REVIEW

An outlook on potential protein targets of COVID-19 as a druggable site

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Abstract

Background SARS-CoV-2 which causes COVID-19 disease has started a pandemic episode all over the world infecting millions of people and has created medical and economic crisis. From December 2019, cases originated from Wuhan city and started spreading at an alarming rate and has claimed millions of lives till now. Scientific studies suggested that this virus showed genomic similarity of about 90% with SARS-CoV and is found to be more contagious as compared to SARS-CoV and MERS-CoV. Since the pandemic, virus has undergone constant mutation and few strains have raised public concern like Delta and Omicron variants of SARS-CoV-2.

Objective This review focuses on the structural features of SARS-CoV-2 proteins and host proteins as well as their mechanism of action. We have also elucidated the repurposed drugs that have shown potency to inhibit these protein targets in combating COVID-19. Moreover, the article discusses the vaccines approved so far and those under clinical trials for their efficacy against COVID-19.

Conclusion Using cryo-electron microscopy or X-ray diffraction, hundreds of crystallographic data of SARS-CoV-2 proteins have been published including structural and non-structural proteins. These proteins have a significant role at different aspects in the viral machinery and presented themselves as potential target for drug designing and therapeutic interventions. Also, there are few host cell proteins which helps in SARS-CoV-2 entry and proteolytic cleavage required for viral infection.

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Graphical abstract
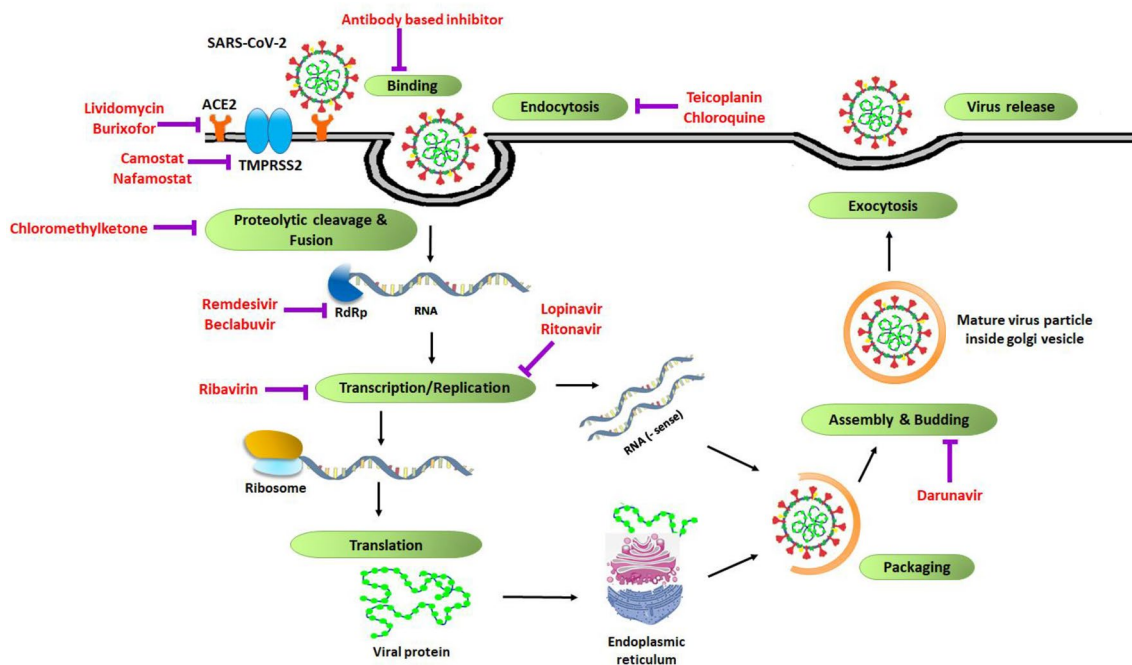
Abbreviations

CCDC	Chinese Centre for Disease Control and Prevention
2019-nCoV	2019 Novel coronavirus
WHO	World Health Organisation
ICTV	International Committee of Taxonomy of Viruses
SARS-CoV-2	Severe acute respiratory syndrome corona-virus 2
COVID-19	Corona virus disease 19
MERS	Middle eastern respiratory syndrome
VOC	Variants of concern
VOI	Variants of interests
RBD	Receptor binding domain
HCoV	Human coronavirus
ARDS	Acute respiratory distress syndrome
S protein	Spike protein
M protein	Membrane protein
E protein	Envelope protein
nsps	Non-structural protein
PL^{pro}	Papain-like protease
3CL^{pro}	3-Chymotrypsin-like protease
M^{pro}	Main protease
ACE2	Angiotensin-converting enzyme 2
DPP4	Dipeptidyl peptidase 4
TMPRSS2	Transmembrane protease serine 2
FP	Fusion peptide
Ub	Ubiquitin
FDA	Food and Drug administration
RdRp	RNA dependent RNA polymerase
NiRAN	N-terminal extension nidovirus-unique RdRp-associated nucleotidyl transferase
HAT	Human airway trypsin-like protease
HIV	Human immunodeficiency virus
CRISPR	Clustered regularly interspaced short palindromic repeats
LNP	Lipid nanoparticles
NIAID	US National Institute of Allergy and Infectious Diseases
aAPC	Artificial antigen presenting cells
VLP	Virus-like particles
CEPI	Coalition for Epidemic Preparedness Innovations
mAbs	Monoclonal antibodies

Introduction

Coronavirus is a new name for chaos that has developed since December 2019 with pandemic features and proved to be a threat to humans claiming millions of lives till now. The 2019 new coronavirus marked its onset from the Huanan

Seafood Wholesale Market, Wuhan city, a Hubei province in China. 27 cases of pneumonia with unknown etiology were reported from this city on 31st December 2019. These patients who worked at or live around the seafood market showed the clinical symptoms of fever, dyspnea, dry cough and bilateral lung infiltrates on imaging [1]. The virus was identified from swab samples of patient's throat conducted by the Chinese Centre for Disease Control and Prevention (CCDC) as novel beta coronavirus (a member of beta group of coronavirus) on 7th January 2020 and initially named as 2019-nCoV (2019 novel coronavirus) by World Health Organisation (WHO) [2]. Later, International Committee of Taxonomy of Viruses (ICTV) named this novel virus as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [3]. As the infectious diseases gradually spread worldwide and became a massive global outbreak, WHO declared the virus as sixth Public Health Emergency of International Concern on January 30th, 2020. WHO officially named this disease as COVID-19 (where CO stands for corona, VI for virus, D for disease and 19 represents the year 2019 in which it first emerged) on February 2020 [2].

Origin and progress of COVID-19

Wuhan is an emerging business hub of China and the seafood market trades in fish and variety of live animal species including poultry, bats, snakes and marmots. The outbreak of novel coronavirus gradually affected more than seventy thousand individual and killed more than eighteen hundred within the first fifty days of pandemic [4]. It was suggested from the genetic sequence of virus that the patients infected with coronavirus in Wuhan, China may have visited this market or may have consumed infected animals as source of food. While cases started increasing exponentially with no record of visiting the seafood market, thus, suggesting the virus having strong potential for human to human transmission [5]. Environmental samples from the Huanan sea food market was taken and tested positive, suggesting that the virus originated from there and likely there is a chance of transmission of pathogens from animals to human [6]. According to a genomic study, it was claimed that the role of Huanan seafood market in propagating of disease is not clear and suggested that the virus may be introduced from an unknown location into seafood market where it spread rapidly [7]. SARS-CoV-2 reported to be phylogenetically related to SARS-like bat CoV, with a sequence similarity of more than 90%, thus, suggesting that bats could be the key reservoir or zoonotic source [8]. Until recently, Lam et al. isolated Malayan pangolin CoV genomes and found 85.5–92.4% similarity to SARS-CoV-2, hence, concluded that it may be the intermediate host for SARS-CoV-2 [9]. Nonetheless, bats either directly transmit SARS-CoV-2

virus or requires an intermediate host to cause infection-this theory needs to be confirmed so that zoonotic transmission patterns could be established and understood [10]. The novel coronavirus has since spread overseas in other regions in Asia, North America, South America, Europe, Africa and Oceania and thus, making it global pandemic. The new coronavirus outbreak has not only caused the downfall of economy in all countries but also brought down medical and public health infrastructure in a tight spot [2]. The novel coronavirus has proven to be more contagious having enhanced transmission rate than SARS and MERS (middle eastern respiratory syndrome) [11].

Novel coronavirus 2019 (SARS-CoV-2)

Coronavirus are large group of viruses that mainly causes infection in respiratory and gastrointestinal tract and present in various species of birds, bats, snakes and other mammals. Coronavirus are named so due to the presence of crown-like bulbous appearance ("corona" means crown) [3]. SARS-CoV-2 belong to the subfamily *Orthocoronavirinae* in *Coronaviridae* family and order *Nidovirales* that consists of enveloped, positive sense ssRNA (single-stranded) genome [12]. They are spherical in shape with club-shaped spikes and a particle size of 125 nm as shown in Fig. 1a.

The subfamily *coronavirinae* are further subdivided on the basis of serological pattern into four genera: (a) *alphacoronavirus* that includes human coronavirus (HCoV)-229E and HCoV-NL63; (b) *betacoronavirus* includes severe acute respiratory syndrome (SARS-HCoV), HCoV-OC43, HCoV-HKU1 and MERS-CoV; (c) *gamma-coronavirus* contains viruses of whales and birds and; (d) *delta-coronavirus* consists of viruses of pigs and birds. SARS-CoV-2 along with SARS-CoV and MERS belong to *beta-coronavirus* [13]. The life cycle of SARS-CoV-2 infection is illustrated in Fig. 1b.

On the basis of genomic analysis, SARS-CoV-2 showed > 90% homology with bat SARS-like -CoVZXC21, 82% with human SARS-CoV and 50% with MERS-CoV [14]. SARS spread out in 2002 from Guangdong province of south-eastern China, an epidemic with unusual pneumonia and acute respiratory distress syndrome (ARDS) cases affecting 26 countries and affected 8096 people with 774 deaths by 2004. A decade later, similar case of respiratory tract infection came to light in middle east countries (Saudi Arabia, UAE) in 2012 affecting 27 countries in total including US and Malaysia with 2428 cases and 838 deaths [11]. Table 1 summarizes few differences between SARS-CoV-2, SARS and MERS.

SARS-CoV-2 consists a genome of about 20–30 kb in size, encoding a large non-structural polyprotein which are proteolytically cleaved and thus, generate 15/16 proteins, accessory proteins (ORF3a, ORF6, ORF7, ORF8, ORF9) as well as four structural proteins. It also contains 14 open
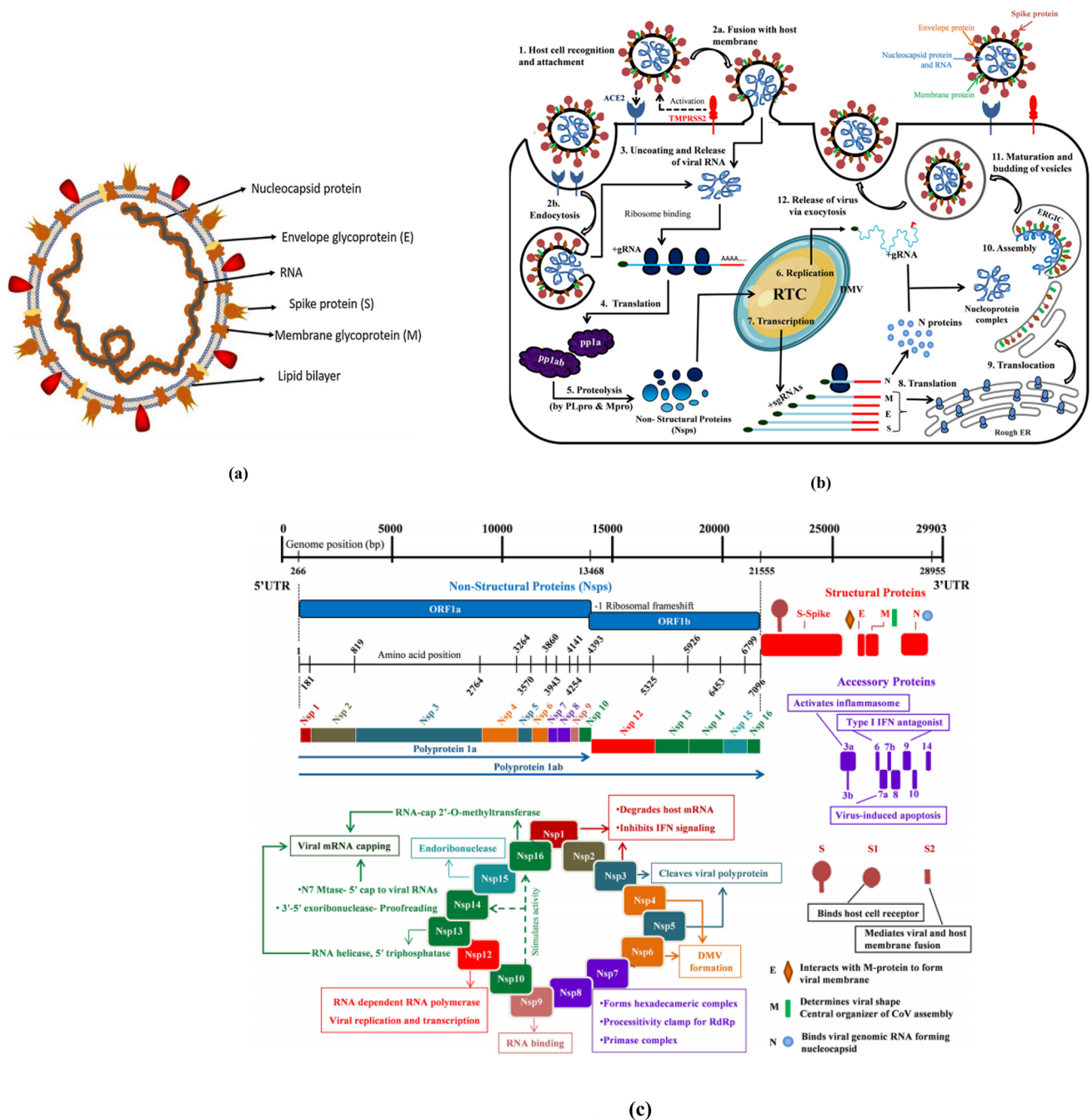
(a)

(b)

(c)

Fig. 1 a Structure of respiratory syndrome causing human coronavirus. This is an Open Access article distributed under the terms of the Creative Commons Attribution Licence (http://creativecommons.org/licenses/by/2.0), which permits unrestricted use, distribution and reproduction in any medium provided the original work is properly cited. Copyright@ Elsevier [11]. b The infection cycle of SARS-CoV-2 inside the host cell. The sequence of events, from host cell recognition through the release of new virion, is represented graphically as steps 1 to 12. Reprinted with permission from [91]. c Genome organization of the SARS-CoV-2. The viral genome encodes 16 Non-structural proteins (Nsps) required for replication/transcription along with the structural proteins required for the assembly of new virions. The proteins are marked below the genome with their respective coding regions. A short description of the functions of different proteins is also shown. Reprinted with permission from [91]

reading frames [14]. At the 5' terminal region of the genome, ORF1 and ORF2 encode non-structural proteins (nsps) important for virus replication and 3' terminal encodes

structural proteins. The 4 structural proteins are outer spike glycoprotein (S), membrane (M), envelope (E) and nucleoprotein (N) which are important for virus assembly and

Table 1 Characteristics and features of SARS-CoV-2, SARS-CoV and MERS

Features	SARS-CoV-2	SARS-CoV	MERS-CoV
Emerging location	Wuhan, China (December 2019)	Guangdong, China (November 2002)	Jeddah, Saudi Arabia (2012)
Possible Animal reservoir/ Hosts	Bats, Pangolins	Bats, Palm civets	Bats, Camels
Incubation time	2–14 days	2–7 days	2–15 days
Receptor	Angiotensin-converting enzyme 2 (ACE2)	ACE2	Dipeptidyl peptidase 4 (DPP4)
Presence of cleavage sites	Furin-like cleavage site, TMPRSS2 cleavage site	Trypsin, TMPRSS2 cleavage site	Furin-like cleavage site, Cathepsin L, TMPRSS2 cleavage site
Clinical symptoms	Dry cough, fever, shortness of breath	Fever, headache, dry cough, malaise, muscle aches, difficulty in breathing	Fever, cough, fatigue, chills, vomiting, diarrhoea, shortness of breath
Total infected individuals	534,245,759	8096	2428
Total deaths	6,317,736	774	838
Mortality rate	3.4%	9.5%	34.5%
Reproductive number (R_o)	3–6	1.7–1.9	< 1.0

infection. SARS-CoV-2 consists of 16 nsps encoded by largest gene, *orf1ab* as well as by *orf1a* gene [15]. SARS-CoV-2 genomic organisation is depicted in Fig. 1c.

It also expresses other polyproteins and membrane proteins, such as RNA polymerase, papain-like protease (PL[pro]), 3-chymotrypsin-like protease (3CL[pro]) and helicase [14]. To gain entry into the human cell, SARS-CoV-2 and SARS-CoV recognizes angiotensin-converting enzyme 2 (ACE2) as a key receptor while MERS requires dipeptidyl peptidase 4 (DPP4). Some other variations have been seen by researchers between SARS-CoV-2 and SARS-CoV. It is marked by the absence of 8a protein and change in number of amino acids in 3c and 8b protein in SARS-CoV-2 [16].

Current status of COVID-19

Antarctica was the only continent free of novel coronavirus but at the end of December 2020, 36 COVID-19 cases were reported. Scientists and WHO are now accessing the risk of potential transmission of coronavirus from humans to Antarctic wildlife and taking appropriate measures to protect the wildlife population (seabirds, penguins, seal, dolphins, whale) [17]. Since its emergence, the virus has undergone some mutations to adapt itself to various environmental factors like weather and population. These mutations of concern have raised public alarm. These mutations are related to proteins such as spike, envelope and membrane. Center for Disease Control and Prevention has classified few of them as variants of concern (VOC) and variants of interests (VOI). The D614G mutation at amino acid position 614 in S protein was reported in the early phase of the pandemic raised public concern. D614G mutant transmitted quickly enough to became globally dominant by June-July 2020 [18]. Due to high evolutionary rate of the virus, its transmissibility has

reported to be increased. Around September 2020, another mutation emerged from South Africa with a new variant designated as B.1.351 (Beta variant, VOC) or 501Y.V2 and number of COVID-19 cases started to rise rapidly. In this variant, the mutation, N501Y, was seen in the receptor binding domain (RBD) of S protein along with E484K mutation. It was also reported that due to mutation, the binding efficiency of the virus to cell surface receptor has drastically increased and the virus can also reduce its neutralization against LY-CoV016 (monoclonal antibody); this strain has already spread over 20 countries [19]. Another new variant B.1.1.7 (Alpha variant, VOC) with N501Y mutation similar to 501Y.V1 reported to have arisen independently in SARS-CoV-2 strain in the UK and found to have 70% more transmission capacity [20]. In B.1.1.7 variant, besides N501Y, mutations in 17 other amino acids (including 8 in S protein) and a deletion at amino acid positions 69 and 70 in S protein was also reported. In early 2021, this variant rapidly spread around more than 100 countries in Europe, America and Asia [20]. Scientists reported that antibodies are created against multiple parts of S protein of SARS-CoV-2, so there is a high chance that the vaccines will retain efficacy for these variants [21]. Brazil reported another variant P.1 (Gamma variant, VOC) derived from the lineage B.1.1.28 with mutation present in the S protein primarily responsible for entry of viral particles into human cells [22]. Mutations N501Y and E484K was found in this variant and has high transmissibility. Zeta variant (lineage P.2) carrying E484K mutation derived from gamma emerged in Brazil but has low transmission rate than gamma [22]. In India, two VOIs B.1.617 and B.1.618 as well as B.1.617.2 (Delta variant, VOC), a sub-lineage of B.1.617 was reported and found to be more infectious and transmissible [23]. It has 50% more transmission rate than B.1.1.7 and has already

spread across many countries. Delta variant has E484Q and L452R mutations which is involved in increased interaction of virus particles with human receptor cells and hence, increased rate of infection. Shortly after Delta variant, a new strain B.1.617 + (Delta plus variant) was emerged in some part of India during second wave of COVID-19 with a new P618R mutant which is responsible for reduced antibody binding capability as well as evasion of natural immunity along with E484Q and L452R. B.1.617 + has spread four times faster than alpha variant and rapidly expanded to other countries [23]. Another variant of concern known as Omicron (B.1.1.529) has emerged with a large number of mutations including at least 34 mutation in S protein and is more transmissible than Delta variant in late 2021 [24]. This variant has two lineages, BA.1 and BA.2 and has raised major concerns due to its ability to evade protection conferred by therapeutics monoclonal antibodies and vaccines [24]. As per WHO, total COVID-19 cases of 534,245,759 have been reported with 6,317,736 deaths and 505,168,553 recovered worldwide in 228 countries and territories till this date [25].

In this review, all the structural proteins and non-structural proteins (nsps) of SARS-CoV-2 that are involved in causing COVID-19 infection in humans have been comprehensively discussed. The interaction of these proteins with the cell receptor (ACE2) to gain entry into the host and its role in processes such as proteolytic cleavage, fusion, transcription, translation, viral packaging, assembly and exocytosis in life cycle of the virus have been explained in extensive detail. Repurposing of the antiviral drugs which have shown the efficacy to target proteins in any step of the viral life cycle have been outlined as well as illustrated. Other therapeutic options such as immunotherapy and cellular therapy as well as vaccines approved have been summarised as well.

Key proteins responsible for SARS-CoV-2 and possible druggable sites

Spike protein and its interaction with ACE2

The spike (S) protein of coronavirus is a large glycoprotein of about 180 kDa containing approximately 1273 amino acids and 20 asparagine-linked glycans. Spike glycoprotein present on the surface of novel coronavirus (SARS-CoV-2) as a homotrimer, plays an important role in the attachment of virus to receptors of the host cells as well as membrane fusion. The trimers are formed from S monomers in the endoplasmic reticulum (ER) of virus producing cells [26]. S protein consists of three segments: large ectodomain, single-pass transmembrane anchor and short intracellular tail. Ectodomain are composed of two functional domains/ subunits: S1 domain is responsible for receptor binding and

S2 domain is responsible for fusing viral and host cell membrane. The S1 domain (14-685 residues) is further divided into N-terminal subdomain (NTD) and C-terminal subdomain (or C-domain) [27]. S2 domain (686-1273 residues) consists of fusion peptide, heptapeptide repeat sequence (HR1, HR2), transmembrane domain and cytoplasmic domain. S protein trimer is located on the surface of viral envelope and have large number of N-linked glycans that are essential for proper S folding and for controlling the accessibility of host proteases and neutralizing antibodies of host. There are 22N-linked glycosylation sequons per protomer in SARS-CoV-2 and out of which 20 are in homology with SARS-CoV S protein [28]. Studies have reported that the degree of amino acid sequence homology between S protein of SARS-CoV-2 and SARS-CoV is 76% [29]. Researchers have found that the receptor binding motif (RBM) of S glycoprotein of SARS-CoV-2 is similar to that of pangolin coronavirus S protein and it has been suggested that pangolin is involved in evolution of SARS-CoV-2 [30]. As compared to other coronavirus, SARS-CoV-2 have been found to contain 27 mutations in genes encoding viral S protein [26]. SARS-CoV-2 recognizes exopeptidases while other coronavirus also recognizes exopeptidases as well as aminopeptidases or carbohydrate as receptor for entry into human cells. SARS-CoV-2's S protein was confirmed to have increased binding affinity to human ACE2 receptor than 2002 strain of SARS due to the single N501T mutation in S protein of SARS-CoV-2 which significantly enhanced its binding efficiency [31]. However, Othman et al. stated that mutation of residue Q493 to N493 rather than N501T is the main reason for higher binding affinity as it satisfies Van der Waals due to the presence of longer side chain of asparagine [32].

S protein is multifunctional which controls the invasion of virus into host cells and ultimately causing infection. Receptor recognition is the initial step in viral infection and the key determinant of host cell and tissue tropism. ACE2 is present on plasma membrane of cell of various tissues, especially on lower respiratory tract, heart, lung, small intestine, kidney, and gastrointestinal tract. It is a type I transmembrane metallo-glycoprotein which consists of an extracellular catalytic domain. An 805-amino acids long ACE2 has amino-terminal as well as carboxy-terminal domain. The major function of ACE2 is to degrade angiotensin II (potent vasoconstrictor) to form angiotensin-(1–7) and therefore, negatively regulates renin-angiotensin system (RAS). A single amino acid is cleaved by ACE2; hence they are called mono carboxypeptidase. It plays protective function in cardiovascular system and other organs [33]. A study conducted by Zhou et al. showed that SARS-CoV-2 uses ACE2 from humans, horseshoe bats, pigs and civet cats to enter the ACE2-expressing HeLa cells [8]. An in vitro study revealed that cytopathic effects occurs when SARS-CoV-2 is present on the surface of human airway epithelial cells followed by

cessation of cilia movements [18]. Downregulation of this ACE2 is responsible for pathogenesis of acute lung injury and ultimately ARDS [34].

During infection, the viral S protein is processed at the boundary between S1 and S2 subunits (S1/S2 cleavage site) by the host cell, furin-like proteases. This step is known as priming which divides the S protein into N-terminal S1 subunit that recognises cell receptor and membrane-bound C-terminal S2 region that helps in viral entry. Both the subunits are reported to be non-covalently bound in prefusion conformation. A conserved receptor binding domain (RBD) is present in S1 region consisting of approximately 193 amino acid fragment which recognizes and binds ACE2 receptor [35]. Zhang et al. investigated the amino acid phylogenetic tree concluding that S1 protein of SARS-CoV-2 is more closely related to Pangolin-CoV [36]. The RBD of both are highly conserved and there is one amino acid change only. Five key amino acid residues at positions 442, 472, 479, 487 and 491 in S protein are critical in binding ACE2 as they are present at receptor complex interface with ACE2. Except Tyr491, all other residues in RBD are not conserved when compared to SARS-CoV [37]. When S1 subunit binds with ACE2, it tends to destabilize the prefusion trimer and thus, causes shedding of S1 subunit. This leads to the transition of S2 into highly stable postfusion conformation [28]. The RBD then undergo hinge-like conformational movements which can hide ('down' conformation) or expose ('up' conformation) the determinants of receptor binding. The 'down' conformation is the inaccessible state of the receptor and 'up' conformation is the accessible state [38]. The most distinctive feature of SARS-CoV-2 S protein is the presence of multibasic furin-like cleavage site (S1/S2) which has been reported to be absent in other SARS-like CoV of beta-coronaviruses. Other SARS-like coronaviruses only contain TMPRSS2 (transmembrane protease, serine 2) or trypsin cleavage site [39].

After receptor binding, S2 domain helps in fusing the viral-host membrane by exposing highly conserved fusion peptide (FP). The S2 domain contains this fusion peptide which is proteolytically cleaved at a site found immediately upstream (S2'). It is the second priming event. FP contains 15–20 conserved amino acids, mainly glycine or alanine which helps in anchoring of virus to target membrane. The S2 domain also contains internal fusion peptide (IFP). Somehow FP and IFP both are likely to be involved in viral entry process, hence, the priming event at both S1/S2 and S2' sites are necessary [40]. The priming event at S2' by host cell protease plays a key role in the final activation of the S protein and also regulates viral tropism and pathogenesis. It has also been proposed that one or more furin-like enzymes are involved in S2' cleavage [35]. After the priming of second site, the S2 subunit undergoes conformational rearrangement when it inserts FP into host membrane and

as a result, HR1 and HR2 (Heptad repeat) interacts to form six-helical bundle (6-HB) which brings viral envelope and host membrane in close proximity and marks the completion of fusion followed by entry of virus into cell, release of its content, viral replication and infection of other cells. Apart from proteases involved in cleaving and activation, ionic interactions (H^+ and Ca^{2+}) also dictate the entry of virus into host, hence, controlling viral stability and transmission. However, the whole molecular pathway involved in viral entry into host cell are still unclear and needs to be understood completely [41]. Once the virus enters the alveolar epithelial cells, it replicates quickly and triggers strong immune response, thus, causing cytokine storm syndromes (also called hypercytokinaemia) and pulmonary tissue damage [42]. SARS-CoV-2 S-protein has binding free energy of −50.6 kcal/mol which is more as compared to −78.6 kcal/mol for SARS-CoV. The reason being loss of hydrogen bond interaction by replacing Arg426 with Asn426 in Wuhan SARS-CoV-2 S-protein [37]. The affinity with which SARS-CoV-2 RBD binds with ACE2 is 10- to 20-fold higher as compared to other CoVs RBD. This may justify the rapid development and enhanced human-to-human transmissibility in COVID-19 [38]. Since the outbreak of pandemic, 96.5% of the mutation has been reported in the S protein sequence [43]. This protein has been an area of interest to target for the development of therapeutic treatment as blocking them will inhibit the growth of infection.

Role of viral proteases

3-chymotrypsin-like protease (3CL^{pro}) is the primary protease of coronavirus that has been characterized as important drug target site. It is the main protease of coronavirus, hence called M^{pro} or 3C-like protease (also known as nsp5). It is a 33 kDa cysteine protease that plays a key role in replication cycle of the virus. M^{pro} targets the viral polyproteins, pp1a and pp1ab translated from viral RNA and digests them at 11 conserved sites. As a result, it produces 12 functional nsps (nsp 4, 6–16) and these nsps further responsible for viral replication and viral assembly. Mpro contains 11 cleavage site and the recognition sequence is Leu-Gln (cleavage site) (Ser, Ala, Gly) [44]. The crystal structure and amino acid analysis revealed that M^{pro} of SARS-CoV-2 showed approximately 96% sequence similarity with other members of coronavirus family and most of the residues are conserved in M^{pro}. The co-crystallized structure showed that M^{pro} functions as an active homodimer with 303 amino acid residues and divide into three domains. Domain I (residues 8–101) and II (residues 102–184) has chymotrypsin-like six-stranded antiparallel β-sheets while domain III (residues 201–303) contains 5 antiparallel α-helices and are connected to domain II via loop region (residues 185–200). The substrate binding site is located between domain I and II with residues 164–168

and 189–191 residues of loop region, near Cys-His catalytic dyad. Inhibiting the activity of M^{pro} will stop the viral replication, hence, this enzyme is an attractive drug target site [45].

Along with M^{pro}, another proteolytic enzyme, papain-like protease (PL^{pro}) is equally important for viral lifecycle. Both the proteases are responsible for processing of pp1a and pp1ab replicase polyprotein precursors into functional proteins. PL^{pro} cleaves the polyproteins at 3 distinct sites, thus, yielding nsp1, nsp2 and nsp3. The proteolytic recognition sequence of PL^{pro} is LXGG↓X [46]. In addition to proteolytic activity, PL^{pro} also represses the innate immune system of the host through de-ubiquitination and de-ISGylation (interferon-stimulated gene product 15) events as they hijack the ubiquitin (Ub). Ubiquitin (Ub) and ISG15 both carries the recognition sequence LXGG at the C-terminus [47]. PL^{pro} hampers the host anti-viral reactions as ubiquitin plays an important role in host defence mechanism. It shuts down the crucial pathway by cleaving ISG15 (two domain Ub-like protein) and Lys48- linked poly Ub chains and thus, inhibiting the activation of interferon regulatory factor-3 pathway. Notably, the overall sequence similarity found between PL^{pro} of SARS-CoV and SARS-CoV-2 is 83% and both the PL^{pro} differs by 54 residues. The ubiquitin-like domain and catalytic domain of SARS-CoV-2 PL^{pro} are distinct and well separated from each other. PL^{pro} is a cysteine protease with zinc ion as central atom coordinated by four cysteine residues. The active site of SARRS-CoV-2 PL^{pro} is conserved and has a catalytic triad (cysteine, histidine and aspartic acid). With dual function, PL^{pro} proves to be an important drug target and inhibition of this protein will improve the antiviral response of host immune system [48]. Many studies have revealed and reported the structures of proteases (PL^{pro} and M^{pro}) of SARS-CoV-2 and drug screening has been reported to find out the potent candidate for inhibition of proteases.

RNA-dependent RNA polymerase

RNA dependent RNA Polymerase (RdRp) is the nsp12 which is 103 kDa long and play a crucial role in the life cycle of viruses like coronaviruses, zika virus, and hepatitis C virus. It is the main component of replication/transcription machinery and hence, participates actively in the replication of viral RNA from RNA template with the help of co-factors nsp-7 and nsp-8 and forms tripartite polymerase complex with them. These nsps activate and confers processivity to the RdRp. Further, this complex gets associated with nsp-14 and confers proofreading exonuclease function [49]. The structure of SARS-CoV-2 RdRp (nsp12)-nsp7-nsp8 complex (160 kDa) was resolved recently by cryo-EM study and found that it is similar to SARS-CoV RdRp complex. SARS-CoV-2 RdRp has two domains: NiRAN (N-terminal

extension nidovirus-unique RdRp-associated nucleotidyl transferase) domain from residues 60–249 and RdRp domain from residues 366–920. Both the domains are interconnected by interface domain. NiRAN domain contains kinase-like fold and N-terminal β-hairpin region located between NiRAN and RdRp domain. Two Zn^{2+} ions are located in the NiRAN domain away from RdRp catalytic site. It has been reported that 96% sequence similarity was found between SARS-CoV RdRp and SARS-CoV-2 RdRp [50]. So, it forms an interesting target for docking studies and molecules used against SARS-CoV RdRp can be effective against SARS-CoV-2 RdRp. Table 2 summarises the functional feature of nsps and structural protein of COVID-19.

Role of other viral structural protein

Nucleocapsid (N) protein

The nucleocapsid (N) protein (46 kDa) of coronaviruses are important structural protein which are highly expressed and abundant in the virus after infection. It is a multifunctional RNA-binding protein that is essential for RNA transcription, and replication [51]. After entering host cell, its main function includes binding the RNA of virus, packing them into a long helical ribonucleoprotein (RNP) complex and processing the viral particle assembly and release. They also modulate infected cell metabolism. They are highly conserved and consists of three parts: N-terminal RNA-binding domain (NTD) responsible for RNA binding, C-terminal dimerization domain (CTD) for oligomerization, and an intrinsically disordered central Ser/Arg (SR)-rich linker for primary phosphorylation [52]. Both NTD and CTD are rich in β-strands with some short helices and surface of both the domain contains highly positively charged regions thus, enhancing the ability of N protein to bind non-specific nucleic acids. It was reported that N protein of SARS-CoV-2 show 90.52% homology with that of SARS-CoV N protein [53]. They are highly immunogenic as they can induce strong immune response against SARS-CoV-2 during infection. It could be a suitable drug-targeting candidate as they play a pivotal role in genome packing, viral transcription and assembly in the host cell [54]. A study conducted by Guo et al. showed that IgG in serum of COVID-19 infected patients can bind with N antigen [55]. Another study found the presence of IgG, IgA and IgM antibodies in COVID-19 recovering patients against N antigen [56].

Membrane and envelope protein

The membrane (M) and envelope (E) structural proteins plays an important role in regulating the assembly of virus particles. S, M and E proteins contains trafficking signal sequences and gets incorporated in endoplasmic reticulum along with ribonucleoprotein complex which is essential for maturation

Table 2 Non-structural proteins (nsps) and structural proteins of COVID-19

S. No	Protein	Length (amino acids)	Function	References
1	NSP1 (Non-structural protein 1)	180	Binds with 40S ribosomal subunit and interferes with translation of host cell protein and cleaves host mRNA. Also facilitates viral gene expression	[12]
2	NSP2 (Non-structural protein 2)	638	Interacts with host PHBs 1, 2 and play an important role in host cell survival signalling pathway	[45]
3	NSP3 (Non-structural protein 3)	1945	Papain-like protease (PL^{pro}) cleaves N-terminal end of a polypeptide to produce NSP1, NSP2, NSP3. NSP3 forms replication-transcription complex by acting as membrane-anchored scaffold as well as interacting with other NSPs and host proteins	[14]
4	NSP4 (Non-structural protein 4)	500	Participates in rearrangement of cytoplasmic double-membrane vesicles	[18]
5	NSP5 (Non-structural protein 5)/main protease (M^{pro})/Chymotrypsin-like cysteine protease (3CL^{pro})	306	Cleaves viral polyproteins at 11 distinct sites to generate functional proteins	[16]
6	NSP6 (Non-structural protein 6)	290	Initiates the induction of autophagosomes from host endoplasmic reticulum	[26]
7	NSP7 (Non-structural protein 7)	83	It dimerizes with NSP8 and forms a hexadecamer	[27]
8	NSP8 (Non-structural protein 8)	198	Performs RNA primase activity during RNA synthesis of virus along with NSP7	[39]
9	NSP9 (Non-structural protein 9)	113	Acts as RNA binding protein and involved in viral replication	[35]
10	NSP10 (Non-structural protein 10)	139	Interacts with NSP14 and NSP16 and forms mRNA cap methylation complex during viral transcription	[38]
11	NSP12 (Non-structural protein 12)/RNA dependent RNA polymerase (RdRp)	103	Participates in viral RNA replication as well as transcription	[51]
12	NSP13 (Non-structural protein 13)/RNA replicase	601	Shows RNA as well as DNA duplex-unwinding activities	[62]
13	NSP14 (Non-structural protein 14)	527	Involved in 3' to 5' exoribonuclease activity and methylation of viral RNA cap (guanine-N7 methyl transferase)	[63]
14	NSP15 (Non-structural protein 15)/Uridylate-specific endoribonuclease	346	Cleaves RNA and evade host immune system by preventing detection of viral dsRNA	[22]
15	NSP16 (Non-structural protein 16)/2'-O-ribose methyltransferase	298	Catalyses 5'-methyl capping of viral mRNA and protects RNA from degradation by host 5'-exoribonucleases	[35]
16	Spike protein	1273	Helps to attach the virus to the host cells and penetrate the cell to cause infection	[33]
17	Nucleocapsid protein	422	Helps in viral replication and genome packaging	[55]
18	Membrane protein	230	Assembly of new virions and determining viral envelope shape	[58]
19	Envelope protein	75	Helps in viral assembly, budding and envelope formation	[60]

and budding of new virus particles. Both M and E proteins show more than 90% sequence similarity with SARS-CoV proteins and are conserved [57]. M protein of SARS-CoV-2 is a type-III transmembrane glycoprotein which is 230 amino acid long and the most abundant of all structural proteins. It consists of 3 domains: N-terminal ectodomain, C-terminal endo-domain and transmembrane helices (TMH1, TMH2, TMH3). The M protein shows homotypic (interaction with itself) as well as heterotypic (interaction with other structural proteins) interaction. These interactions induces membrane bending (budding) and hence, serve as checkpoint for assembly of new virus particles. Homotypic interaction occurs through TM region of M protein while heterotypic interaction with N and E protein occurs through C-terminal endo-domain. M protein can also induce humoral immune response as the antigenic epitopes are located in the TM1 and TM2 region of SARS-CoV-2 [58].

E protein is the smallest structural protein of SARS-CoV-2 with 75 amino acids long and contains 3 domains: hydrophilic N-terminal ectodomain, transmembrane domain (hydrophobic) and hydrophilic C-terminal endo-domain. According to NMR study, E protein display structure similar to viroporins with pentameric helix bundle that surrounds a narrow hydrophilic cationic central pore. These pores or ion channels activates the host inflammasome by causing the loss of membrane potential. The cysteine residues present in C-terminal domain undergoes palmitoylation that are essential for subcellular trafficking and membrane binding. The last four amino acids (Asp-Leu-Leu-Val) ae involved in the interaction of E protein with host associated proteins (PALS1 and syntenin) thus, causing viral dissemination. These events have been reported to induce cytokine storm. Inhibition of E protein can hinder viral maturation as well as viral propagation and thus, developing antiviral drug and vaccine targeting E protein can be good option for treatment [59].

Role of host proteases

Furin-like protease

For cleavage of S protein, the host proteases differ for different coronaviruses which determines the epidemiological as well as pathological features of virus. For example, trypsin, human airway trypsin-like protease (HAT) and TMPRSS2 are some host proteases which are expressed in many essential organs [60]. A study by Wang et al. found that COVID-19 has a novel multibasic unique cleavage site (–RRAR–) in S1/S2 domain, located between residues 682 and 685 which is distinct from other coronaviruses [39]. This site is most likely to be cleaved by convertase furin which enhances viral-host cell membrane fusion. Furin cleaves proteins and peptides precursors and converts them into biologically active state. It is a type 1 membrane-bound serine-protease and a member of calcium-dependent, subtilisin-like proprotein convertase family. It cycles from the trans-Golgi network to the cell membrane and through endosomal system. It specifically recognizes and cleaves the R-X-K/R-R motif in the presence of Ca^{2+} [61]. This protease is highly expressed in organs and tissues including lung, gastrointestinal tract, brain, pancreas, and reproductive tissues and liver as well. Hence, COVID-19 can infect these organs also resulting in systematic infection of virus in the body and an enhanced transmission and pathogenicity [39]. The binding between the furin protease and S protein is in a clamp-like fashion where furin clips tightly to the cleavage S1/S2 site. Substrate-binding pocket of furin has canyon-like crevice and its key amino acid residues are specifically positioned to interact with S glycoprotein. The presence of 12 additional nucleotides upstream of the exposed -RRAR- sequence in S glycoprotein corresponds to unique canonical furin-like cleavage site. These amino acid residues present between N657 and Q690 of S glycoprotein strongly interacts with furin are well organised in a flexible loop [62]. COVID-19 use this convertase to activate S glycoprotein and thus, provide a gain-of-function to the virus for efficient transmission. Van der waal or hydrogen bonding facilitates the interaction of furin and S glycoprotein. MERS-CoV contains -RSVR- sequence which is most probably cleaved by furin during virus egress whereas SARS-CoV's S protein remains uncleaved [63].

TMPRSS2 (Transmembrane protease serine 2)

TMPRSS2 is a type II transmembrane enzyme of the host that belongs to serine protease family and encoded by TMPRSS2 gene. Along from S protein-ACE2 interaction, other proteases also play a major role in entry of the virus particle into the host cell. TMPRSS2 helps in the priming of S protein thereby causing the fusion of cellular and viral membranes. TMPRSS2 are found to be localized in epithelial cells of lungs [64]. A study was reported in which TMPRSS2 cells were overexpressed in Vero E6 cell line due to which chances of corona infection elevated in patients as this overexpression of TMPRSS2 in lung made them more vulnerable to SARS-CoV-2 [65]. Much research has proved that entry of novel SARS-CoV-2 depends on TMPRSS2 priming activity and gets blocked when TMPRSS2 inhibitor, camostat was used [66]. So, TMPRSS2 proved to be another protein target for treatment of SARS-CoV-2. A TMPRSS2 knockout mice model was studied and it was reported that knockout mice were immune to coronavirus [67].

Cathepsin L

Cathepsins are host cysteine proteases and play an important role in the entry of SARS-CoV-2 viral particle into the host cells via endocytic pathway and also in protein catabolism in endosomes and lysosomes. Cathepsin L causes the priming of S proteins after the virus enters the endosomes and hence, causing the fusion of viral and endosomal membranes and release of viral genome into cytoplasm. Cathepsin L can be targeted for the treatment of SARS-CoV-2 as its inhibitors have been reported to prevent pulmonary fibrosis. Some cathepsin L inhibitors are SID 26,681,509 and E-64-d [68]. A study reported that a glycopeptide antibiotic, teicoplanin, was able to block cathepsin L activity and thus, inhibits the entry of SARS-CoV and MERS-CoV [69]. Another study reported the inhibition of SARS-CoV-2 pseudoviruses entry into the host cells. It was demonstrated that SARS-CoV-2 pseudo virus uses the cathepsin L specifically to enter into 293/hACE2 cells and E-64-d (a broad spectrum cathepsin inhibitor) proved to reduce the viral entry by 92.5% while

SID 26,681,509 inhibitor reduced it by 76% [70]. Different types of cathepsins have been found to play a key role in viral entry to host cells and targeting them along with other target protein can be more beneficial in treating SARS-CoV-2 patients [71].

Therapeutic interventions for COVID-19

COVID-19 is a serious international concern and research teams and health officials from all around the world are working tirelessly to cope with the disease. Since its outbreak, countries have taken measures to slow down the spread of virus by announcing lockdown, testing, isolating, and treating patients with drugs, carrying out contact tracing, limiting travel and quarantining citizens. Some of the methods to treat COVID-19 infected patients are listed below.

All the proteins associated with SARS-CoV-2 has been proved to be potential catalytic site to target in order to treat the infection and different treatment options has been developed till now. Initially when there were no specific antiviral drugs developed for coronavirus, drugs developed for MERS and SARS showed promising results, so expectation was shifted to them. Table 3 describes the antiviral drugs which have been developed by scientist for SARS-CoV-2 as well as some repurposed drugs evaluated for their potency to counter SARS-CoV-2 infection. Most synthetic small molecules under clinical trials are being repurposed for COVID-19 which are already reported for their efficiency against other disease states [71]. Drugs are being clinically tested to be used against COVID-19 infection such as Favipiravir, Ribavirin, Nafamostat, Nitazoxanide, Penciclovir, Favipiravir, Baricitinib and Arbidol. However, most of them showed moderate results when tested on clinical samples of COVID-19 patients in vitro [11]. Remdesivir, has caught the attention of many researchers due to its promising impact against the virus. It is an adenosine nucleoside analogue and targets viral RNA-dependent RNA polymerase, invades the viral RNA chains and thus, causing pre-mature chain termination. It also evades proofreading viral exoribonuclease. This drug has been used effectively against Ebola virus infection [72]. Sheahan et al. conducted clinical study stating that SARS-CoV-2 replication was significantly blocked in patients and were clinically recovered when remdesivir alone or in combination with cholorquine/ interferon beta was used [73]. Remdesivir was successfully used in treatment of first COVID-19 patient in USA and ameliorated the worsening condition of pneumonia on 7th day of hospitalization in January 2020 [74]. Remdesivir has been found to work effectively with compassionate use in severe cases of COVID-19 though extensive research is still going on. Controlled trials of antiviral drugs are required to determine side effects, if any [73]. Terali et al. reported in silico study to find out drugs which can be repurposed as potential human ACE2 inhibitors like lividomycin, quisinostat, burixafor, fluprofylline, spirofylline, pemetrexed, diniprofylline and edotecarin. They proved to be promising drug candidate which blocks viral entry [75]. Food and Drug administration (FDA) approved drugs like Lopinavir, Ritonavir, Darunavir, Boceprevir, Telaprevir are being investigated as M^{pro} inhibitors and has shown encouraging result. Compounds like Disulfiram, Baicalein, Ebselen, Carmofur, Shikonin, PX-12, Camostat, Calpeptin, Calpain inhibitor and Tideglusib have been reported to be likeable protease-based drug candidates for SARS-CoV-2 with good potency and selectivity [76]. Scientists are trying to find or develop more effective antiviral drug candidate to treat COVID-19. Figure 2 shows the various inhibitors acting at different stages in SARS-CoV-2 infection cycle.

Use of monoclonal or polyclonal antibodies is another suggested method which can serve as prophylactic and therapeutic tool against viral infection and provide some restitution in this pandemic condition. They are laboratory engineered molecules which are designed to bind antigens. It has been reported that monoclonal antibodies (mAbs) target the S protein of SARS-CoV and prevent virus to enter the host cells [77]. Some of the mAbs have been described in the Table 3. To improve the condition of COVID-19 infected patients, other treatment options were also considered. Convalescent plasma containing IgG, IgA, IgM, IgE and IgD was obtained from patients and has already been used effectively for treating SARS-CoV, poliomyelitis, influenza A (H_1N_1) and Ebola virus infection. The presence of antiviral antibodies in the plasma of clinically recovered patients helps to suppress viremia [78]. Shen et al. reported that after treatment of critically ill patients of COVID-19 and ARDS with convalescent plasma, there was improvement in their clinical condition. The plasma was obtained from 5 patients recovered from this virus. This transfusion with convalescent plasma leads to the normalization of body temperature of patients within 3 days, resolution of ARDS at 12th day of transfusion, decline in viral load and increase in neutralizing antibody titres. The patients were also administered with antiviral agents and methylprednisolone [79]. It is a form of passive immunization that can be achieved from previously viral infected patients. It was authorized by FDA in August 2020 but newer studies suggest that it is less effective [80].

Natural killer (NK) cells, a type of cytotoxic lymphocytes, are immune cells responsible for providing rapid defense response against virus-infected or malignant cells. Antibody-dependent cellular cytotoxicity (ADCC) is a process initiated by NK cells by causing lysis of antibody-coated virus-infected cells. So, they are specific for all virus-infected cells [81]. It has been reported that NK cells can mediate ADCC against SARS-CoV, cytomegalovirus virus,

Table 3 Therapeutic treatment option FDA approved or under clinical trial for COVID-19

Drug/Therapy	Inventor	Mechanism of action	Mode of administration	FDA status	References
Antiviral drugs					
Molnupiravir (Lagevrio)	MERCK and Ridgeback biotherapeutics	Ribonucleoside analog; inhibits the SARS-CoV-2 virus replication	Oral	Approved in December 2021	[92]
Paxlovid (Nirmatrelvir and Ritonavir)	Pfizer	Disrupts viral replication by binding to 3CL-like protease	Oral	Approved in December 2021	[93]
Remdesivir (Veklury)	Gilead Sciences	Adenosine nucleoside analog; targets viral RNA-dependent RNA polymerase, invades the viral RNA chains and thus, causing pre-mature chain termination	Intravenous (IV)	Fully approved in October 2020	[74]
Hydroxychloroquine/Chloroquine	Bayer	Suppress cytokine storm by inhibiting production as well as release of TNF (tumor necrosis factor) and IL-6	Oral	Emergency use authorization (EUA) in March 2020	[73]
Lopinavir/Ritonavir	AbbVie	Protease inhibitor; binds to endo-peptidase C30 of 3CL^{pro} and disrupts viral replication	Oral	Emergency use authorization (EUA) in May 2020	[94]
Ceftazidime	Actavis Pharma Inc	Blocks S protein-ACE2 interaction	Intravenous (IV) or Intramuscular	–	[95]
Baricitinib (Olumiant)	Eli Lilly and Incyte Corporation	Janus kinase inhibitor; inhibits intracellular signalling pathway of cytokine and blocks SARS-CoV-2 from entering and infecting lung cells	Oral	Emergency use authorization (EUA) in November 2020	[71]
Favipiravir	Toyama Chemical	RdRp inhibitor; inhibit the replication of SARSCoV-2	Oral	–	[71]
Ribavirin	Valeant Pharmaceuticals	Guanosine analog; interferes with the viral RNA synthesis and viral mRNA capping	Oral	–	[71]
Umifenovir (Arbidol)		Interfere with the release of SARS-CoV-2 from intracellular vesicles	Oral	–	[71]
Burixafor	TaiGen Biotechnology	CXC chemokine receptor 4 inhibitor	Oral or Intravenous (IV)	–	[71]
Darunavir	Tibotec	Protease inhibitor; prevents maturation of viral particles into infectious virions	Oral	–	[71]
Sofosbuvir (Sovaldi)	Gilead Sciences	Nucleotide analog inhibitor; prevents viral replication by targeting RdRp	Oral	–	[71]
Beclabuvir	AdisInsight	Nucleoside inhibitor; targets RdRp	Oral	–	[73]

Table 3 (continued)

| Drug/Therapy	Inventor	Mechanism of action	Mode of administration	FDA status	References
Nafamostat	AdisInsight	Serine protease inhibitor; suppress membrane fusion between virus and human cells	Intravenous (IV)	–	[71]
Immunotherapy (Monoclonal antibodies)					
REGEN-COV (Casirivimab and imdevimab)	Regeneron	Targets non-overlapping epitopes of RBD in S protein of SARS-CoV-2 by blocking viral attachment as well as its entry into host cell	Intravenous (IV)	Emergency use authorization (EUA) in November 2020	[96]
Bebtelovimab	Lilly	Binds to S protein of SARS-CoV-2	Intravenous (IV)	Emergency use authorization (EUA) in February 2022	[97]
Tocilizumab (Actemra)	Hoffmann-La Roche	IL-6 antagonist; inhibits the binding of IL-6 to its receptor	Intravenous (IV)	Approved in June 2021	[71]
Bamlanivimab and Etesevimab	Eli Lilly	Inhibits surface S protein of SARS-CoV-2 by binding to different but overlapping epitopes in RBD	Intravenous (IV)	Emergency use authorization (EUA) in November 2020	[98]
Sotrovimab	GlaxoSmithKlein and Vir biotechnology	Human made monoclonal antibodies (MoAb); binds to an epitope present in the S protein RBD	Intravenous (IV)	Emergency use authorization (EUA) in May 2021	[99]
Evusheld/AZD7442 (Tixagevimab and Cilgavimab)	AstraZeneca	Targets surface S protein of SARS-CoV-2	Intramuscular or Intravenous (IV)	Emergency use authorization (EUA) in December 2021	[100]
Interferon alpha	Biogen	Suppresses the viral replication and causes enhanced innate and adaptive immune responses	Subcutaneous or intravenous (IV)	–	[24]
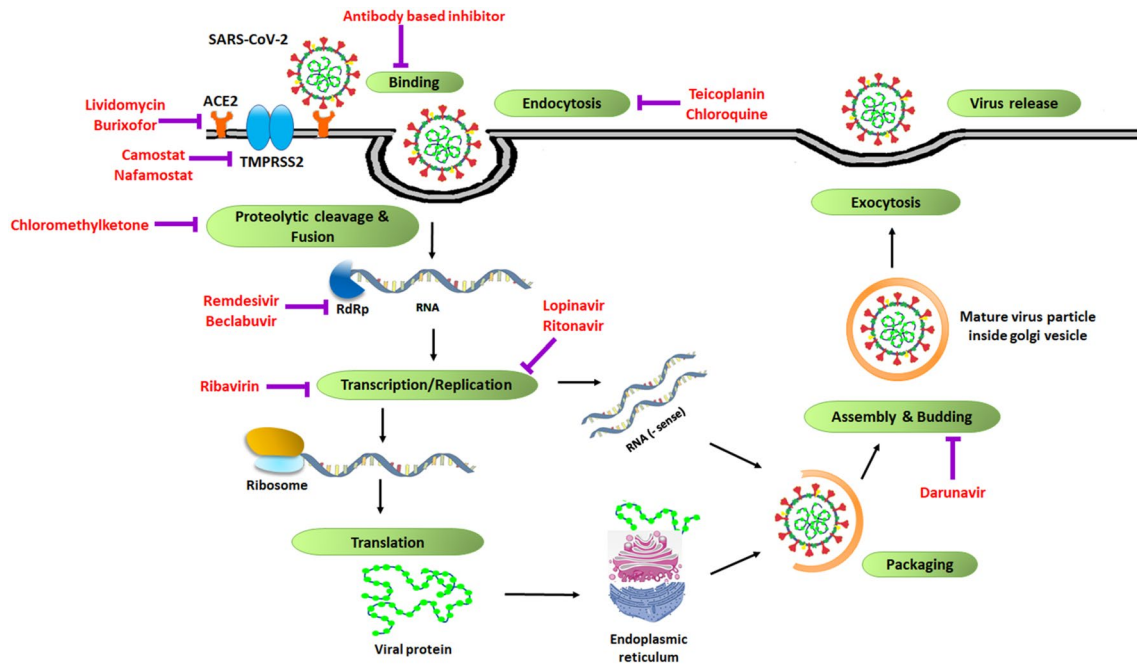
Fig. 2 Inhibitors which act at different stages of SARS-CoV-2 life cycle

HIV and show antiviral activity. Sorrento and Celularity disclosed that a clinical collaboration has been undertaken which aims to utilize the CYNK-001 (an allogeneic, umbilical cord blood-derived) NK cell therapy to treat COVID-19 infected patients. NK cell therapy is a very promising strategy which enhances immunity [10]. Mesenchymal stem cells (MSCs) are multipotent cells which are found in bone marrow, are known to have strong immunomodulatory and anti-inflammatory functions. They have a great potential of self-renewal and differentiation. Besides bone marrow, placenta and umbilical cord blood are also considered as a source of MSCs. MSCs have the ability to inhibit abnormal activation of macrophages and T-lymphocytes and causing them to differentiate into anti-inflammatory macrophages and regulator T-cell subsets (Treg) [82, 83]. Studies have been conducted on MSCs and found that it can improve ARDS and acute/chronic lung injury by reducing pro-inflammatory cytokine secretion [84]. They can suppress cytokine storm by inhibiting the secretion of IL-1, IL-6, IL-12, TNF-α and IFN-γ. They also tend to repair tissue rapidly and reduces lung fibrosis by secreting hepatocyte, vascular endothelial and keratinocyte growth factor [85]. Apart from antiviral drugs, ARDS and lung injury needs to be treated in case of severe COVID-19 patients in order to prevent the progression of disease and reduce the level of mortality [86]. MSCs can be proven to become one of the promising therapeutic candidates.

Different vaccines for COVID-19

Understanding the key features, etiology and pathogenesis related to COVID-19 is the main focus of interest for researchers to come up with a suitable vaccine to deal with the current pandemic situation. After the outbreak of SARS and MERS, researchers worldwide began developing vaccines. Due to the major role of S protein of coronavirus and ACE2 human receptor in causing COVID-19, drugs targeting their interaction should be a promising way. Owing to the genomic resemblance and structural similarities of these proteins, therapies and vaccines developed for SARS and MERS may pave way for treatment or prevention of SARS-CoV-2 infection [11]. Vaccines like inactivated or live-attenuated vaccines, viral vector-based protein sub-unit vaccines etc. were produced using different strains of SARS which showed promising result in animal models. Yang et al. developed a DNA vaccine (inactivated whole virus or live-vectored strain of SARS-CoV, AY278741) which has successfully induced the release of neutralizing antibody and reduced viral infection in animal models [87]. Previously developed vaccines for SARS-CoV might be helpful to re-utilize it to facilitate vaccine development for COVID-19.

Scientists are working at a breakneck speed to develop vaccines for COVID-19 as early as possible. For this, institutes and pharmaceutical companies are working in collaboration worldwide. More than hundred vaccines are in progress and many of them have even entered clinical trial

Table 4 List of vaccines approved or in late phase clinical trial

Vaccine Candidates	Technology Used	Developer	Current Status (Approved/Clinical evaluation)
Sputnik V (Gam-COVID-Vac) and Sputnik Light	Adenoviral-based vaccine (rAd26 and rAd5)	Gamaleya Research Institute	Approved
Spikevax/mRNA-1273	LNP encapsulated mRNA	Moderna Therapeutics and US National Institute of Allergy and Infectious Diseases (NIAID)	Approved
Covishield (Vaxzevria/AZD1222 /ChAdOx1-5)	Chimpanzee adenovirus vector	University of Oxford and AstraZeneca	Approved
Comirnaty (BNT162b2)	mRNA-based	BioNTech and Pfizer	Approved
BBIBP-CorV	Inactivated	Beijing Institute of Biological Products/SinoPharm	Approved
EpiVacCorona	Peptide based vaccine	Federal Budgetary Research Institution State Research Center of Virology and Biotechnology	Approved
CoviVac	Inactivated vaccine	Chumakov Federal Scientific Center for Research and Development of Immune and Biological Products	Approved
JNJ-78436735 (Ad26.COV2.S)	Non-replicating viral vector	Janssen Pharmaceutical Companies	Approved
Convidicea (Ad5-nCoV/PakVac)	Non-replicating viral vector (adenovirus type 5)	CanSino Biologics Inc., Beijing Institute of Biotechnology, Academy of Military Medical Sciences, People's Liberation Army (PLA) of China	Approved
Covaxin (BBV152)	Whole-Virion inactivated	Bharat Biotech, Indian Council of Medical Research	Approved
CoronaVac	Inactivated virus with adjuvant	Sinovac	Approved
ZF2001 (ZIFIVAX)	Protein subunit (Adjuvanted recombinant protein)	Anhui Zhifei Longcom Biopharmaceutical, Chinese Academy of Sciences	Approved
Qaz Vac (QazCovid-in)	Inactivated	Research Institute for Biological Safety Problems, Republic of Kazakhstan	Approved
WIBP-CorV	Inactivated vaccine	SinoPharm group and Wuhan Institute of Biological products	Approved
KCONVAC	Inactivated	Kangtai Biological Products Co. Ltd., Minhai Biotechnology Co	Approved
COVIran Barekat	Inactivated	Shifa Pharmed Industrial Group	Approved
IMBCAMS (Covidful)	Inactivated	Chinese Academy of Medical Sciences, Institute of Medical Biology	Approved
Abdala (CIGB 66)	Protein subunit	Center for Genetic Engineering and Biotechnology, Cuba	Approved
Soberana 02	Protein subunit, RBD with adjuvant	Finlay Institute of Vaccines, Pasteur Institute	Approved
MVC-COV1901	Protein subunit with adjuvant	Medigen Vaccine Biologics Corporation, NIAID, Dynavax	Approved
ZyCoV-D	DNA vaccine /plasmid	Zydus Cadila Healthcare Limited	Approved
NVX-CoV2373 (Nuvaxovid/ Covovax)	Recombinant protein nanoparticle technology	NovaVax, CEPI, Serum Institute of India	Approved
MIVAC/ FAKHRAVAC	Inactivated	Organization of Defensive Innovation and Research	Approved
Turkovac/ ERUCOV-VAC	Inactivated	Health Institute of Turkey, Erciyes University	Approved
Corbevax (BioE COVID-19)	Adjuvanted protein subunit	Biological E. Ltd., Baylor College of Medicine, Dynavax, Coalition for Epidemic Preparedness Innovations (CEPI)	Approved
Spikogen/ COVAX-19	Recombinant spike protein using Advax adjuvant	Medytox, Vaxine Pty Ltd	Approved

Table 4 (continued)

Vaccine Candidates	Technology Used	Developer	Current Status (Approved/Clinical evaluation)
Covifenz (CoVLP)	Plant-based Virus-like protein (VLP) with adjuvant	Medicago Inc., Dynavax, GSK	Approved
VLA2001	Inactivated	UK National Institute for Health Research, Valneva	Approved
Noora	Recombinant protein	Baqiyatallah University of Medical Sciences	Approved
Unnamed	Recombinant vaccine (Sf9 cells)	WestVac Biopharma Co. Ltd., West China University, Sichuan University	Phase 3
ARCoV	mRNA-LNP	People's Liberation Army Academy of Military Sciences (PLA), Walvax Biotechnology Co., Abogen Biosciences Co. Ltd., Yuxi Walvax Biotechnology Co. Ltd	Phase 3
Vidprevtyn	Recombinant S-protein (influenza virus, baculovirus)	Sanofi Pasteur, Glaxo Smith Kline (GSK)	Phase 3
Razi Cov Pars	Recombinant spike protein	Razi Vaccine and Serum Research Institute, Iran	Phase 3
Nanocovax	Recombinant spike protein	Nanogen Biopharmaceutical	Phase 3
GBP510	Nanoparticle-based	GSK, SK Biosciences Co. Ltd., CEPI, University of Washington	Phase 3
V-01	Recombinant protein	Guangdong Provincial Center for Disease Control and Prevention, Zhuhai Livzonumab Biotechnology Co. Ltd	Phase 3
CVnCoV	LNP-encapsulated mRNA	CureVac, GSK	Phase 2/3
HIPRA (PHH-1 V)	Recombinant protein	Laboratorios Hipra	Phase 2/3
Bacillus Calmette Guerin (BCG)	Live attenuated strain of *Mycobacterium bovis*	University of Melbourne and Murdoch Children's Research Institute	Phase 2/3
INO-4800	DNA plasmid with electroporation	Inovio Pharmaceuticals and Advaccine	Phase 2/3
Unnamed	Adenovirus based	ImmunityBio, NantKwest	Phase 2/3
UB-612	Multitope peptide	Vaxxinity	Phase 2/3
GRAd-COV2	Replication defective Simian (Gorilla) Adenovirus vector encoding S-protein	ReiThera, Univercells, Leukocare	Phase 2/3
SCB-2019	Protein subunit (Native like trimer subunit spike protein)	Clover Biopharmaceuticals Inc., Glaxo Smith Kline, CEPI, Dynavax	Phase 2/3
BBV154	Intranasal	Bharat Biotech	Phase 2/3
HDT-301 (HGCO19)	RNA	University of Washington, National Institute of Health, HDT Bio Corp, Gennova Biopharmaceuticals, SENAI CIMATEC	Phase 2/3
S-268019	Recombinant protein	Japan Agency for Medical Research and Development, Shionogi & Co. Ltd	Phase 2/3

[88]. Among them, more than 25 have already been gone through clinical trial and has been approved for use till this date. The approved vaccines are being given to people around the world in doses and its efficiency and side effects are being analysed. Till now, some of these vaccines have shown good productivity with little side effects. However, vaccinating people worldwide is a long way to go in completely making world COVID-19 free. Scientists at Gamaleya Research Institute in Russia have successfully made and registered world's first vaccine, Gam-COVID-Vac, using adenovirus. LNP-encapsulated (lipid nanoparticles) mRNA-based vaccine has been developed by US National Institute of Allergy and Infectious Diseases (NIAID) along with a biotechnology company called Moderna Therapeutics and is currently being administered to people in various countries. The scientists have already investigated the efficiency and side effects of vaccine in adult volunteers. It is a nanoparticle encapsulated vaccine encoding full length, prefusion stabilized S protein [89]. University of Oxford and AstraZeneca has developed a vaccine using Chimpanzee Adenovirus vector (ChAdOx1-5). It has also been tested for safety, reactogenicity and immunogenicity profile as well as tolerability. This vaccine is now called AZD1222/ covishield and is now being given as vaccine in many countries. These adenovirus vectors are weakened version of a common cold virus and is replication-deficient carrying one or few encoded antigens and can stimulate both humoral and cytotoxic T-cell immune responses efficiently [90]. All the vaccines which are approved and those currently in clinical trial in late phase are listed in Table 4.

There are still many challenges which are being faced by scientists working around the clock to fight the battle against COVID-19. Development of vaccines which can perform efficiently can only be done with detailed understanding of the pathway involved in infection. The evolving nature and strain of virus remains the biggest challenge in developing virus-specific vaccine. Many parameters are taken into consideration for rational vaccine design development and for evaluation of vaccine efficacy.

Conclusion and perspective

The novel coronavirus 2019 has challenged the socio-economic, medical and health care foundation worldwide. The deadly virus has already caused devastating impact on human life. The zoonotic source of COVID-19 still needs to be confirmed further which originated from seafood market in Wuhan, China. Bats and pangolins are being considered as key reservoirs according to sequence-based analysis. Research on SARS-CoV-2 has showed many similarities as well genomic variations from SARS and MERS so, a detailed phylogenetic and pathogenetic study will enhance the understanding of virus and help in developing preventive measures. Rapid diagnosis of SARS-COV-2 needs to be done in suspected patients to control the transmission of virus which has already claimed the lives of thousands of people including doctors, health care workers and paramedical staff and infected millions. The human-to-human transmission is a serious concern and a threat to public health. The rigorous surveillance and on-going research will unravel new research findings regrading host adaptation, molecular mechanism, transmissibility, clinical manifestations, evolution, epidemiological pattern and pathogenicity. The new information about COVID-19 is being available every week in scientific journals that will help the public to understand the virus better. Researchers are developing efficient and promising therapeutics strategy to cope with the pandemic situation. Comprehensive measures need to be devised to curb not only this global health emergency but also take care of future outbreak of infection of zoonotic origin.

Data availability Not applicable.

Declarations

Competing interest The authors declare that there are no competing interests.

Ethical approval Not applicable.

Consent to participate Not applicable.

Consent to publish Not applicable.

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