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Review

Emergence, Transmission, and Potential Therapeutic Targets for the COVID-19 Pandemic Associated with the SARS-CoV-2

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COVID-19 • SARS-CoV-2 • Transmission • Therapeutic options • Antiviral therapies

Abstract
The pandemic of the severe acute respiratory syndrome coronavirus (SARS-CoV)-2 at the end of 2019 marked the third outbreak of a highly pathogenic coronavirus affecting the human population in the past twenty years. Cross-species zoonotic transmission of SARS-CoV-2 has caused severe pathogenicity and led to more than 655,000 fatalities worldwide until July 28, 2020. Outbursts of this virus underlined the importance of controlling infectious pathogens across international frontiers. Unfortunately, there is currently no clinically approved antiviral drug or vaccine against SARS-CoV-2, although several broad-spectrum antiviral drugs targeting multiple RNA viruses have shown a positive response and improved recovery in patients. In this review, we compile our current knowledge of the emergence, transmission, and pathogenesis of SARS-CoV-2 and explore several features of SARS-CoV-2. We emphasize the current therapeutic approaches used to treat infected patients. We also highlight the results of *in vitro* and *in vivo* data from several studies, which have broadened our knowledge of potential drug candidates for the successful treatment of patients infected with and discuss possible virus and host-based treatment options against SARS-CoV-2.

Introduction

Beginning in December 2019, a cluster of pneumonia-like cases of unidentified etiology emerged at the Wuhan livestock market in Wuhan, China [1, 2], initially referred to as novel coronavirus 2019 (2019-nCoV) [3, 4]. On 30 January 2020, the World Health Organization (WHO) declared this an outbreak, which was recognized as a pandemic on 11 March 2020 [5]. Genome sequencing of 2019-nCoV showed the virus shared 79.5 % similarity in genetic sequence with SARS-CoV, the previously known coronavirus responsible for the 2002-2003

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SARS epidemic [6]. Therefore, the International Committee for the Taxonomy of Viruses has renamed the coronavirus 2019-nCoV to SARS-CoV-2, causing Coronavirus Disease 2019 (COVID-19). The coronaviruses are named after their crown-like spines on the surface [7]. SARS-CoV-2 was spread to other Asian countries through people who became infected and then traveled outside of China [8]. On 13 January 2020, the first known infection outside Mainland China was reported in Thailand [9], and then soon after, in Japan on 15 January 2020 [10]. Since then, the infection has spread to more than 188 countries and territories, resulting in community transmission in those countries, which caused a widespread outbreak resulting in a significant death toll worldwide.

The SARS-CoV-2 is the most recent in a whole family of seven coronaviruses known to infect humans. Although SARS-CoV and MERS-CoV are the deadliest coronaviruses of the group, the other four human coronaviruses such as HCoV-OC43 [11], HCoV-229E [12], HCoV-NL63 [13], and HCoV-HKU1 [14] are known to cause the majority of all common cold cases [15, 16]. In several instances, these coronaviruses can lead to severe illnesses such as pneumonia and bronchiolitis [13, 14]. These coronaviruses are also known to be associated with the development of neurological diseases [17, 18]. Of the entire family of the virus, SARS-CoV-2 has proven to be the deadliest coronavirus to date, infecting more than 16 million people globally, with an approximate mortality rate of 4.0 % at the time of writing this review [19]. Respiratory droplets primarily spread the virus by coughing and sneezing [20]. In addition, it is known that the virus can live on various surfaces for hours, and on some, up to several days [21]. Individuals can become infected by coming into contact with a contaminated surface and then touching their face soon after without a proper washing in between [20]. Once on the body, the coronavirus can pass through the eyes, nose, or mouth, and may enter the upper airways of the respiratory system [20]. Like SARS, SARS-CoV-2 can penetrate the respiratory system and the lung epithelial cells where the primary viral replication occurs. It can then further spread to the epithelial membranes of the upper gastrointestinal tract (GI), secondary lymphatic organs, and small systemic vessels [6, 22-26]. The virus can then infiltrate the cells, which can lead to frequent symptoms such as fever, cough, and fatigue, although it can also cause symptoms such as shortness of breath, sore throat, and diarrhea [27, 28]. Most cases lead to mild symptoms, while others can develop into an acute respiratory distress syndrome (ARDS), multiple organ failure, septic shock, and blood clots [2, 29-31]. Additionally, patients affected by SARS-CoV-2 have shown neurological symptoms such as seizures, stroke, encephalitis, and Guillain-Barre syndrome [32]. A significant percentage of COVID-19-infected patients have shown elevated levels of liver enzymes, including alanine transaminase (ALT) and aspartate aminotransferase (AST), indicating severe immunopathology causing liver damage [33].

The exponential spread of SARS-CoV-2 infection has presented a severe threat to public health even with universal prevention, social distancing, and quarantine measures employed throughout most countries. The lack of specific antiviral treatments/drugs, along with a high load of infected patients, has resulted in several thousands of direct and indirect deaths worldwide. This review addresses the pandemic and possible treatment options for emerging SARS-CoV-2. In general, we focus on the current state of knowledge regarding SARS-CoV-2, including its transmission, pathogenesis, the possible antiviral and immunotherapeutic approaches and alternatives available to treat infected patients.

The pathogenesis of coronaviruses

In humans, coronaviruses (CoVs) cause various diseases, including central nervous system diseases, gastroenteritis, and respiratory illness. CoVs are associated with a high mutation rate, which makes the *Coronaviridae* family dynamic and diverse in terms of pathogenicity [34]. Seven coronaviruses are known to infect humans (HCoVs) circulating worldwide, with a higher infection rate being observed mainly in infants. The first human coronaviruses identified in the mid-1960s, HCoV-OC43 [11], and HCoV-229E [12], were associated with a range of respiratory symptoms. At the beginning of the 21st century in

November 2002, the first known case of the SARS-CoV was reported in Foshan, southern China [35]. This virus soon became a global outbreak spreading to neighboring regions and countries with 8437 cases reported along with a mortality rate of 10.0 % [36]. Subsequently, in 2004 and 2005, two new strains of human coronaviruses were discovered, HCoV-NL63 [13] and HCoV-HKU1 [14], respectively. The next coronavirus outbreak occurred nearly a decade after SARS-CoV, in 2012, when a second highly pathogenic CoV, known as the Middle East Respiratory Syndrome Coronavirus (MERS-CoV), emerged in Saudi Arabia with 2494 confirmed cases and with a 35.0 % mortality rate [37-39]. The identification of diverse coronaviruses in bats, including many SARS-related coronaviruses, provides strong evidence that zoonotic transmission events may continue in the future, resulting in periodic outbreaks of coronaviruses in humans over time [6, 40, 41].

The SARS and MERS outbreaks were zoonotic transmissions resulting from hospital-acquired human-to-human transmissions associated with high mortality rates [38]. The hypothesis has been put forward that CoVs entered the human population through one or more intermediate animal hosts. In SARS and MERS, the intermediate host animal is believed to be civet cats, and dromedary camels, respectively [42-44]. The virus probably jumped from bats to such hosts [40, 45]. The virus then underwent several rounds of replication and acquired mutations in the hosts that facilitated its transmission to the human population [46-48]. Unlike SARS, the MERS infections are still periodic, and probably not circulating in the human population. Although this virus does not transmit very well from humans to humans, the new cases are thought to occur from occasional recurrent spillovers from dromedary camels into the human population. It is of enormous concern that the third deadliest coronavirus in recent times, SARS-CoV-2 has caused zoonotic leaps into the human population in less than twenty years. It has posed another challenge to virologists and pathologists to understand the mechanism of viral transmission.

At the overall genome level, Pangolin-CoV showed 91.02 % similarity to SARS-CoV-2, and 90.55 % to Bat-CoV-RaTG13. The genome of Pangolin-CoV is most closely related to SARS-CoV-2, suggesting that pangolin could serve as a reservoir and intermediate host for the zoonotic transmission of the new SARS-CoV-2 (Fig. 1) [49, 50].

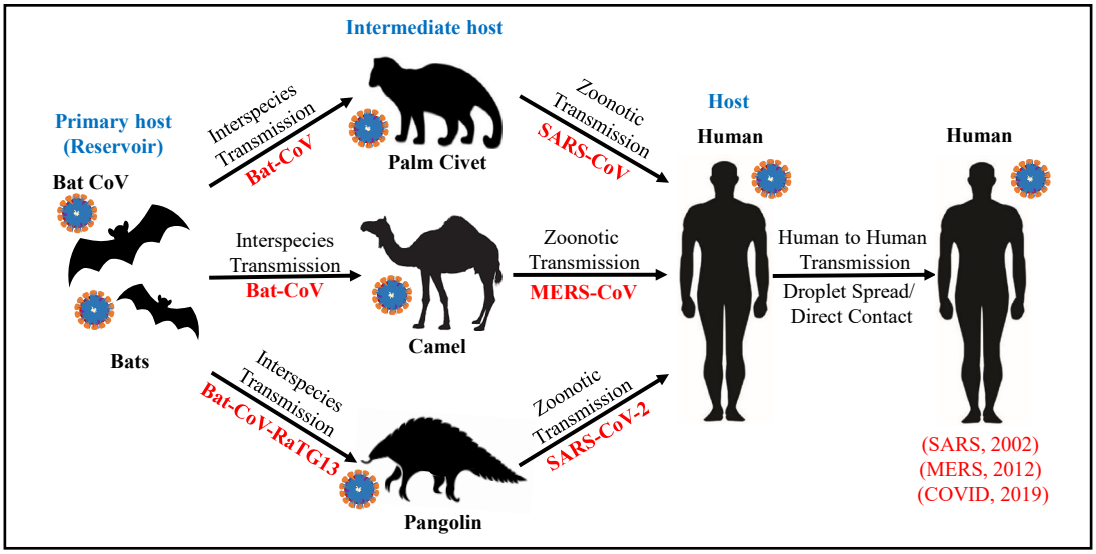

Fig. 1. Transmission path of coronaviruses (CoV). The family of coronaviruses has caused two major outbreaks in the last two decades, the SARS-CoV epidemic in 2002-2003 and the MERS-CoV in 2012. SARS-CoV, caused by the zoonotic transmission from palm civet was infected by interspecies transmission from wild bats, which spread to humans by droplet spread or direct contact. MERS-CoV infection resulted from zoonotic transmission from dromedary camels, which was later transmitted to humans. Similarly, the novel SARS-CoV-2 coronavirus is believed to have jumped from bats to humans via pangolins at the end of 2019 at a local seafood market in Wuhan, China. The virus is transmitted between individuals by direct contact with respiratory droplets of an infected individual.

Structure and Genomics of SARS-CoV-2

Coronaviruses contain the largest genomes ranging from 26 to 32 kilobases (kb) of all RNA virus types. The RNA genome of SARS-CoV-2 is composed of single-stranded RNA with a size of 29.9 kb [51]. Human CoVs, including the novel 2019 SARS-CoV-2, are positive-stranded RNA viruses [52, 53]. CoVs are enveloped viruses (envelope is a lipid bilayer derived from the host cell membrane) with the viral structure formed primarily of structural proteins such as envelope (E), membrane (M), nucleocapsid (N) proteins, hemagglutinin-esterase (HE) protein, and spike (S) protein (Fig. 2A left panel) [34, 54, 55]. According to the International Committee for the Taxonomy of Viruses, the human coronaviruses HCoV-OC43 and HCoV-HKU1 are members of the betacoronavirus genus [56, 57] and bind to the 9-O-acetylated sialic acid (9-O-Sia) receptor located on the host cell [58, 59], which causes illnesses such as cold and upper and lower respiratory diseases. However, HCoV-229E and HCoV-NL63 belong

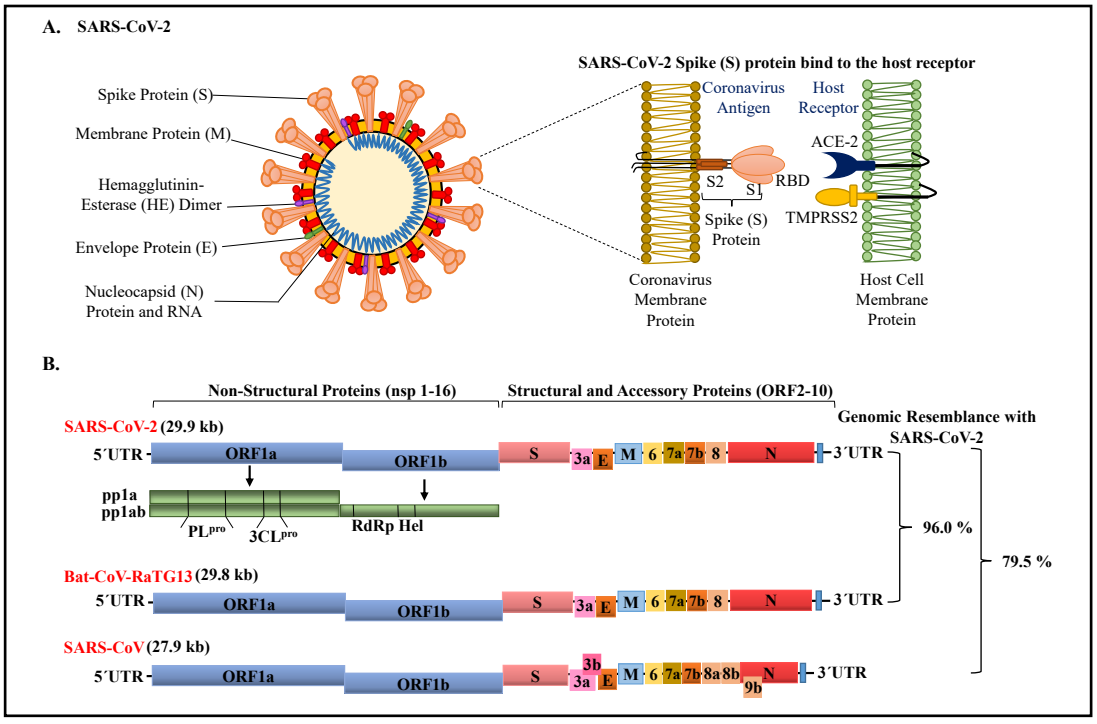

Fig. 2. Structure and genome of SARS-CoV-2. A. The left panel shows the structure of SARS-CoV-2. The virion is a spherical particle composed of four structural proteins: spike (S), membrane (M), envelope (E), and nucleocapsid (N). Within the viral envelope is the helical nucleocapsid, which consists of the viral single-strand RNA genome. The hemagglutinin Esterase (HE) is a glycoprotein that mediates the infiltration of SARS-CoV-2. The right panel shows S protein containing a receptor-binding domain (RBD) responsible for attaching the virus to the host cell membrane by recognizing a specific ACE-2 receptor. The RBD domain in the S1 subunit of the S protein binds to the ACE-2 receptor on the host cell followed by S2 mediated fusion of the viral and cellular membrane. The spike protein priming by TMPRSS2 is crucial for the invasion of the host cell membrane by SARS-CoV-2. B. Comparison of the single-stranded RNA (ssRNA) genome of SARS-CoV-2 (29.9 kb) with SARS-CoV (27.9 kb) and BAT-CoV-RaTG13 (29.8 kb) genomes. The 5′-methylated caps contain two-thirds of the CoV genome compared to 3′-polyadenylated tails, which include the open reading frame (ORF) 1a/b replicase polyproteins 1a (pp1a) and pp1ab. However, these are cleaved by papain-like cysteine protease (PL^{pro}) and 3C-like serine protease ($3CL^{pro}$) into 16 non-structural proteins (nsps), such as the RNA-dependent RNA polymerase (RdRp) and helicase (Hel) that are major enzymes involved in the transcription and replication of CoVs. In addition, the genome encodes the structural proteins (S, E, M, and N) that are essential for virus-cell-receptor binding and virion assembly, as well as other non-structural and accessory proteins.

to the genus of alphacoronaviruses [60, 61], which trigger the common cold in humans by binding to the aminopeptidase N (APN) [62] and angiotensin-converting enzyme 2 (ACE-2) [63] receptors respectively. While SARS-CoV, MERS-CoV, and SARS-CoV-2 are members of the genus of betacoronaviruses [53], MERS-CoV attaches to human dipeptidyl peptidase 4 (hDPP4) [64] while SARS-CoV and SARS-CoV-2 bind to the human ACE-2 (hACE-2) receptor [65, 66] located on the host cell via spike (S) protein to enter the target cells [67, 68].

The receptor-binding domain (RBD) in the spike (S) protein recognizes the ACE-2 receptor expressed on the epithelial layer of lungs, heart, kidneys, and intestine and is responsible for the attachment of the virus to the host cell membrane [69]. During infection, the monomer of the homomeric S protein of the viral particle is cleaved into two subunits (S1 and S2) by proteases [70, 71]. The cleavage and subsequent activation of the S protein prior to membrane fusion is necessary to release the fusion peptide into the host cell membrane. Within the structure, the N- and C-terminal sections of S1 fold up in two independent domains, the N-terminal domain (NTD) and the C-terminal domain (CTD). Either the NTD or the CTD can serve as RBD, depending on the virus. However, the majority of other CoVs, such as SARS-CoV and MERS-CoV, utilize the CTD to bind their receptors [72, 73]. The S2 subunit is further cleaved and activated by the host transmembrane protease serine 2 (TMPRSS2), which is crucial for the invasion of SARS-CoV-2 (Fig. 2A, right panel) [74, 75]. Following the attachment of a SARS-CoV-2 viral particle to a target cell, the cellular protease TMPRSS2 cleaves the spike protein of the virus, thereby releasing a fusion peptide. The virion subsequently releases RNA intracellularly via mechanisms described below, which causes the cell to generate and disseminate replicas of the viral particle that can infect other cells.

The SARS-CoV-2 genome consists of 5' and 3' terminal sequences (265 nt in the 5'-terminal and 229 nt in the 3'-terminal region) [51]. The genome of CoVs contains a variable number of open reading frames (ORFs) [76]. The viral RNA of the first ORF (ORF1a/b) codes for two polyproteins, pp1a and pp1ab, and encodes 16 non-structural proteins (NSP). The rest of the ORFs encode accessory and structural proteins, which are processed by virally encoded chymotrypsin-like protease ($3CL^{pro}$) or main protease (M^{pro}), and further by two viral papain-like proteases $PL1^{pro}$ and $PL2^{pro}$ to produce 16 non-structural proteins (nsp1 to nsp16) (Fig. 2B). It also produces various proteins, including RNA-dependent RNA polymerase (RdRp), RNA helicase, and exoribonuclease (ExoN) [52, 77]. This leads to the formation of a replication complex, including RdRp, which directly facilitates the synthesis of negative-sense genomic RNA from positive-sense. After replication and subgenomic RNA synthesis, the viral structural proteins S, E, and M are translated and packed into the endoplasmic reticulum (ER). As a result, the proteins migrate along the secretory pathway into the endoplasmic reticulum-Golgi (ERGIC) inter compartment [52, 78]. The N protein, capsid, and viral genomes in ERGIC membranes are assembled with viral structural proteins and form mature virions [79]. These newly synthesized virions are transported in vesicles to the cell surface and released by exocytosis (Fig. 3).

According to Zhou P. *et al*., a short region of RdRp isolated from bat coronavirus (Bat-CoV-RaTG13) has shown high sequence similarity with SARS-CoV-2 [6]. Additionally, the spike (S) protein of SARS-CoV-2 shares about 76.0 % and 97.0 % of the amino acid (AA) sequence with SARS-CoV and Bat-CoV-RaTG13, respectively. The AA sequence of the RBD of SARS-CoV-2 is approximately 74.0 % and 90.1 % homologous to SARS-CoV and Bat-CoV-RaTG13, respectively [80].

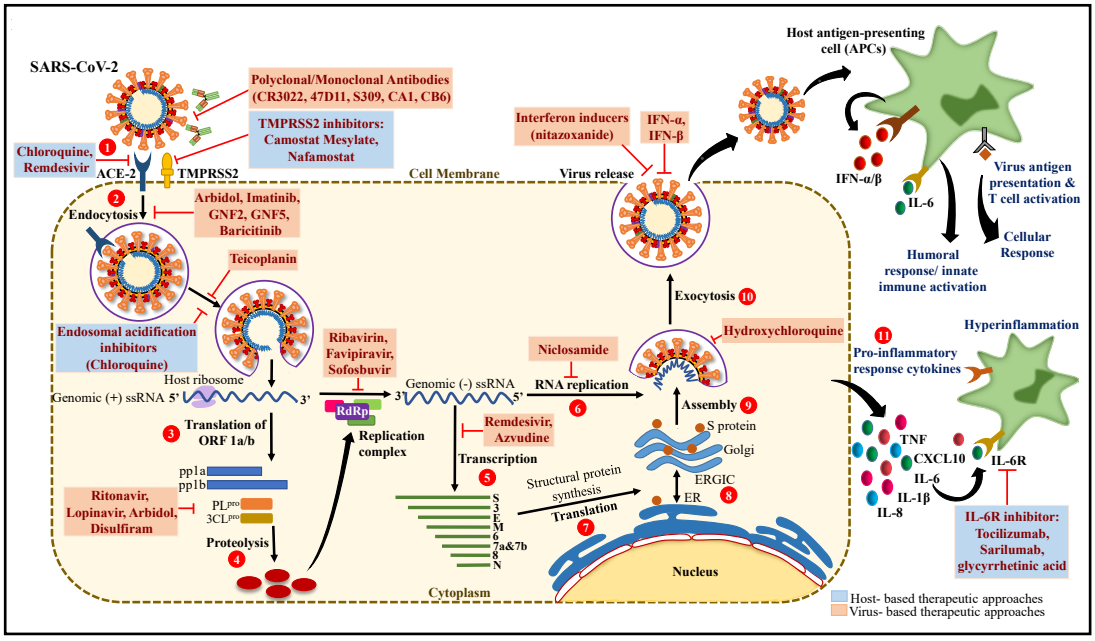

Fig. 3. Illustration of the SARS-CoV-2 viral lifecycle in the host cell and potential therapeutic targets. SARS-CoV-2 entraps the host machinery to translate, replicate, and transcribe the viral genome as well as its structural protein and then reassembles, encapsulates, and exocytose mature virion out of the cell. (1) Attachment of SARS-CoV-2 to the surface receptor of the host cell: SARS-CoV-2 enters the host cell by binding the viral spike (S) protein to the host cell receptor ACE-2. The S protein is cleaved into S1 and S2, S1 region binds to the host ACE-2 receptor, and S2 which is activated by TMPRSS2 allows membrane fusion. (2) Endocytosis: After attaching to the host cell, the SARS-CoV-2 RNA is trafficked into the cell by cathepsin L mediated endocytosis and released into the cell by endosomal acidification. (3 & 4) Translation and Proteolysis: The genomic RNA is then released in the cytoplasm and encodes multiple structural and nonstructural polypeptide genes. The host machinery is used to translate ORF1a and ORF1b into pp1a and pp1ab (polyproteins), which are cleaved into 16 nonstructural effector proteins by $3CL^{pro}$ and PL^{pro}. Some nonstructural proteins form a 'replication-transcription complex', including the viral RNA-dependent RNA polymerase (RdRp) and helicase (Hel). (5 & 6) Transcription and Replication: Replication-transcription complex then uses (+) stranded genomic RNA as a template and synthesizes (—) strand genomic RNA template, which later is used to replicate the complete viral RNA genome and sub-genomic mRNA templates. (7) Translation of structural and accessory protein: In the course of transcription, a subset of 7-9 subgenomic mRNAs encoding structural proteins (S, E, M, and N and a set of accessory proteins) are produced. (8) Trafficking of viral protein from the ER to the Golgi: After newly synthesis, viral structural and accessory proteins are migrated from the endoplasmic reticulum (ER) to the Golgi apparatus. (9) Virion Assembly: A combination of genomic RNA and viral proteins are subsequently assembled into virions in budding Golgi lumen. (10) Exocytosis: Afterwards, the virions are discharged through exocytosis from the infected cell. (11) Immune activation: Upon viral infection, the infected epithelial/endothelial cells secret type I interferons, pro-inflammatory cytokines, and chemokines. This creates an anti-viral state leading to the recruitment of additional immune cells that result in viral clearance with minimal inflammation and damage. In a severe SARS-CoV-2 infection condition, an uncontrolled inflammatory response resulting from the release of large amounts of pro-inflammatory cytokines by immune effector cells results in hyperinflammation and cytokine storm leading to ARDS. Virus- and Host-based therapeutic approaches are highlighted in orange and blue, respectively. +, positive-strand RNA; –, negative-strand RNA; ACE-2, *Angiotensin-converting enzyme 2; CCL2,* C-C motif chemokine ligand 2; *CXCL10,* C-X-C motif chemokine 10; ER, endoplasmic reticulum; ERGIC, ER-Golgi intermediate compartment; IFN-α and β, Interferon- α and -β; IL-6, Interleukin 6; *IL-8,* Interleukin 8; mAb, monoclonal antibody; ORF, open reading frame; RdRp, RNA-dependent RNA polymerase; ssRNA, single-stranded RNA; TMPRSS2, Transmembrane protease serine 2; TNF, *Tumor necrosis factor.*

Current and potential treatment options for SARS-CoV-2

The interaction between the RBD in the S protein of SARS-CoV-2 and the ACE-2 receptor on the cell surface of the host triggers the infection. Current therapeutic approaches to eradicate the infection are based mainly on either use of antiviral drugs or therapeutic molecules that target any phase of the viral life cycle in the host cell or targeting the cell surface receptor, which can block the interaction of the virus with the receptor ACE-2, and its entry in the host cell (Fig. 3 and Table 1).

Antibody treatment against SARS-CoV-2

As the global spread of SARS-CoV-2 continues to harm large populations, development of an antiviral antibody-based treatment could effectively produce a passive immunity against viral infection. Neutralizing antibodies secreted by B cells are potent in the antiviral immune defense system as they last longer compared to T cell memory [81]. Previously, we along with others, have shown that neutralizing antibodies are more efficient in priming CD8+ T cells and viral control with minimal immunopathology [82, 83]. Several studies carried out using various animal models indicate that neutralizing antibodies targeting the spike (S) protein of SARS-CoV is efficient in protecting against disease by directly reducing viral titers in the lungs [84-86]. SARS-CoV can elicit both humoral and cellular immune response as high levels of neutralizing antibodies, and virus-specific T cell responses have been detected in patients who have successfully recovered from this infection [86-88]. Neutralizing antibodies, which are capable of targeting RBD in spike protein or antibodies that bind to the ACE-2 can effectively block the entry of the virus and improve the outcome of the infection. In addition, antibodies that recognize epitopes within the RBD could prevent the virus from attaching to its receptor. In line with this, an antibody that had previously shown binding to epitopes upstream of the RBD prevented the SARS-CoV entry by inhibiting post-binding events [89]. Although recent studies report the development of few SARS-CoV-2 specific neutralizing antibodies, the previous research and data generated for SARS-CoV and MERS-CoV can be used to identify effective monoclonal antibodies against SARS-CoV-2 [90]. To this end, CR3022, a SARS-CoV-specific human monoclonal antibody, showed potent binding only to the RBD of SARS-CoV-2, which leaves the ACE-2 receptor to target for combinational antibody therapy [91]. One of the most recent studies identified 47D11 H2L2 as a potent monoclonal antibody (mAb) showing an effective inhibition of the pseudotyped Vesicular Stomatitis Virus (VSV) SARS-CoV-2 infection by an unknown mechanism [92]. However, literature on RBD-targeting antibodies suggests that the most likely mechanism could be antibody-mediated inactivation of the spike (S) protein [92]. In addition, the combination of the mAbs identified from memory B cells of SARS-CoV infected individual showed an effective cross-neutralization of SARS-CoV-2 [93]. Similarly, two SARS-CoV-2 specific mAbs CA1 and CB6 isolated from a convalescent COVID-19 patient demonstrated potent neutralization activity *in vitro* [94]. Therefore, antigen cross-reactivity and complete cross-neutralization of the live virus must be analyzed for immunogen design and vaccine development, and the use of a combination of neutralizing antibodies could be a better strategy to nullify escape mutants.

Considering the severity and urgency of the current situation, critically ill or high-risk patients infected with SARS-CoV-2 require immediate treatment options. A potentially useful approach could be the use of intravenous immunoglobulin (IVIg) pull of IgG from fully recovered donors from the same city or area to neutralize the virus in patients effectively [95]. According to present knowledge on the treatment of the viral infections, administration of convalescent plasma or hyper-immune immunoglobulin from the patients who have successfully recovered from SARS-CoV-2 infection and are without detectable levels of viral titers in sera is likely able to reduce the viral load and mortality in infected patients [85, 96]. In this scenario, the administration of convalescent plasma containing neutralizing antibodies in patients infected with SARS-CoV-2 improved their health status within 2 to 5 weeks, with reduction in body temperature (within three days) and negative viral loads (within 12 days)

Table 1. Selected drugs in use and suitable for the possible treatment of SARS-CoV-2

Type of Intervention	Medicine/ Treatment	Method/ Technique	Mechanism of Action	Reference
Antibody therapy	47D11	In vitro study	Probably antibody meditated inactivation of spike protein	[92]
	Convalescent plasma	Patient data	Neutralizes viral particles	[96, 97]
	Human mAb CR3022	In vitro study	Binds to the RBD	[91]
	S309, CA1, CB6	In vitro study	Engaging the RBD of the S glycoprotein	[93, 94]
Antiviral/ Inhibitor of target receptor	Chloroquine	In vitro study and reports	Blocking viral replication by changing endosomal pH levels	[104-107]
	Remdesivir	In vitro study and patient data	A nucleotide analogue blocking viral entry as well as reducing viral copy numbers in the cell supernatant	[104, 122, 123]
	Azvudine	Clinical trials and report	Nucleoside reverse transcriptase inhibitor	[198]
Inhibitor of target receptor	Camostat mesylate	In vitro study and report	A serine protease inhibitor blocking TMPRSS2 and suppressing viral entry into the cell	[75, 115, 116]
	Nafamostat mesylate	In vitro study and report	TMPRSS2 inhibitor	[104, 116]
	Losartan and Telmisartan	Patient data and clinical trial	AT1R inhibitor	[109, 110]
Inhibitor of Endocytosis	Baricitinib	Using Benevolent-AI graph	Janus Kinase inhibitor binding to AP2-associated protein kinase 1 (AAK1)	[121]
	Imatinib, GNF2, GNF5	In vitro study	an Abelson (Abl) kinase inhibitor blocking virus-cell or cell-cell endocytic fusion and viral entry into cytoplasm	[119, 120]
Antiviral	Favipiravir	In vitro studies and report	Inhibiting RNA polymerase activity resulting in inhibition of viral replication	[138-141]
	IDX-184, Sofosbuvir, Ribavirin	Sequence analysis and molecular docking	Antiviral agents	[130]
	Melatonin	Report and suggestion	Antiviral agent	[151, 152]
	NHC (EIDD-1931)	In vitro and in vivo study	Ribonucleoside analogue reducing viral copy numbers	[124, 125]
	Niclosamide	In vitro studies and report	Antiparasitic, antiviral agent that suppresses viral replication	[131-133]
	Nitazoxanide	In vitro study	An antiprotozoal antiviral agent	[104]
	Tilorone	Patients data and in vitro study	Antiviral drug that boost serum interferon levels, and leukocyte and lymphocyte function	[136, 137]
Antiviral/ Proteolytic	Disulfiram	In vitro, in silico studies	Inhibit PL^{pro} protease	[154]
	Ebselen, TDZD-8, N3	Structure-assisted drug design, virtual screening	Inhibits M^{pro}	[161]
	Ledipasvir or Velpatasvir	Virtual screening	Inhibit 3C-like protease ($3CL^{pro}$)	[156]
	Lopinavir/Ritonavir, Arbidol	Patient data, and reported guideline	Inhibits the activity of the $3CL^{pro}$ protease results in decreasing viral load, boost lymphocyte counts	[126-129, 142, 155]
	Nelfinavir	Virtual screening and homology modeling	Inhibiting SARS-CoV-2 M^{pro}	[163]
	Atazanavir, Efavirenz, Ritonavir, Dolutegravir	Molecule Transformer-Drug Target Interaction (MT-DTI) model	Inhibiting SARS-CoV-2 3C-like proteinase ($3CL^{pro}$)	[164]
Anti-inflammatory/Antiviral	IFN-α/β	In vitro data	Inhibits viral replication, viral protein synthesis, assembly and release of progeny virus particles	[148]
	Tocilizumab	Patient data	IL-6 receptor antagonist improves ARDS	[175]
Antiviral/ Inhibitor of cathepsinmediated endocytosis	Teicoplanin	In vitro study	Preventing the entry of SARS-CoV-2-Spike-pseudoviruses into the cytoplasm	[118]

after transfusion [97]. However, a vital challenge of this method is the availability of enough samples, donors, and viral kinetics data. Developing highly specific antiviral monoclonal antibodies is an effective and safe way to prevent the spread of infectious diseases. However, an anti-SARS-CoV antibody response may be short-lived compared to SARS-CoV-specific memory CD8+ T cells, which can be detected up to 6 years post-infection [98, 99]. Although anti-SARS-CoV neutralizing antibodies are effective in controlling viral infection [100], pre-existing SARS-CoV-specific CD8+ T cell response in mice protected the host against a fatal second SARS-CoV infection due to an efficient effector/memory CD8+ T cell response that resulted in faster elimination of viral load in the host [101]. However, this approach requires an effective CD4+ T cell help and antibody response too [98, 101, 102]. Therefore,

the therapeutic outcome of the treatment with antibody or convalescent plasma depends on other effector functions and T cell help. Thus, immunotherapeutic approaches can be a breakthrough in the current pandemic situation by providing additional support through the administration of antibodies that bind to multiple epitopes in RBD as well as other regions that either can block the binding of the virus and its cellular receptor or neutralize the virus to minimize the mutant escape.

Inhibitors for target receptors

Inclusion of SARS-CoV in the host cell is associated with the binding of the spike (S) protein to its cellular receptor ACE-2 in the type II pneumocytes in the lungs. TMPRSS2, a type II transmembrane protease mediates cleavage of ACE-2, which facilitates the internalization and activation of the viral particle in the cell [74, 103]. Recently, it was discovered that SARS-CoV-2 binds to the receptor ACE-2 [68]. Therefore, targeting ACE-2 and/or TMPRSS2 are effective strategies for reducing viral invasion and replication of the virus in the host cells. Chloroquine, which is generally used in malaria treatment, showed a significant antiviral response against SARS-CoV-2 both prior and post viral infection [104]. Mechanistically it interferes with the terminal glycosylation of cellular receptor ACE-2, which blocks the virus-cell fusion [105]. Although there is sufficient preclinical evidence for the efficacy of chloroquine treatment, the clinical value of this drug in patients with SARS-CoV-2 infection and the drug dosage should be further evaluated in ongoing clinical trials [106-108]. Losartan and Telmisartan are angiotensin II type 1 receptor (AT1R) antagonists that are widely used in the clinic to treat hypertension and kidney disorders may limit the entry of SARS-CoV-2 into the cell and could help to reduce ARDS and aggressive inflammation [109, 110]. Patients with previous health conditions such as hypertension, heart disease, diabetes mellitus, chronic kidney diseases, as well as elderly patients receiving renin-angiotensin treatment or angiotensin-converting enzyme inhibitors (ACEIs), and angiotensin receptor blockers (ARBs) are not required to discontinue current treatment due to the increased expression of ACE-2 receptor in the bloodstream [111, 112]. ACEIs and ARBs do not lead to any complications associated with COVID-19 [113, 114]. Similarly, a TMPRSS2-targeting serine protease inhibitor Camostat mesylate efficiently blocked the entry of replication-deficient VSV carrying SARS-CoV-S protein, which is a licensed drug for oesophagitis and pancreatitis in Japan [75, 115]. Nafamostat mesylate, another clinically approved TMPRSS2 inhibitor, is also found to be effective in inhibiting the cell entry of SARS-CoV-2 [104, 116]. Collectively, preventing the binding of the viral particles by targeting the cell surface receptors can affect virus-cell fusion and viral invasion and may significantly improve the health status of COVID-19 patients.

Endocytosis blockers

Viral entry and subsequent replication in cells depend on the interaction between the viral envelope and the host cell membrane receptors. Following the binding of SARS-CoV-2 to the cell surface receptors, the virus requires exposure to host cytosol by the fusion of viral and cellular membranes by endocytosis, which is the formation of the endosome, internalizing viral particles surrounded by the cell membrane. Subsequently, the viral genome is released by endosomal acidification and exocytosis into the cytoplasm of the host cells [52]. A recent study has shown that cathepsin L mediated endocytosis transmits SARS-CoV-2 into the cell [80]. Therefore, agents that block the virus-cell or cell-cell endocytic fusion are potentially interesting candidates to suppress viral replication in patients infected by SARS-CoV-2. Teicoplanin, a glycopeptide antibiotic, was shown to be effective in blocking the entry of Ebola by inhibiting cell invasion, as well as both SARS-CoV and MERS-CoV by specifically inhibiting the activity of cathepsin L [117]. Teicoplanin was also shown to effectively inhibit the entry of SARS-CoV-2 spike pseudoviruses into the cytoplasm of A549, HEK293T, and Huh7 cells [118]. Coleman CM *et al.* showed Imatinib, an Abelson (Abl) kinase inhibitor, effectively blocked the entry of pseudotyped virions which expressed the S protein of SARS-CoV, and MERS-CoV [119]. Using the infectious bronchitis virus model, Sisk JM *et al.*,

have shown that Imatinib and two other Abl kinase inhibitors, GNF2 and GNF5, significantly reduced infectious bronchitis viral (IBV) levels by inhibiting virus-cell and cell-cell fusion events [120]. Baricitinib (a Janus Kinase inhibitor) a known regulator of endocytosis, which also inhibits AP2-associated protein kinase 1 (AAK1), and binds to cyclin G-associated kinase, could be trialed to reduce the viral entry into the cell and inflammation in patients infected with SARS-CoV-2 [121]. Together, blocking the host-based cellular process of pathogen internalization could be an effective method to impede the transmission of viral RNA into the host cytoplasm.

Antiviral agents/drugs

In the context of the rapid increase in the number of positive cases for SARS-CoV-2, assessing the benefits of current antiviral agents and drugs against this infection has become a great interest. Such drugs have an advantage over newly developed drugs due to their known pharmacokinetic and pharmacodynamics properties such as safety, toxicity, dosage, and treatment period. These already acquired data can save a significant amount of time in establishing the clinical potential of antiviral agents in COVID-19 patients. According to *in vitro* cytotoxicity assay, both Remdesivir and Nitazoxanide inhibited SARS-CoV-2 viral infection even at relatively modest levels [104]. Remdesivir, a nucleotide analog that inhibits viral RNA-dependent RNA polymerase (RdRp), effectively impeded viral replication upon entry into the cell [104, 122]. A recent study involving 1063 patients showed that compared to placebo, treatment with Remdesivir shortened the recovery period in patients infected with COVID-19 [123]. Besides, the ribonucleoside analog β-D-N4-hydroxycytidine (NHC, EIDD-1931) and its orally bioavailable prodrug (EIDD-2801) has produced efficacy against MERS-CoV, SARS-CoV, and SARS-CoV-2 with minimal cytotoxicity in human airway epithelial cell cultures [124, 125]. NHC also has an increased sensitivity to mutant strains of mouse hepatitis coronavirus (MHV) as well as genetically distinct Bat-CoV compared to Remdesivir due to its ability to induce high genetic mutation rates in the viral genome [124, 125]. Previously, a combination treatment of Lopinavir/Ritonavir and Ribavirin had shown better outcomes in SARS-CoV patients, which resulted in a steady decrease in viral loads on day 5, as well as increased lymphocyte counts after the treatment [126]. Following this approach, three out of four patients infected with SARS-CoV-2 received Lopinavir/Ritonavir, Arbidol, and traditional Chinese medicine (Shufeng Jiedu Capsule, SFJDC) showed improved pneumonia symptoms [127]. Lopinavir/Ritonavir (Kaletra, AbbVie) treatment for SARS-CoV-2 patients also showed a significant reduction of the viral load on the first day after treatment [128]. However, in a randomized, controlled, open-label trial with Lopinavir/Ritonavir in hospitalized patients with COVID-19 no benefit was observed [129].

Furthermore, anti-hepatitis C virus drugs targeting RdRp that showed potent antiviral activity against SARS-CoV-2 includes IDX-184, Sofosbuvir, and Ribavirin [130]. Niclosamide, an anthelminthic drug reported to have a strong anti-SARS-CoV activity at a moderate concentration. Considering its extensive antiviral properties, Niclosamide would be a promising candidate to study its effectiveness against SARS-CoV-2 [131-133]. Also, Ciclesonide, a corticosteroid approved by the FDA for the treatment of asthma and allergic rhinitis, is effective in suppressing viral replication by targeting NSP15 of SARS-CoV-2 at significantly lower concentrations than Camostat and Lopinavir [134, 135]. Tilorone, a broad-spectrum antiviral drug tested against respiratory tract infections in humans in Russia and neighboring countries, possesses high efficacy and a better IC_{50} value compared to chloroquine, which could be further analyzed against SARS-CoV-2 infection [136, 137]. Favipiravir is also known to effectively inhibit RNA polymerase activity and has already been shown to be effective against several RNA viruses that could have an advantage in inhibiting the replication of the SARS-CoV-2 virus in the host cell [138-140]. Patient data suggested that Favipiravir together with interferon-α showed faster SARS-CoV2 viral clearance and a better improvement rate in chest imaging with fewer adverse reactions than patients treated with Lopinavir/Ritonavir plus interferon-α [141]. A retrospective trial in China involving 69 patients infected with SARS-CoV-2 showed that treatment with Arbidol, which has been used to treat influenza A/B virus infections, showed a tendency of improving the condition of the

patients and reduced the fatality rate. In contrast, the use of corticosteroids deteriorated the outcome [142].

Type I interferons (IFN-α/β) are potent antiviral agents; they represent the first antiviral cytokines secreted within hours after the viral infection and essential for activating an effective antiviral CD8+ T cell response leading to rapid control of viral spread [143, 144]. Previous studies showed that human interferons have a high antiviral potential against SARS-CoV and MERS-CoV [145, 146]. Interferon-α2b, along with Ribavirin as well as interferon-β acting alone or with the combination of mycophenolic acid, showed a significant reduction of the viral titers of SARS-CoV and MERS-CoV, respectively [145-147]. In line with a recent study that showed that the pre-treatment of Vero cells with IFN-α and IFN-β at a concentration of 50 international units (IU) resulted in an approximate four-fold reduction in viral titers of SARS-CoV-2 [148]. RNA viruses are potent in triggering the type I interferon signaling pathway, which encodes hundreds of interferon-stimulated genes (ISGs) that can target several steps of the viral life cycle, including entry, uncoating, transcription, translation, assembly, or exocytosis [149, 150]. One of the advantages of such antiviral drugs and reagents is that they can be easily accessible with known pharmacological properties. Another anti-inflammatory and anti-oxidative molecule, Melatonin, with a high efficacy profile and well-known antiviral properties, could also be useful for patients infected with SARS-CoV-2 [151, 152]. In summary, targeting distinct steps of viral replication could be useful in limiting viral load and subsequent spread of the virus, leading to an effective antiviral T-cell response and could improve the outcome of the disease.

Proteolytic agents

Following successful penetration of SARS-CoV-2 into the cytoplasm of the cell by attachment to the cell surface and subsequent ingestion, the virus releases its genomic material into the cytoplasm of the host to translate the viral polyproteins pp1a and pp1ab. A pair of proteases, $3CL^{pro}$ and PL^{pro}, mediate this process and translate the product from viral RNA into the protein components necessary for the generation of fully functional virus that is ready to emerge and replicate (Fig. 3) [153]. Disulfiram, an alcohol-aversive drug was shown to inhibit PL^{pro} protease of MERS-CoV and SARS-CoV [154]. Furthermore, it is also known that Lopinavir/Ritonavir inhibits the activity of the $3CL^{pro}$ protease and is currently studied to treat SARS-CoV-2 patients [129, 155]. Another study using the three-dimensional model of the SARS-CoV-2 3C-like protease ($3CL^{pro}$), proposed 16 potent purchasable drugs, including Ledipasvir or Velpatasvir, for treatment [156]. Additionally, it is also well known that lipid rafts serve as a platform in trafficking the virus into the cell [157-159]. In the case of the coronavirus IBV model, depletion of cholesterol activity by the treatment with methyl-β-cyclodextrin (MβCD) or Mevastatin significantly suppressed IBV infection by impairing the attachment of the virus to the cell surface [160].

In order to discover drug leads that target the main protease for therapeutic use, a group at Shanghai Tech University, Shanghai, China, initiated an integrated structure-assisted drug design, virtual drug screening, and high-throughput screening program to transform existing drugs into therapies against the SARS-CoV-2 M^{pro} [161]. M^{pro}, a crucial enzyme of the coronavirus, acts as a mediator of viral replication and transcription, making it an interesting target for treatment [162]. After analyzing over 10,000 different compounds, Ebselen, and N3 showed potent anti-SARS-CoV-2 activity in cell-based assays [161]. This new approach could employ an efficient screening strategy and establish a new paradigm for the rapid discovery of drug targets with the potential to develop a clinical response to viral infectious diseases [161]. Similarly, utilizing homology models based on the SARS M^{pro} structure and docking score suggested that Nelfinavir may be a potential inhibitor against SARS-CoV-2 M^{pro} [163]. Another approach that utilizes deep learning Molecular Transformer Drug-Target Interaction (MT-DTI) model to target viral proteins of SARS-CoV-2 showed that Atazanavir, an antiretroviral drug which is in use to treat human immunodeficiency virus (HIV), has high inhibitory potency against the 3C-like proteinase of SARS-CoV-2 compared to Remdesivir, Efavirenz, Ritonavir, and Dolutegravir [164]. In summary, patients infected with SARS-CoV-2

might benefit from treatment with drugs that inhibit the action of the proteases $3CL^{pro}$ and PL^{pro} by lowering the viral load.

Blocking the cytokine responses

A tight balance between innate immune activation and resulting adaptive immune responses is crucial for regulating viral control. Dysregulation of this tightly controlled axis can result in an overwhelming immune reaction resulting in severe immunopathology [165]. A deregulated immune response can lead to hyperinflammatory conditions, which patients with pre-existing health problems may be potentially at higher risk for. The average fatality rate of elderly patients, cancer patients, patients with other health conditions, and males compared to females infected with SARS-CoV-2 is significantly higher than that of infected young patients [166-169]. Recently, many studies have shown that some patients infected with SARS-CoV-2 can develop ARDS. In many cases, this leads to multi-organ failure due to cytokine storm. Several studies have reported that patients with severe symptoms more often had dyspnea, lymphopenia, and hypoalbuminemia with severe immunopathology than patients with mild symptoms due to elevated levels of ALT, AST, and cytokines such as interleukin (IL)-2R, IL-6, IL-10, and TNF-α with a reduction in T cell numbers [170-172].

A separate study conducted by the Chinese Academy of Science, involving 33 patients, showed that infection with SARS-CoV-2 induced rapid activation of CD4+ T cells, which proliferated and differentiated into T helper 1 (T_h1) cells secreting cytokines including IL-6, IFN-γ, and GM-CSF [173, 174]. Therefore, the use of Tocilizumab (an IL-6 receptor antagonist) approved for the treatment of rheumatoid arthritis (RA), and glycyrrhetinic acid (an IL-6 blocker) were reported to improve the health condition of critically ill patients with elevated levels of IL-6 [173, 175]. Sarilumab, a monoclonal antibody against the IL-6 receptor approved for treating moderate to severe active RA may be another candidate for the treatment of COVID-19 patients with ARDS [176]. Other cytokines and chemokines showed a dramatic increase in infected patients include IL-1, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12, IL-17, IFN-γ, TNF-α, monocyte chemoattractant protein (MCP), IFN-gamma-inducible protein-10 (IP-10). This induction of cytokines together with significant alterations in the number of leukocytes presumably lead to the development of ARDS [2, 173, 177-180]. While IL-37 and IL-38 are potent suppressors of IL-1β, other proinflammatory IL-family members may improve viral load and inflammation with the potential to function as an additional therapeutic strategy to treat SARS-CoV-2 patients [181]. A Chinese traditional medicine Lianhuaqingwen has also been shown to lead to a significant reduction in SARS-CoV-2 viral replication and pro-inflammatory cytokines (IL-6, TNF-α, CCL2/MCP-1, and CXCL-10/IP-10) levels by *in vitro* assays [182]. Therefore, combinations of antibodies capable of blocking these inflammatory cytokines could prevent the development of an ARDS. This may improve the fatality rate in elderly patients and in those with secondary health conditions.

Vaccine development against SARS-CoV-2

Although several studies are demonstrating the success of vaccination as a treatment for SARS-CoV, it is enigmatic that there are currently no approved vaccines or therapeutics to treat coronavirus infections that can induce protective neutralizing antibodies. A study has shown that intranasal administration of the inactivated vaccine candidate, the RBD region of the Fc domain of human IgG1 (RBD-Fc) fused with the SARS-CoV S protein and recombinant adeno-associated virus (RBD-rAAV), induced both potent anti-SARS-CoV neutralizing antibodies and a healthy cytotoxic T-cell (CTL) response [183]. Similarly, the administration of a vaccine based on parainfluenza virus 5 (PIV5), expressing the MERS-CoV envelope spike protein induced a potent neutralizing antibody and T cell response, and protected mice from a lethal MERS-CoV challenge [184]. Taken together, these data indicate that it is possible to use existing knowledge and test the previous vaccine candidates from SARS-CoV research to validate their potency to prevent SARS-CoV-2 infection. The SARS-CoV-2 RBD region binds explicitly to the ACE-2 receptor with high affinity on the host cell surface. The CoV spike (S) protein is essential for viral invasion of the host, and therefore the SARS-CoV-2 spike protein

can be useful in neutralizing SARS-CoV-2 infection [68, 185]. Accordingly, it has been shown that the SARS-CoV-2 RBD protein efficiently blocked the entry of the SARS-CoV-2 pseudovirus into human ACE-2 expressing 293T cells [185]. As a result of the phylogenetic similarity between SARS-CoV and SARS-CoV-2, anti-SARS-CoV-specific antibodies were also potent in neutralizing SARS-CoV-2 pseudovirus infection [185]. Intracutaneous delivery of the SARS-CoV-2 S1-subunit vaccine into mice by microneedle array (MNA) generated significant anti-SARS-CoV-2 specific neutralizing antibody response within two weeks post-immunization [186]. A recent study showing the development of purified inactivated SARS-CoV-2 virus vaccine candidate (PiCoVacc) generated neutralizing antibodies against ten representative SARS-CoV-2 strains, demonstrating its broader neutralizing capacity [187]. In addition, a DNA-based vaccine candidate INO-4800, targeting the SARS-CoV-2 S protein, led to the generation of anti-SARS-CoV-2 neutralizing antibodies that block the interaction of the spike (S) protein with the ACE-2 receptor and induced a potent cytotoxic T cell response [188].

At the moment, several research institutes and biopharma industries worldwide are in the race to develop a SARS-CoV-2 vaccine, while many vaccine candidates are currently in clinical trials (phase II and III) [189]. Early human trials confirm that the vaccine developed by the University of Oxford (Oxford COVID Vaccine Trail Group, UK) and Moderna Therapeutics (mRNA-1273 Study Group, USA) triggered strong anti-SARS-CoV-2 antibody responses and cellular immune responses without serious adverse events [190, 191]. Various vaccine development strategies are being tested, including live attenuated vaccines, vaccines based on viral vectors, recombinant vaccines based on proteins and DNA, and mRNA vaccines [192-194]. Vaccines can potentially trigger immune hyperactivation, which can cause severe immunopathology due to exhilarating T cell activation. Therefore, due to the novelty of the strain, all vaccine candidates must undergo rigorous testing, including toxicology, immunogenicity, safety, and efficacy, and need to follow ongoing good manufacturing practices (cGMP) to meet the FDA rules and regulations. Given the urgency of the current situation, even with a probable acceleration of some approval and licensing steps, it may take 12-18 months before the vaccine is available.

Herd immunity

Herd immunity or the herd effect is the indirect protection of non-immune individuals from an infectious disease or outbreak. This is due to the presence of a large part of the population that is immune to infection through vaccination or the presence of an immunological memory because of the previous infection [195]. In a population where many individuals are immune, herd immunity protects the transmission of disease by interrupting the chain of virus spread [196]. A person can become immune through vaccination or due to recovery from a previous infection or immunosuppression. This leads to a steady decline in the infection rate due to a decrease in the basic reproduction number (R_0). The R_0 of COVID-19 is estimated to be between 2.39 and 4.13 [197]. Considering that other coronaviruses do not provide lifelong immunity, developing a vaccine against COVID-19 can be considered essential. Vaccinating or immunizing several members of the population against SARS-CoV-2 can be a reliable and potentially quicker way to re-open the economy and bring back the normalcy that has been lost due to the spread of this virus.

Outlook and future prospective

The COVID-19 pandemic highlights that existing treatment options for potentially life-threatening zoonotic coronavirus infections remain limited. Although the previous outbreaks of SARS in 2003 and MERS in 2012 have triggered significant research efforts, there are currently no direct treatments or vaccines available against any zoonotic coronavirus that may resurface in the future and pose a threat to global public health and the world economy. The discovery of broad-spectrum therapeutic options that can reduce the consequences of human coronavirus infection remains a significant challenge ahead. As our understanding

of the pathogenesis of newly emerging coronaviruses continues to grow, the possibilities for the rational development of therapeutics targeting viral replication or immunosuppression continues to increase.

In this review, we have summarized the current state of knowledge on the origin, zoonotic transmission, pathophysiology, and genome of the novel SARS-CoV-2. In detail, we have also discussed the virus- and host-based treatment options reported in various studies targeting different stages of the viral life cycle. Most strategies are based on the use of therapies aimed to treat different types of diseases, viral infections, and the suppression of specific signaling pathways in the infected cell. The so far collected preclinical and COVID-19 patient data show that the use of antiviral drugs in combination with anti-inflammatory agents has the potential to emerge as a successful strategy for the treatment of young and elderly individuals as well as patients with ARDS. Although progress has undoubtedly been made in the identification of several vaccine candidates by leading pharmaceutical companies and research institutes to develop potential vaccines and antiviral therapies against SARS-CoV-2, more research and rigorous testing options are needed to advance the development of these candidates [189].

Clinical trials were quickly initiated when the status of the virus had elevated to a pandemic, and some of the leading candidates developed for alternative applications were approved in a fast-track procedure for the treatment of SARS-CoV-2. Though some of these therapies are already showing promising results in the early stages of trials, the results must be closely monitored over a specified period. The drugs currently in use specifically target the replication cycle of the virus, and those based on immunotherapeutic approaches aim either to enhance the innate antiviral immune response or to reduce inflammatory damage caused by dysregulated immune reactions. The effects of vaccines and therapeutic antibodies specifically directed against SARS-CoV-2 also need to be studied, as this is the long-term solution providing immunity against SARS-CoV-2 infection. In addition to current approaches and strategies, research must be encouraged, and facilities should be made available to study and prevent the zoonotic transmission of viruses from animals to humans and the re-emergence of current strains. Efforts must be made to collect and study wild viruses and their potential for zoonotic transmissions or transmission to the host, and they should be screened for pathogenicity in advance, as this could be a way to avoid future pandemics.

Abbreviations

2019-nCov (Novel coronavirus 2019); $3CL^{pro}$ (Chymotrypsin-like protease); Abl (Abelson kinase inhibitor); ALT (Alanine aminotransferase); ARDS (Acute respiratory distress syndrome); AST (Aspartate aminotransferase); CCL2 (C-C Motif Chemokine Ligand 2); COVID-19 (Coronavirus Disease 2019); CoVs (Coronaviruses); CXCL10 (C-X-C motif chemokine 10); E (Envelope); ER (Endoplasmic reticulum); ERGIC (Endoplasmic reticulum Golgi intermediate compartment); hACE-2 (Human angiotensin-converting enzyme 2); hDPP4 (Human dipeptidyl peptidase 4); HE (Hemagglutinin-esterase protein); IBV (Infectious Bronchitis virus); IFN-α (Interferons α); IFN-β (Interferons β); IL6 (Interleukin 6); IL-8 (Interleukin 8); M (Membrane); mAb (Monoclonal antibody); MHV (Mouse hepatitis coronavirus); MNA (Microneedle array); M^{pro} (Main Protease); MβCD (Methyl-β-cyclodextrin); N (Nucleocapsid proteins); NTD (N-terminal domain); ORF (Open reading frame); PIV5 (Parainfluenza virus 5); PL1, 2^{pro} (Papain-like proteases); RBD (Receptor-binding domain); RdRp (RNA-dependent RNA polymerase); S (Spike protein); ssRNA (Single stranded RNA); TMPRSS2 (Transmembrane protease serine 2); TNF (Tumor necrosis factor).

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Author contributions

AMP initiated and designed the review. AMP and VK collected literature, prepared figures, wrote the article, and finalized the draft. JRG was involved in discussing the literature and reviewed final draft.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors declare no competing financial interest.

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