10, IL-18, TNF- α , Macrophage Colony-Stimulating

Factor (M-CSF), Granulocyte Macrophage-Colony-Stimulating Factor (GM-CSF), Granulocyte-Colony-Stimulating Factor (G-CSF), 10 kD interferon-gamma-induced protein (IP-10), Macrophage Inflammatory Protein 1- α (MIP 1- α) and Monocyte Chemoattractant Protein-1 (MCP-1) in the serum (Huang et al. 2019; Liu et al. 2020; Wang et al. 2020). These studies focused on the potential role of immunosuppressive or immunomodulatory approaches to combat unregulated proinflammatory response.

The COVID-19 infection involves three phases. It starts from an asymptomatic phase in which virus is shredded in high amount in the upper respiratory tract. In the second phase, which is the non-severe symptomatic phase, adaptive immune activation occurs which allows the development of B (generation of specific antibodies) and T cell responses (Fig. 7). In approximately 80% of the patients, this phase marks the end of the disease. Final phase involves the release of high levels of inflammatory cytokines. This phase is also characterized by MOF, progressive fever, hypercoagulability and shock (Berlin et al. 2020). Studies have shown that the inhibition of excessive inflammatory mechanisms contributes in eliminating the viral resistance. Immunomodulatory strategies involved in the treatment of COVID-19 infection targeting certain cytokines are listed in Table 3.

Role of plasma therapy and its mechanism

The convalescent plasma of patients recovered from COVID-19 infection can be used to meet the requirements of antiviral antibodies in newly affected COVID-19 patients. Various beneficial actions of convalescent plasma can, therefore, be availed to help fight against new COVID-19 infection cases. Most viral illnesses manifest a viremia peak within the first week of infection, and it takes about 10–14 days for the host to develop a primary immune response that signals virus clearance. However, viral antibodies contained in convalescent plasma enable viremia suppression, especially if given at an early stage of the disease. Antibody-dependent cellular cytotoxicity (ADCC), complement activation and phagocytosis are also some of the mechanisms that come in effect to clear the virus load. Inflammatory-response suppression and coagulation factors restoration are also plausible mechanisms that help fight against the COVID-19 disease, especially when convalescent plasma is administered early, even to asymptomatic cases (Gunn et al. 2018; Van Erp et al. 2019).

Donor criteria

US FDA has given the approval for the use of COVID-19 convalescent plasma in COVID-19 patients who are at a serious or immediate life-threatening stage of the disease on

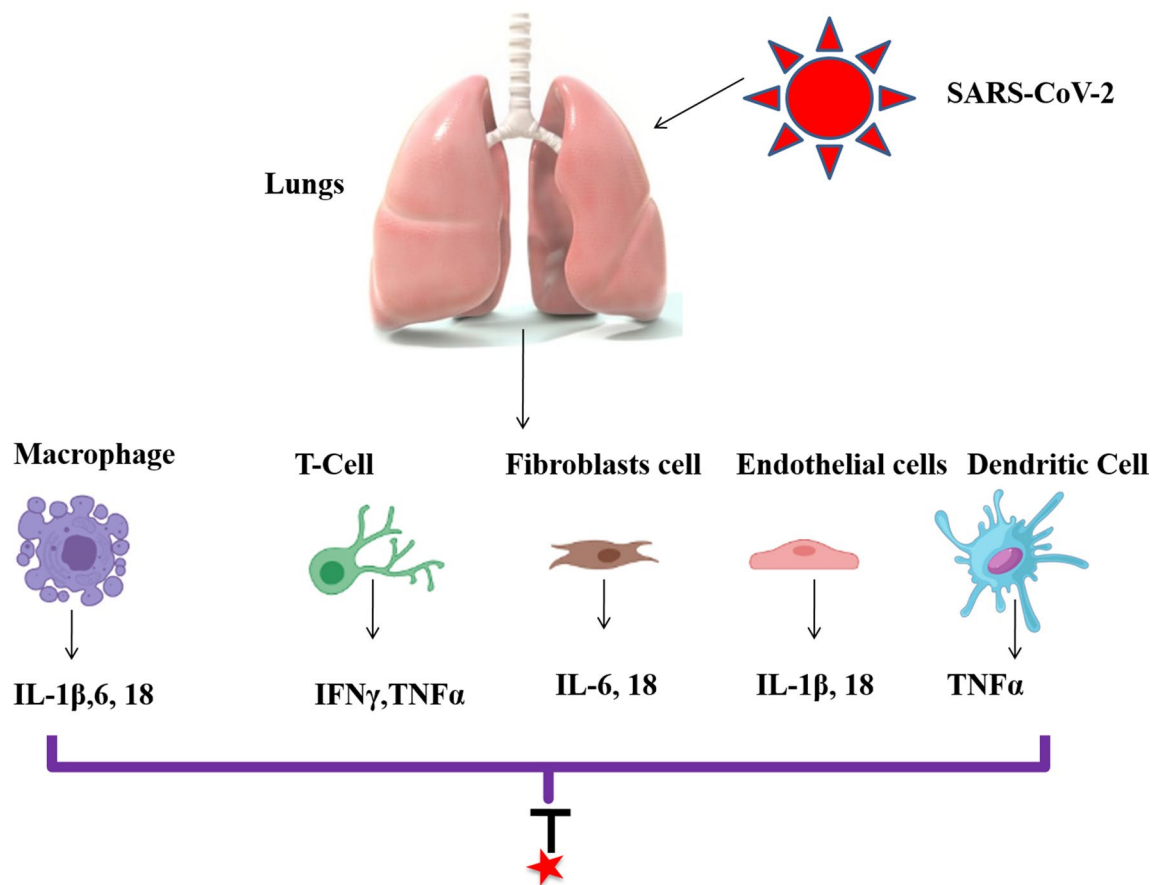


Fig. 7 COVID-19 infection and cytokine generations ((IL)-1 β , IL-2, IL-6, IL-7, IL-8, IL-9, IL-10, IL-18, TNF- α) from different cells. Anti-COVID drugs are investigated to block inflammatory pathways

Table 3 Experimentally proved treatments available for targeting cytokines

COVID-19 treatment	Cytokine target	Clinical effect	References
Glucocorticoids	IFN- γ	Inhibits IFN- γ signaling	Hu et al. 2003
Azithromycin	TNF- α	TNF- α blockage	Gautret et al. 2020; Wang et al. 2020
Chloroquine		TNF- α suppression	
Anakinra	IL-1	IL-1 and IL-1 β blockage	Shakoory et al. 2016; Abbate et al. 2020; Ucciferri et al. 2020
Canakinumab	IL-1 β		
Cyclosporin A (CsA)	IL-2	Binds to cellular cyclophilins to inhibit calcineurin	Tanaka et al. 2013
Tocilizumab	IL-6	Inhibits cytokine release syndrome (CRS)	Dholaria et al. 2019
HuMax-IL8	IL-8	Neutralizes IL-8	Gabellini et al. 2009
Enokizumab	IL-9	Block IL-9	Oh et al. 2013; Lloyd and Hessel 2010
Rituximab	IL-10	Downregulates BCL-2	Alas et al. 2001
GSK1070806	IL-18	Block IL-18	Mistry et al. 2014

March 24, 2020. Only certified blood laboratories and technicians should collect plasma with proper approved equipment. The volume of the plasma collected at any one time can be between 200 and 600 ml, with a gap of at least 7 days

before another collection from the same donor. Donors eligible to give convalescent plasma are defined as meeting the following criteria: (1) recovered COVID-19 patients that were COVID-19 positive either a positive nasopharyngeal

swab at the time of illness, or those who were antibody-positive even if no diagnostic test was done during their illness. (2) A minimum antibody titer of 1:160 should be there in the convalescent plasma. A titer of 1:80 may be accepted only if alternative matching units are unavailable. (3) They should be totally symptom-free for a minimum of 28 days prior to their donation. Exemptions may be considered if the donors are at least symptom-free for 14 days before donation, and they have negative nasopharyngeal swab reports, or negative blood-based molecular diagnostic test results. (4) Female donors must be screened for human leukocyte antigen (HLA) antibodies negativity in case of prior pregnancies; however, male donors are eligible without performing this screening. Transfusion-related acute lung injury (TRALI) is a serious complication that can occur within 6 h of transfusion, and therefore, male donors are preferred, and prior pregnancy and abortion must be ruled out in females before donor consideration. (5) Donors must be eligible generally, with a minimum 14-day interval between full recovery and donation, and consideration of their infection control status and plasmapheresis should be done. Their samples should be negative for HIV, hepatitis B virus (HBV), hepatitis C virus (HCV), syphilis, and locally transmitted infections (Franchini et al. 2020).

Recipient criteria

Convalescent plasma transfusion is generally considered to be safe and without serious adverse effects. However, the risk of TRALI should be kept in mind, and donor selection criteria should be adhered to, meticulously. After getting an informed consent from the patient, convalescent plasma should be given to COVID-19 positive patients who have severe disease symptoms as defined by the following criteria like respiratory rate should be $\geq 30/\text{min}$ whereas blood oxygen saturation must be $\leq 93\%$. On the other hand, the ratio of partial pressure of arterial oxygen to fraction of inspired oxygen ratio should be less than 300 otherwise, it may lead to life-threatening disease conditions such as respiratory failure, septic shock, or multiple organ dysfunction (Franchini et al. 2020).

Therapeutic role of convalescent plasma

More than 15,521,145 patients have already recovered from COVID-19 globally by 19 September 2020. The convalescent plasma is definitely a powerful life-saving therapeutic option for newly affected COVID-19 patients. In addition, more donors can also be channeled for providing therapy, if they are asymptomatic but antibody-positive. Convalescent plasma administration within 10–11 days after symptoms, may result in a quick rise in lymphocyte counts, diminished CRP levels, and an obvious resolution of lung lesions of CT scans. Results

obtained from convalescent plasma administration have been considered to be promising without any serious adverse effects. Convalescent plasma administration should be given as early as possible to severe cases to maximize its efficacy which could certainly alter the morbidity and mortality burden associated with the COVID-19 pandemic (Chang et al. 2020a, b; Chen et al. 2020).

Conclusions

From the past hundreds of years, the SARS virus has been proved to be the greatest worldwide public health crisis. The present century also became the victim of SARS-CoV-2 causing the disease popularly known as COVID-19. Till now there are approximately more than 10 million of people have suffered from this disease and lost their lives. The literature proved that there is no proper vaccine and drugs for the treatment of virus. Various in vitro and in silico studies should be considered and given a due attention to eradicate COVID-19. The in vitro data in most cases has been proved to be beneficial but more drugs and vaccine candidates should be studied and taken under consideration for future pandemic. Preventive measures need to be strictly adopted by the population across the world to protect themselves from the current pandemic. Combination of drugs and various inhibitors for blocking the entry and replication process should be considered. Simultaneously, identification of new treatment modalities needs to be investigated. Proper sharing of resources and knowledgeable information could prove to be helpful in fighting this deadly coronavirus disease. Present review will definitely lead us to understand the complexities of this disease and to design novel and potent drugs along with inhibitors against SARS-CoV-2. In addition, mechanistic insight may help us to understand virology of mutated strains of South Africa 501.V2 (variant), and UK variant.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest in the publication.

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