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Race to arsenal COVID-19 therapeutics: Current alarming status and future directions

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A B S T R A C T

The on-going pandemic of COVID-19 wreaked by a viral infection of SARS-CoV-2, has generated a catastrophic plight across the globe. Interestingly, one of the hallmarks of COVID-19 is the so-called 'cytokine storm' due to attack of SARS-Cov-2 in the lungs. Considering, mesenchymal stem cells (MSCs) therapy could contribute against SARS-CoV-2 viruses attack because of their immune modulatory and anti-inflammatory ability linked to their stemness, to the arsenal of treatments for COVID-19. Another novel therapeutic strategies include the blockade of rampant generation of pro-inflammatory mediators like acute respiratory distress syndrome (ARDS), degradation of viral protein capsids by PROTACs, composed of Ubiquitin-proteasome framework, and ubiquitination-independent pathway directing the SARS-CoV-2 nucleocapsid protein (nCoV N) and proteasome activator (PA28γ), etc. This review is consequently an endeavour to highlight the several aspects of COVID-19 with incorporation of important treatment strategies discovered to date and putting the real effort on the future directions to put them into the perspective.

1. Introduction

The COVID-19 disease has become a household name, which puts fear into everyone's heart and mind. It gained fame due to how quickly it spread around the world since its birth in Wuhan city, China. It felt like almost overnight, this disease caught on globally, bringing both business and travel to a grinding halt and the government tried to curb its spread among our citizens. At any given time, hundreds of people are rushing into an emergency room nearby looking for urgent care trying to fight for their lives. COVID- 19 manifests itself as a respiratory illness that is quite like a flu. It took doctors and scientists a few weeks to distinguish between the COVI-19 and normal flu, as both diseases have the same means of transmission and share some key symptoms. This similarity between both the diseases generated some confusion when the pandemic first broke out early this year because patients with COVID-19 mistook it as an ordinary flu.

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has now spread quickly to 213 countries and caused a large scale COVID-19 pandemic. Presently, the newly identified SARS-CoV-2 has caused a high mortality rate with tens of thousands of positive cases across globe, posing a grave threat to public health. COVID-19 has caused severe human pneumonia since the beginning of the 21st century [1]. Initially, the world health organization (WHO) alluded the term 2019 novel coronavirus (2019-nCov) to underline the spread of this infection, which was officially turned into COVID-19 caused by SARS-CoV-2 virus [2].

Importantly, the availability of clinically approved vaccines or specific therapeutic drugs for COVID-19 is still awaited. Furthermore, to elucidate the pathogenesis, epidemiology, and to identify potential drug candidates, extensive researches is urgently needed endowing to the discovery of effective therapeutic strategies [3]. At present, various diagnostic kits to test for COVID-19 and diverse ranges of clinically effective "repurposing therapeutics" are available and accessible. Furthermore, various healthcare organizations have initiated to formulate vaccines to prevent COVID-19 [4]. A large subfamily of single-stranded positive RNA viruses enveloped under the viral coat carrying one of the biggest genome sizes of around 30–32 Kb is capable of infecting organisms in the wild as well as the humans [5]. Studies suggest that these viruses fall under the category of *Coronavirinae* subfamily being a part of the family *Coronaviridae* and the order *Nidovirales* [6], which splits into three distinguished genera (α-, β-, and γ-coronavirus) which are affirmed by the antigenic property and genome sequencing. Further, international committee on scientific categorization of viruses (2009) added another genus named δ-coronavirus, which

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was suspected to be evolved from the bird's family [7].

Despite the acknowledged delicacy of the protein coat, other curiosity that may include is coronavirus's potential natural resistance [8]. The changes in the genetic diversity and increased human-animal interaction, lead to the frequent recombination across the genomes may also lead to the generation of new strains of coronavirus [9]. To date, six variations of human coronavirus have been reported, α-CoVs (NL63 and 229E), β-CoVs (OC43 and HKU1), SARS-CoV-1&2, and middle east respiratory syndrome-CoV (MERS-CoV) [10]. Among them, SARS-CoV-2 is known to be the seventh viral category to infect the people and are serious ailment causing organisms now-a-days. To curb the current outbreak, stringent measures to mitigate person-to-person transference of COVID-19 have been executed. Globally, countries are responding differently to the COVID-19 outbreak. Overloading of the local health systems has been resulted due to delayed detection and response across globe. On the contrary, effective and strong therapeutic strategies have been put in place by several nations that led to fewer deaths since the beginning of the pandemics [11].

Despite the availability of plethora of literatures, emphasising the symptoms, epidemiology, transmission, pathogenesis, diagnosis and clinical manifestations, none of the previous state-of-the-art has been devoted the real efforts on repurposing as well as the novel therapeutic strategies at current level of the global hallmarks of COVID-19, in the best of our knowledge. This article is consequently devoted to review the explored scientific insights on our substantial attention towards cytokine storm syndrome (CSS), mesenchymal stem cells (MSCs) therapy, pro-inflammatory mediators like acute respiratory distress syndrome (ARDS), degradation of viral protein capsids by PROTACs, Ubiquitin-proteasome framework, SARS-CoV-2 nucleocapsid protein (nCoV N), proteasome activator (PA28γ), etc to the arsenal of treatments for COVID-19. Furthermore, extensive searches have been attempted to design a schematic illustration of recently discovered repurposing and novel therapeutics that blocks the different steps in the COVID-19 replication signalling pathway. Moreover, the current review also covers the current scenario of COVID-19 epidemiology, pathogenesis, symptoms, transmission, pathogenesis, diagnosis, and clinical manifestations by representing heat-map diagram showing the database of antiviral agents COVID-19. The last section of the review encompasses our creative and real effort to steal the attention of emerging scientists towards the unexplored insights into the notable therapeutic strategies in an anticipation to combat COVID-19 disease. These future directions ultimately could inform the utility of a proof-of-principle in discovery of drugs to fight against the pandemic.

2. Epidemiology

Coronavirus disease 19 (COVID-19) is an extraordinarily transmittable and pathogenic viral infection caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), which originated in Wuhan, China in December 2019 and spread across the globe [12]. The infectibility of these viruses ought to be in the wild only until the world spotted the outbreak of severe acute respiratory syndrome (SARS) in 2002 and middle east respiratory syndrome (MERS) in 2012 [12,13]. (SARS-CoV) spreading to five landmasses in 2002 and Middle-East Respiratory Syndrome Coronavirus (MERS-CoV) in Arabian Peninsula in 2012 indicated that these gathering of infections are zoonotic, which can transmit from the animals to people and from people to people [6,14]. Although the disease spread in the wild across the globe, the transmission to humans from the wild was negligible, and still unclear of the mode. However, analysis in the whole genome sequence of the bats was found with similarity index to be 96% identical with a severe acute respiratory syndrome-like (SARS-like) bat viruses and 79.5% similar with SARS-CoV, suggesting it to be the probable means of transmission to the humans [15,16]. Table 1 shows the comparative study of the epidemiological characteristics among the SARS-CoV, MERS-CoV, and 2019-nCoV. Although the standard mode of communication is still unclear due to its interspecies jumping capacity [8,12], subsequent studies have shown that snakes [17], bats and minks [18], pangolins [15] could be the intermediate hosts for the transmission to humans. Still, intermediate hosts may have multiple hosts [19]. The key reservoirs and the probable modes of transmission pathway of the disease is described in (Fig. 1).

SARS-CoV's pandemic origin believed in assimilating by people from feral wild predators, such as civet cats and raccoon dogs, who, in turn, thought to have caused by rhinolophid bats infection [20]. Although the transmission is not by natural vectors, however, relying upon the disease, species can transmit through fomites or aerosols as well as fecal-oral courses [11]. One of the essential zoonotic reservoirs for the virus could be the domestic animals that facilitate transmission to humans [21]. Nonetheless, the human-to-human transmission has been the essential mode of spreading pandemics, which has happened in working environments, homes, and open transportation. The most significant course of human-human spread seems, by all accounts, to be directly or indirectly through contact of the mucosae with irresistible

Table 1
Comparative study of the epidemiological characteristics among the SARS-CoV, MERS-CoV, and 2019-nCoV. DPP4 - Dipeptidyl peptidase-4; CD26 - Cluster of Differentiation 26; TMPRSS2- Transmembrane protease, serine 2; ACE-2- Angiotensin-Converting Enzyme 2; ORF –Open Reading Frame; SARS-CoV - Severe acute respiratory syndrome coronavirus; MERS-CoV – Middle East Respiratory Syndrome Coronavirus; 2019-nCoV – 2019 Novel Coronavirus.

Characteristics	SARS-CoV	MERS-CoV	2019-nCoV
Year	2002	2012	2019
Origin	Guangdong, China	Arabian Peninsula, Republic of Korea	Wuhan, China
Genus	*Beta coronavirus* Lineage B	*Beta coronavirus* Lineage C	*Beta coronavirus* Lineage B
Gene	RNA	RNA	RNA
Nucleotide length	29,727 ntds	30,119 ntds	29,903 ntds
Natural Host	Bats	Bats	Bats
Intermediary Host	Civets, Raccoon Dogs	Dromedary Camels	Pangolins, Marmots
Affected Countries	26	27	216
Total Cases (Global)	8422 (June 30, 2020)	2494 (June 30, 2020)	10,185,374 (June 30, 2020)
Total Deaths	916	858	503,862 (June 30, 2020)
Total Cases (India)	03	–	585,493 (June 30, 2020)
Total Deaths (India)	–	–	17,400 (June 30, 2020)
Transmission mode	Zoonotic	Zoonotic	Zoonotic
Binding site	ACE-2	DPP4/CD26	TMPRSS2, ACE-2
Susceptible cell line	Respiratory Tracts; Liver; Kidney	Respiratory; Monocytes; Lymphocytes; Intestinal; Liver; Neural; Kidney; Histiocytic cell lines	Respiratory Tracts; Neural; Kidney
Viral replication efficiency	Low	High	Extremely High
Gene order characteristics	5′-Replicase ORF1ab, spike (S), envelope (E), membrane (M), and nucleocapsid (N)-3′	5′-Replicase ORF1ab, spike (S), envelope (E), membrane (M), and nucleocapsid (N)-3′	5′-Replicase ORF1ab, spike (S), envelope (E), membrane (M), and nucleocapsid (N)-3′

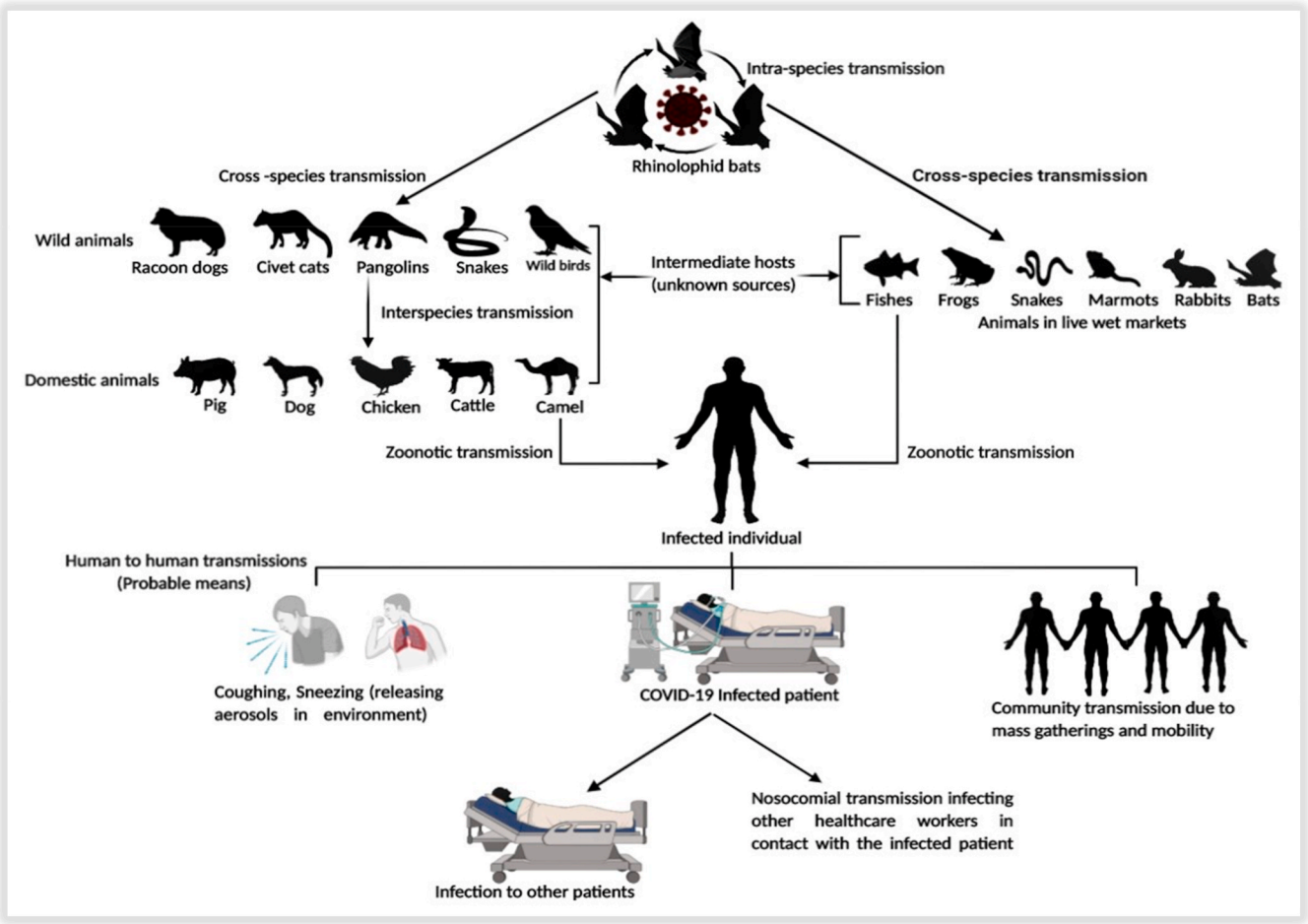


Fig. 1. Key reservoirs and probable modes of transmission of SARS-CoV2.

respiratory droplets or fomites [22]. However, reports have suggested that the SARS-CoV found in tears, but the infection through conjunctival or oral means is still unclear [23]. SARS-CoV2 spreads for the most part by air-droplets created because of the coughing or sneezing of an infected individual. One can get the disease by being in close contact with the infected patient, mainly if they do not cover their face when coughing or sneezing. Another means of the transmission is contacting any such contaminated surface or fabric. Afterward, communicating one's mouth, nose or eyes can transmit the disease as the droplets reside on surfaces and garments for a long time [24]. However, some individuals with the disease, yet with no genuine symptoms, can likewise spread the infection [25]. Still, a significant threat prevails due to asymptomatic and pre-symptomatic virus transmission to infection prevention. In comparison, people with moderate and unspecific signs and isolation are often challenging to classify [26]. It is essential to know the exact incubation time of any disease to control its spread as it gives the establishment for epidemiological counteraction, clinical activities, and medication revelation. This period is the time from infection to the phase where the disease symptoms are seen [27]. The incubation period of SARS-CoV2 in the host ranges from 2 to 14 days as estimated by WHO, contagious during that period. After that, the infection may transmit during the incubation time wherein the asymptomatic carriers of SARS-CoV2 accounting for 1% confirmed by the laboratory testing [28]. They ought to infect the people with immunosuppression, older people, and young neonates, responsible for upper respiratory infections, common cold, and nosocomial viral infections as a significant symptom with the fatality emergence in humans. In severe cases, the disease can lead to the condition of pneumonia, respiratory syndrome, chest and muscle pain, kidney failure, and even death [15].

2.1. *Pathogenesis*

The immune response in the host is associated with the infiltration and pathogenesis SARS-CoV-2. The trimeric transmembrane spike (S) glycoprotein mediates the entry of the virus into the host cells. S is class I viral fusion protein synthesized as a chain of ~1300 amino acids forming a crown-like structure, which leads the role in neutralizing the antibodies [29]. The infection initiates when the virus enters the host cell attaching the "Viral Spike Protein" to the cellular receptors. Attachment of the virus, the host cell's proteolytic enzymes cleaves and activates the spike macromolecule attached to the receptor [30], accompanied by cell membrane fusion, the primary target being the lung epithelial cells [31]. In this context, the inter-human transmission of the disease ought to have caused by the binding of the receptor-binding domain (RBD) of the viral spike protein to a cellular receptor known as the angiotensin-converting-receptor-2 (ACE-2) [32, 33] and the transmembrane protease serine-2 (TMPRSS2) [34]. Alveolar cells in the lung contain plenty of ACE2, enabling COVID-19 to be harbored within the alveoli [35]. The binding protein of the SARS-CoV2 to the ACE-2 receptor possesses almost 10–20 times higher affinity than the SARS, indicating that the efficiency of SARS-CoV2 transmitted to the others is readily higher [21]. TMPRSS2 is an alveolar protease and human airway, which colocalize captured by the immunoprecipitation of ACE-2 [36]. ACE-2 is a type I membrane protein consisting of *N*-terminal peptidase domain (P.D.) and C-terminal collection-like domain (CLD) ending with ~40 residues intercellular segment and forming single

transmembrane helix [37], expressed in heart, lungs, intestine, and kidneys and associated with cardiovascular disorders [38].

Studies from the electron microscopy suggested that the ACE-2 receptor exists in the dimeric form, able to be in both "open" as well as "closed" confirmations [39]. Together, ACE-2 and TMPRSS2 facilitate the virus's entry into the cells [36]. The hypothesis suggests that the renin-angiotensin-aldosterone system (RAAS) inhibition boosts the regulation of ACE-2 expression, thereby facilitating the entry of virus and replication [40]. Coronavirus RNA has a 5′ methyl group and 3′ poly-A tail, attaching to the host's free ribosomal unit contributing to translation and the chain formation of polypeptides [30]. Binding of the receptor is regulated via the receptor-binding domain (RBD) of the subunit S1. Proteolytic activation of the S2 subunit after binding to the ACE2 receptor mediates the interaction between the virus and the cellular membranes (Fig. 2). Because of S glycoprotein's important function in cellular infection, antibodies attachment to S1 and S2 prevents infection [41]. ACE2 generally shows high articulation in alveolar type 2 cells, hence permitting the virus to enter and duplicate in enormous numbers. SARS-CoV-2 gets into alveolar cells and quickly multiplies, which cause quick and massive production of various types of cytokines, including interleukins (I.L.s), interferons (IFNs), colony-stimulating factors (CSFs), chemokines and tumor necrosis factors (TNFs) in body fluids. Such cytokines activate the immune cells continuously and accumulate at inflammation site leading to "cytokine storm," resulting in causing up edema, fever, respiratory congestion, injury in lung tissues, eventually leading up to the situation of acute respiratory distress syndrome and respiratory failure [42]. ACE2 is not only found in the respiratory tract organs but also duodenum, small intestine, rein, and the testis. Spread of the infection in target cells can cause bowel dysfunction, kidney failure, reduced fertility, and other disorders [42]. COVID-19's pathological results showed that over activation of T cells, evidenced by an increase in Th17 and high cytotoxicity of CD8 T cells, partly accounts for the extreme immune injury [43].

Insights on the pathogenesis of SARS are studied through quantitative analyses of viral load. In the lower respiratory tract, the viral load is higher than in the upper airways. During the first 4 days, the viral load in the upper respiratory tract and stool is low and peaks at about day 7–10 of the disease. In strong comparison, influenza virus loads peaks immediately after the onset of clinical symptoms. This rare SARS-CoV infection trait explains its poor transmissibility early in the epidemic [24]. Studies suggested that no substantial correlation was observed between viral load and health effects, including oxygen support, or survival. Interestingly, some publications have reported extreme cases of COVID-19 with high morbidity that arise late in the disease phase, meaning that severe symptoms are unlikely to be associated with high viral load. In short, evidence indicates that SARS-CoV-2 RNA can be identified in individuals 1–3 days before their onset of symptoms, with the highest viral loads observed about the day of symptom onset as measured by RT-PCR, accompanied by a steady decline over time [44].

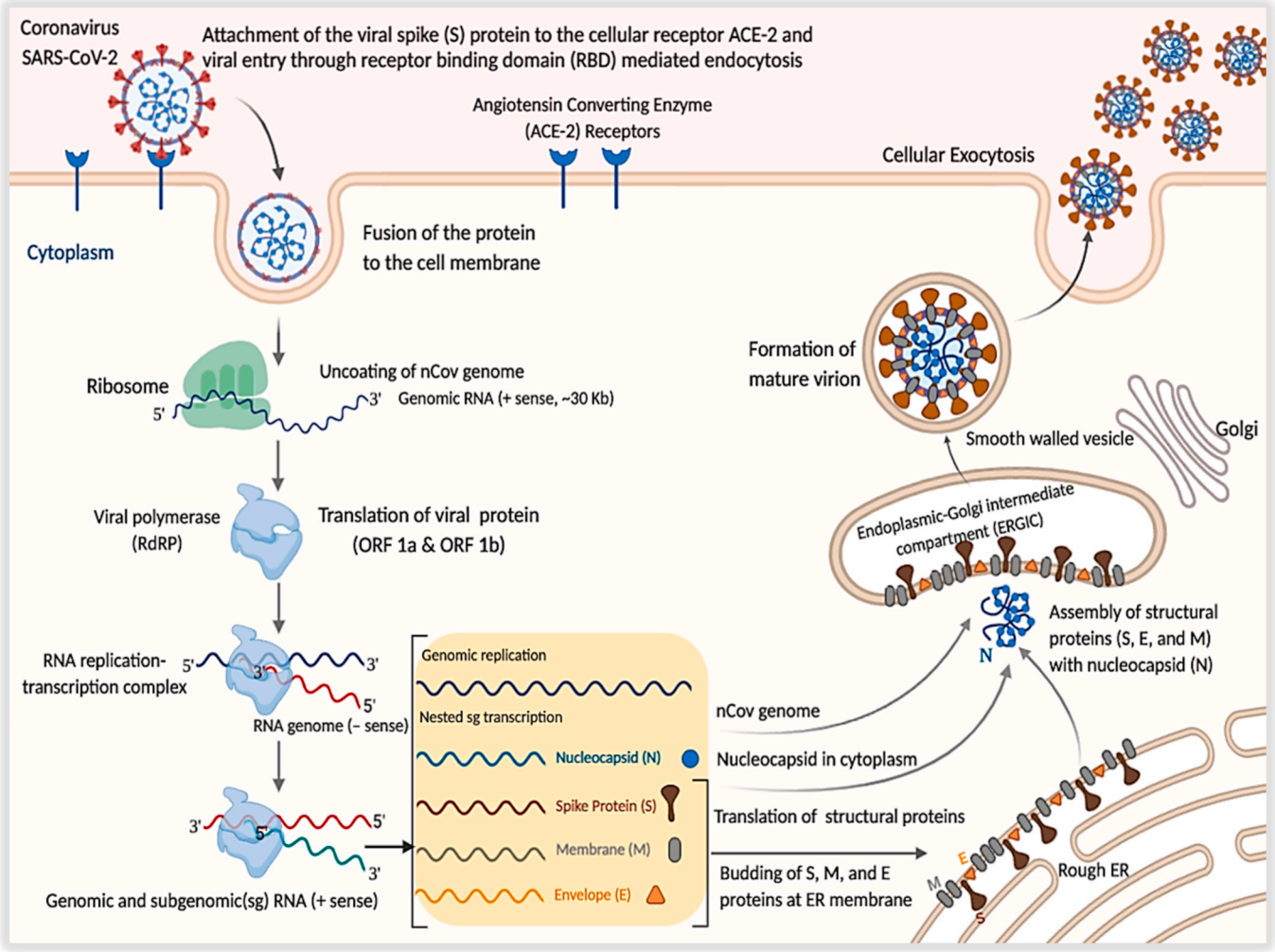


Fig. 2. The SARS-CoV-2 pathogenesis mechanism.

2.2. Clinical manifestations

The mean period of incubation is approximately 3–9 days, ranging from 0 to 24 days [1]. The mean interval is around 3–8 days, which shows up earlier than the end of incubation, suggesting that one becomes contagious before symptoms are present (about 2.5 days before symptoms start) [45]. It is estimated that around 44% of transmission occurs before symptoms develop, which are asymptomatic, thereby, increasing the chance of transmission [46]. The initial clinical manifestations of the viral disease begin to occur after some 4–6 days of incubation. The time from the onset of COVID-19 symptoms to death ranged from 6 to 40 days, depending on the status of the patient's age and immune system [48]. Patients with pre-existing medical conditions and those with age >70 years were likely to have a shorter duration in showing symptoms [47]. Most people at the onset show symptoms like fever (88%), dry cough (68%), fatigue with muscle pain (38%), and shortness of breath with some minor respiratory disorders like rhinorrhoea, sore throat etc. (Fig. 3). In contrast, other clinical signs are nausea, diarrhoea, headache, sputum production, dyspnoea, lymphopenia, and haemoptysis [48]. Patients diagnosed with COVID-19 displayed irregular breathing counts, and elevated pro-inflammatory cytokines in plasma [31]. Some of the patients may show variation in the counts of leukocytes and drop in the lymphocyte's levels [49]. Mainly if they are elderly or have some pre-existing health condition, patients may experience breathing difficulties. In such cases, the situation may need the patient to hospitalize. In worsening cases, the person may experience a condition where the pleural cavity of the lungs is filled with fluids, leading to a situation of acute respiratory distress syndrome (ARDS). Further, the development of the disease ends in the worsening of the symptoms, and at this factor, the patient is shifted to ICU. Patients with milder symptoms probably have more abdominal pain and lack of appetite [30]. However, the signs in the earlier days of the infection are hard to find out. Symptoms reported ranged from mild to severe disease and death due to confirmed coronavirus disease 2019 [50]. The overview of systemic progression of the COVID-19 symptoms from the early stage to the fatality stage with the recovering phase is summarized in Table 2.

Table 2
Systematic progression of symptoms in COVID-19 patients and their recovery stages.

Case Types	Day	Symptoms	Recovery Stages	Source
Mild	1	Common cold		[30]
	2	Mild sore throat		[51]
	3	Throat pain, Rise in body temperature, vomiting, nausea.		[51]
	4	Severe throat pain, weakness, joint pains		[51]
	5	Mild fever, dry cough, dyspnoea		[30]
	6	Breathing difficulty, Tiredness	Mild Cases Recovery	[52]
Moderate	7	Severe coughs, breathing difficulties, high fever, headache, body pain, worsening diarrhoea, and pneumonia. Patients need to admit to the hospital.		[30,51, 53]
	8	Symptoms worsen for patients with pre-existing medical conditions.		[30]
	9	Frequent breathing, Average Sepsis infection starts (affects 40% of patients)		[51]
	10	Chest Diagnosis for Respiratory Distress	Moderate Cases Recovery	[54]
Severe	11	Loss of appetite, abdominal pain		[53]
	12	Fever relaxes slowly, breathing difficulties ceases.		[52,55]
	13			
	14	Mouth cough persists, even after hospital discharge.		[52]
	15	Possible Cardiac Injury or Kidney	Severe Cases	[56]
	16	Injury	Recovery	
Critical	17	Vulnerable patients develop a secondary infection in the lower respiratory tract, ARDS.		[30,54]
	18	Cases Become Fatal requiring treatment in ICU.		[57]
	19	Severe conditions lead to blood coagulation and ischemia.		[54]
	20	Requires oxygen therapy and ventilation		[54]
	21	Survivors recover Completely but are still contagious and prone.	Critical Cases Recovery	[54]

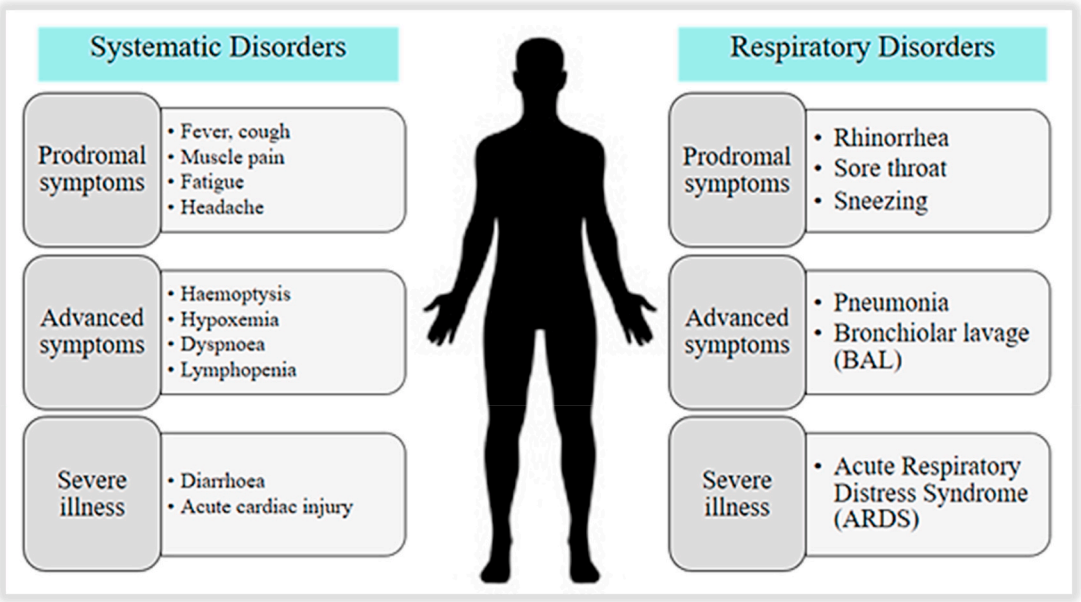


Fig. 3. The systematic and respiratory symptoms of COVID-19 infection.

3. Diagnosis

Tracking and diagnosing the suspected individual is critical in understanding the epidemiological link, suppressing the chance of transmission, and informing the management of the case. A suspected case of health problems with respiratory problems, fever, sore throat and any chance of contact with the person from the areas of persistent local transmission or patient contact with a similar travel history or those with confirmed COVID-19 infection is likely to be the carrier of the disease [58]. However, some individuals with the condition may also spread the virus without any genuine symptoms (asymptomatic) [25]. Clinical specimens from sputum, nasal secretions, blood, and broncho-alveolar lavage (BAL), collected from suspected patients used for the laboratory diagnosis [59]. There are different ways of diagnosing the disease based on clinical diagnosis, molecular diagnosis, immunodiagnostics, microbial examination, etc. [60]. The following procedures used for the determination of patients with suspected infection: real-time fluorescence (RT-PCR) to detect the positive nucleic acid of SARS-CoV-2 in sputum, throat swabs, and lower respiratory tract sample secretions [61, 62].

Nevertheless, the test's reliability is uncut, as the PCR can only identify the virus if it is present in the suspect's sample. Consequently, output about the infection becomes uncertain, leading to sometimes false-negative results depending upon the concentration and sensitivity [55]. Chest X-Ray may be other diagnostic criteria. C.T. imaging shows ground-glass opacities, bilateral infiltrates, and sub segmental consolidation, even in cases with no clinical evidence of respiratory tract infection (asymptomatic), considering being sensitive and specific diagnostic approach [63]. In cases with the negative molecular test, C.T. imaging has been used to diagnose suspects with COVID-19 infection [64]. Immunodiagnostics is also playing a crucial role in the diagnosis, where the epidemiological link of the suspected individual is found to be useful. Still, then again, the molecular correlation is negative [65]. This tests the presence of antigens (viral proteins) within the COVID-19 patients with the immunoglobulins (IgG and IgM) protein detection reagents and SARS-CoV-2 antigen detection reagents victimization the assay (ELISA) technique, diagnosed by rapid diagnostic test (RDT) from the tract of a respiratory tract of the infected individual [66]. Other lab diagnoses are generally non-specific. The count of white cells is typically normal or low and may lead to lymphocytopenia; serious illness associated with a lymphocyte count <1000 [58].

4. Treatment Strategies

More cases of COVID-2019 are coming up with the passing of each day, and the fear of the novel coronavirus unfortunately has true becoming a pandemic disease. Treatments provide doctors with resources to support the patients to produce a vaccine. Therefore, the development of vaccines at the earliest is of the utmost to curb the disease. Further, to understand the host, genomics, epidemiological links, and transmission modes of nCoV, constant efforts are being made at international, national, and individual levels [67]. Globally, drug manufacturers, research labs, and other organizations are producing several specific kinds of pharmaceutical drugs for COVID-19 therapy. Potential drugs include medications already employed or tested for the diagnosis of certain diseases and recently discovered or specially developed medicines (Fig. 4). Still, scientists worldwide are working unceasingly, intending to create an optimal antiviral agent and SARS-CoV-2 vaccine [69]. Yet the screening of new small molecule drugs in combinations and other agents with potent *anti*-SARS-CoV-2 effects can successfully derive new and better chief compounds and agents, which may be useful in COVID-19 therapy [26]. Several methods of general aspects in discovering antiviral therapy [68], like testing of the broad-spectrum existing antiviral drugs using standard assays [69], screening of existing molecules or libraries including transcription properties in cell lines [70], new drug redevelopment of the genome specificity and biophysical understanding of the human coronavirus pathogen [71] can assess the potential therapy for the human pathogen coronavirus [70]. Further progress of clinical trials worthy of antiviral agents includes lopinavir and ritonavir, ribavirin, interferon α2b, chloroquine phosphate, protease inhibitors, interferon β, and Arbidol. SARS-CoV-2 virions can be inactivated to utilize the cause of neutralizing antibodies; inactivated vaccines could be an approach for the conventional vaccine that can relate through this strategy [26]. Doctors in different medical centers worldwide to manage their cases of COVID-19 are presently using such antiviral drugs either individually or in combinations, but the precise effectiveness remains uncertain. To date, this is still not obvious that a single medication or a mixture of several antiviral agents is sufficient for the care of COVID-19 patients [67]. Studies suggested that the corresponding enzymes drug-binding sites in SARS-CoV-2, SAR-CoV, and MERS-CoV might be similar. Therefore, the drugs used against SARS and MERS at the emergency stage may guide the quick development of specific medications to treat COVID-19 [72].

4.1. Drug repurposing as well as novel drugs treatment strategies

Drug repurposing also known as drug reprofiling or repositioning that assures to recognize antiviral agents for the novel coronavirus disease in a transient fashion. We also propose a perspective that antiviral combinations with a 'double hit effect' may present the best possibility of positive result and clinical translatability. Drug repurposing is a budding approach where existing medicines, already tested on safety parameters in humans, are rationalized to fight difficult-to-treat diseases. Such repurposed drugs may conclusively not yield a substantial clinical benefit when used individually but scrupulously combined cocktails could potentially be very effective, as demonstrated for HIV in the 1990s; the pressing challenge now being which combination. Based on the early phase clinical trials testing, broad-spectrum antiviral agents (BSAAs) that have been presumed 'safe-in-man' have been vaunted as good drug repurposing candidates [73]. In a highly accessible database of 120 experimental, investigational and approved agents, 31 potential candidates have been summarized for COVID-19 trials [74] (Fig. 5). Ideally, taking merit of the promiscuity of viral replicative mechanisms and host interactions, BSAAs target two or more viral families [75]. In the wake of COVID-19 outbreak in December 2019, fistful existing BSAAs have been expeditiously put forward into clinical trials, traversing Phases II though IV. Umifenovir (a membrane fusion inhibitor targeting viral entry) and lopinavir/ritonavir (a drug combination targeting viral protease), both are accepted for the indications of Influenza and HIV. They are presently being contemplated in various combinations in a Phase IV clinical trial for pneumonia related with COVID-19 [NCT04255017]. A novel nucleotide analog prodrug, Remdesivir, is being investigated at Phase III level for mild and moderate SARS-CoV-2 [NCT04252664]. In preclinical studies, remdesivir demonstrated activity against coronaviridae species involved in SARS-CoV and Middle East respiratory syndrome (MERS-CoV) [76]. Prominently, in a randomized, controlled trial for Ebola virus disease, remdesivir displayed an antiviral effect [77]. In accordance with promising in vitro data (NCT04261517), antimalarial hydroxychloroquine, is also being evaluated in combination therapy as Phase III agents for viral pneumonia [NCT04261517]. Chloroquine, demonstrated to have antiviral activity at entry and post-entry stages of the SARS-CoV-2 infection. It can boost the antiviral activity of remdesivir and significantly act as a synergizer of BSAAs [78]. At more initial phases, favipiravir (broad-spectrum inhibitor of viral RNA polymerase) in combination is also on a Phase II clinical trial for novel coronavirus-associated pneumonia [ChiCTR2000029544]. Ultimately, preclinical studies of ribavirin (ribonucleic analog) have demonstrated in vitro activity against SARS-CoV-2 [79].

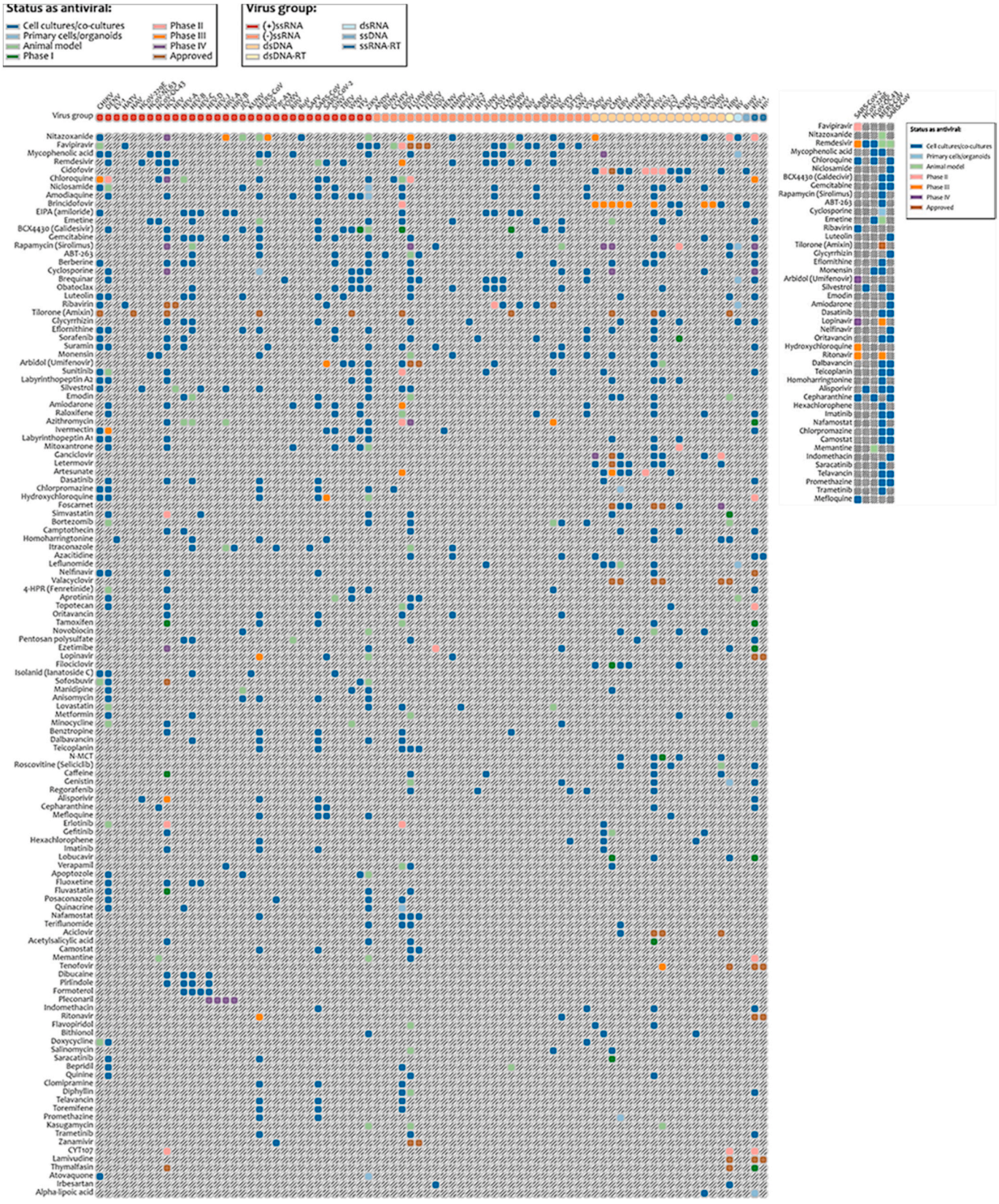


Fig. 4. A heat-map showing the database of antiviral agents against different categories of viruses clustered in groups from highest to lowest number of targeted viruses (left) (https://drugvirus.info/). Antiviral agents in current trials against different strains of coronavirus (right). Shadings in different colours indicate different statuses of antiviral-agents; ray scale indicates no reported results. Abbreviations: ds-double-stranded; RT-reverse transcriptase; ss-single-stranded.

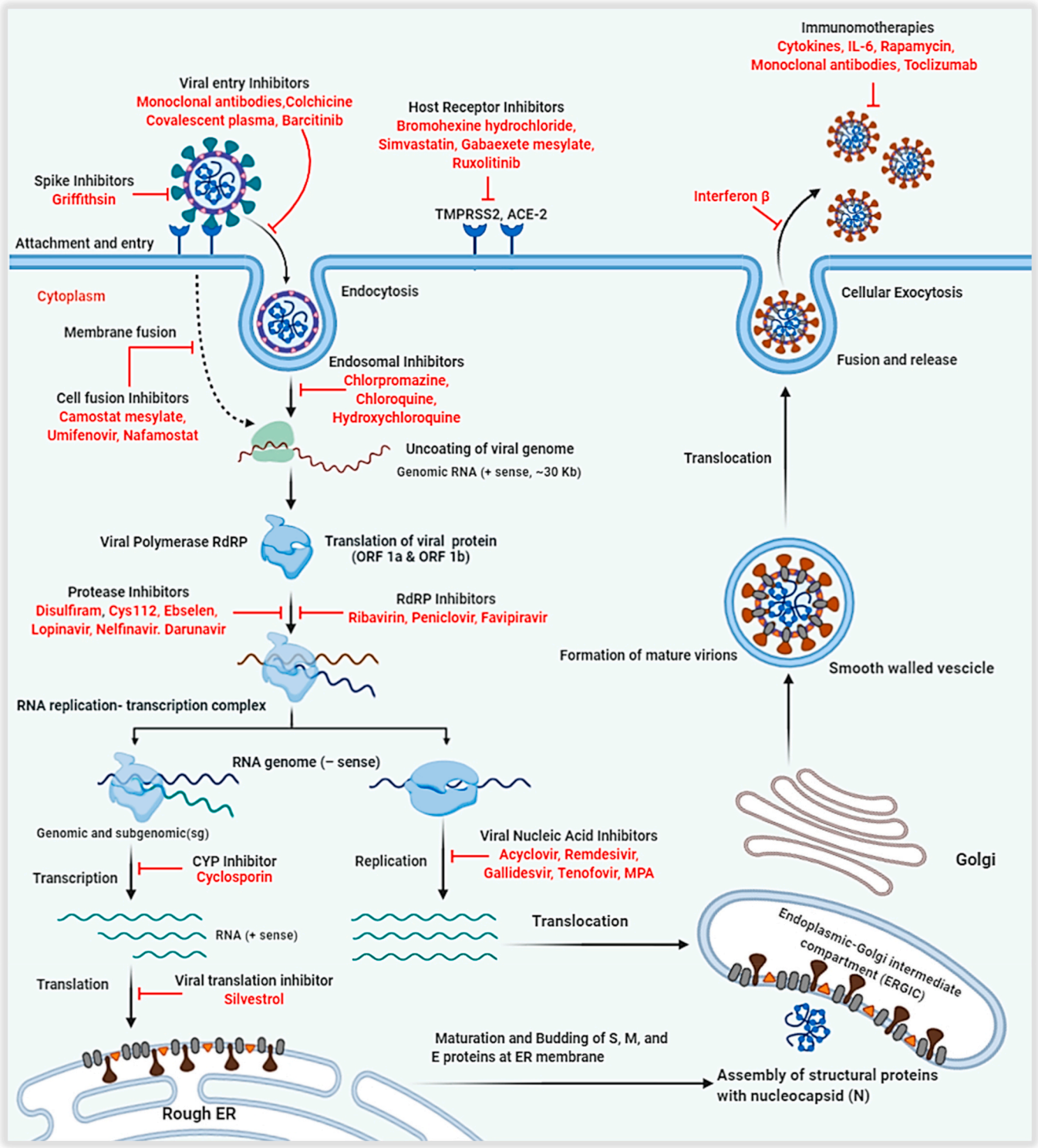


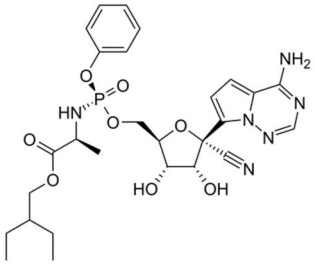
Fig. 5. Schematic illustration of the coronavirus replication process demonstrating possible therapeutics against multiple virus-based, host-based and immunotherapy goals for repurposing coronavirus drugs used against SARS and MERS. TMPRSS2- Transmembrane protease, serine 2; ACE-2- Angiotensin-converting enzyme 2; RNA-Ribonucleic Acid; IL-6- Interleukin 6; CYP- Cytochrome P450; ORF- Open Reading Frame; RdRP- RNA dependent RNA Polymerase; MPA- Mycophenolic acid.

4.2. BSAA (Broad Spectrum Antiviral Agents) combination therapy

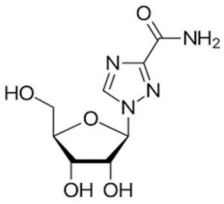
The poor potency of hit compounds as single agents is one of the constraints of phenotypic screens since their maximal tolerated dose is many times sub therapeutic for the new indications being focused [80]. One way to elude this concern is to assess two or more drugs acting on different cellular signalling pathways involving viral replication with limited prolixity. One more approach, which may enable researchers to curb the spectrum of individual antimicrobials for emerging and re-emerging infectious diseases, is high-throughput screening of compound libraries for synergistic combinations at the host–virus interactome level [75,81,82]. These approaches promise to resolve the often-weak activity of BSAAs by enhancing efficacy while strengthening dose mitigation, reducing duration, cost of the drug development

pipeline, decreasing toxicity and reducing appearance of secondary resistance. Currently, therapies for patients with SARS-CoV-2 infection primarily repurpose the medicinal medications available are focused on symptomatic symptoms. The medication regimens include ARDS, accompanied by secondary infections, antibiotics, antiviral therapy, systemic corticosteroids, and anti-inflammatory medications [83]. Remdesivir, an *anti*-Ebola drug, may hold promise is found to be useful as a nucleotide analog in preventing replication of MERS-CoV in monkeys, providing a basis for a rapid test in beneficial aspects of COVID-19 treatment [84]. The treatment therapies applied in the ongoing scenario using antiviral drugs can be categorized into Virus based, Host–based, Immunotherapy and Cellular therapy.

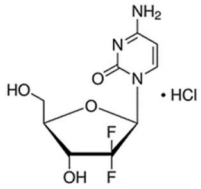
Nucleoside Analogues



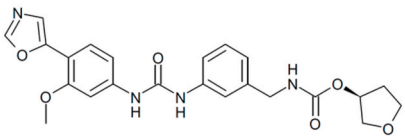
Remdesivir (GS-5734)
Target - Replicase protein 1ab
Route- IV
Mode of action - Prevents RNA polymerase function resulting in ending the transcription of RNA and reduces the production of viral RNA.
COVID-19 trial - **YES**
Phase – III (NCT04252664)



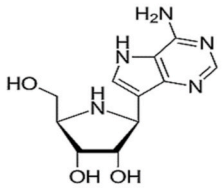
Ribavirin (SCH-18908)
Target - Replicase protein 1ab
Route- PO
Mode of action - Prevents binding of the right nucleotides, resulting in reduced viral replication or the development of defective virions.
COVID-19 trial - **YES**
Phase – II (NCT00578825)



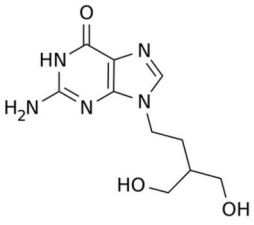
Gemcitabine Hydrochloride
Target - Ribonucleotide-Diphosphate Reductase Inhibitor
Route- IV
Mode of action - Inhibitor of ribonucleotide reductase a deoxycytidine analogue that inhibits DNA synthesis and repair.
COVID-19 trial - **YES**
Phase – II (DB00441)



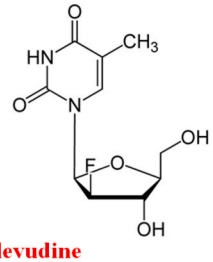
Merimepodib (VX-497)
Target - inosine monophosphate dehydrogenase (IMPDH) inhibitor
Route- PO
Mode of action - IMPDH inhibits synthesis of DNA and RNA, and results in antiviral and immunosuppressive effects.
COVID-19 trial - YES
Phase – II (NCT04410354)



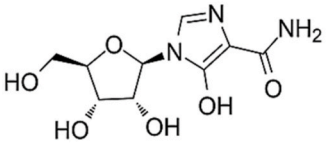
Galidesivir (BCX-3340)
Target - RNA-directed RNA polymerase L
Route – IV/IM
Mode of action - Viral RNA polymerase disruption results in premature termination of RNA strand.
COVID-19 trial - **YES**
Phase – I (NCT03891420)



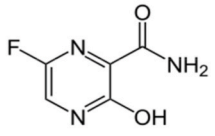
Penciclovir
Target – RNA Dependent RNA Polymerase
Route- PO
Mode of action - Inhibition of DNA synthesis of virus-infected cells inhibiting viral replication.
COVID-19 trial - **YES**
Phase – IV (NCT00820534)



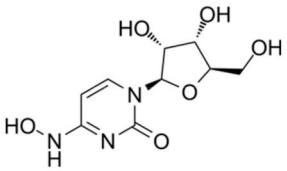
Clevudine
Target – Reverse Transcriptase
Route- PO
Mode of action - DNA-directed DNA polymerase inhibitors causing chain termination and inhibiting the function.
COVID-19 trial - **YES**
Phase – II (NCT04347915)



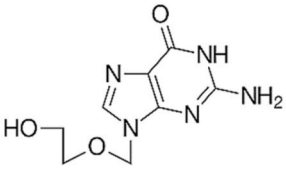
Mizoribine (MZB)
Target - Inosine Monophosphate Dehydrogenase (IMPDH) inhibitor
Route- PO
Mode of action- Inhibition of DNA synthesis in the S phase of the cell cycle.
COVID-19 trial - **YES**
Phase – II (DB12617)



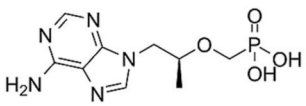
Favipiravir (T-705)
Target - RNA-directed RNA polymerase catalytic subunit
Route – IM, ID, SC, PO
Mode of action - Inhibits RNA polymerase preventing RNA strand elongation and viral proliferation and prevents replication of the viral genome.
COVID-19 trial - **YES**
Phase – IV (NCT04359615)



N4-hydroxycytidine
Target - RNA-directed RNA polymerase catalytic subunit
Route – IP/PO
Mode of action - Antiviral effect primarily through mutagenesis of viral RNA.
COVID-19 trial - **YES**
Phase – Pre-clinical (DB15660)



Acyclovir
Target - RNA-directed RNA polymerase
Route – IV
Mode of action - Doubly flexible nucleoside analogues inhibit RNA dependent RNA polymerase
COVID-19 trial - **YES**
Phase – Pre-clinical (DB00787)



Tenofovir (GS 1278)
Target- Reverse Transcriptase inhibitor
Route- PO
Mode of action - Block reverse transcriptase, an enzyme necessary for viral production.
COVID-19 trial - **YES**
Phase – III (NCT04334928)

Fig. 6. Re-purposed nucleoside analogues drug molecules.

4.3. Virus-based therapy

It utilizes monoclonal antibodies or antiviral peptides that attack specific targets at different stages of viral devices such as enzyme inhibitors, spike glycoprotein, and nucleoside analogues inhibitors [85].

4.3.1. Nucleic acid analog inhibitors

The nucleoside analogues are significant class of antiviral agents that are now widely used in the treatment of numerous types of human viruses. The nucleoside analogues mimic naturally existing nucleosides, which function by terminating the nascent DNA chain [79]. Subsequent incorporation of dinucleotides in the replication and transcription machinery of viral genomes, nucleic acid analogues via such processes change the genetic structure of the virus, resulting in decreased viral fitness with increasing successive replication period may lead to the chain termination [80]. Premature chain termination with the binding

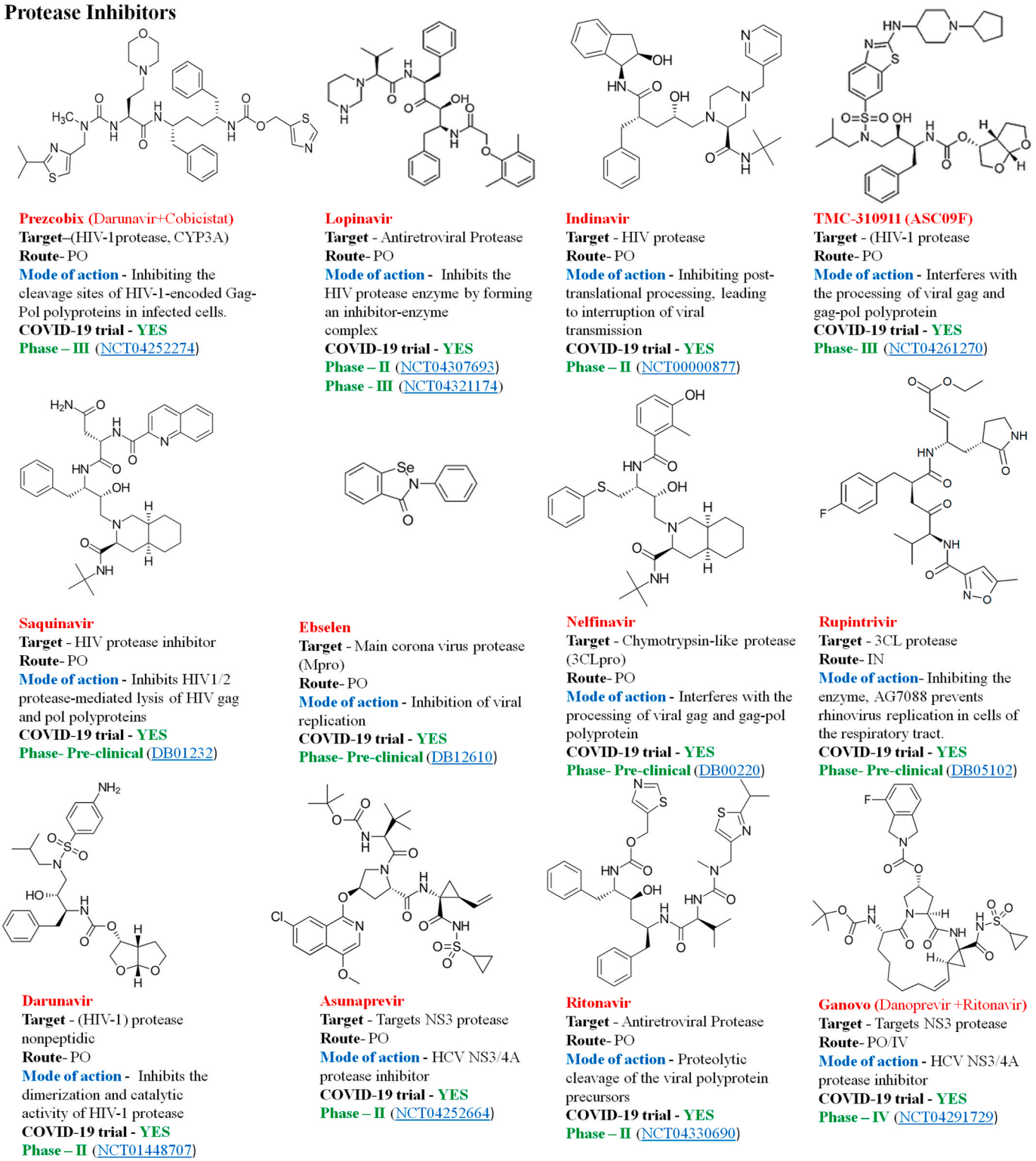


Fig. 7. Some of the common protease inhibitors.

of the chain terminator reduces replication fidelity due to the incorporation of mutagens and depletion of clusters of naturally occurring nucleotides. This presents a strong resistance barrier since the structural stability of the viral binding site in the polymerase targets is large among virus families and resistance mutations [86]. The viral RNA dependent RNA polymerase (RdRP) is conserved across the genera, which ranges from the 70–100%, suggesting nucleic acid analogues could be a potent inhibitor of SARS-CoV disease [87]. Several antiviral nucleic acid analogues as evidence to support their effectiveness against SARS-CoV-2 are described (Fig. 6).

4.3.2. *Protease inhibitors*

Protease inhibitors are synthetic drugs that block the activity of HIV-1 protease, an enzyme that cleaves precursor proteins into smaller fragments required for viral development, infectivity and replication [71]. Protease inhibitors mediate by binding to the active site of the protease enzyme and block the maturation of the freshly formed virions. They usually target the papain-like proteases (PLpro) and chymotrypsin-like proteases (3CLpro) in the family of coronaviridae cleaving the polyprotein (pp1a and pp1ab) [88,89]. Since both the proteins are essential for virus reproduction and regulation of host cell response, thereby are main targets in the production of antiviral drugs. Coronaviruses PLpro are multifunctional enzymes with protease activity to cycle the viral replicase polyprotein and deubiquitinating activity, which presumed to change the innate immune response to infection [90]. 3CLpro are another protease enzyme that cleaves replicase polyproteins during replication. Studies suggest that the 3CLpro has a homology of 96% between SARS-CoV and SARS-CoV2, with negligible variations between the two proteins. Therefore, the drug inhibitors of the SARS-CoV 3CLpro are likely to inhibit the SARS-CoV2 3CLpro becoming a potential target for the disease [91] Fig. 7 demonstrates some of the common protease inhibitors with the potential activity

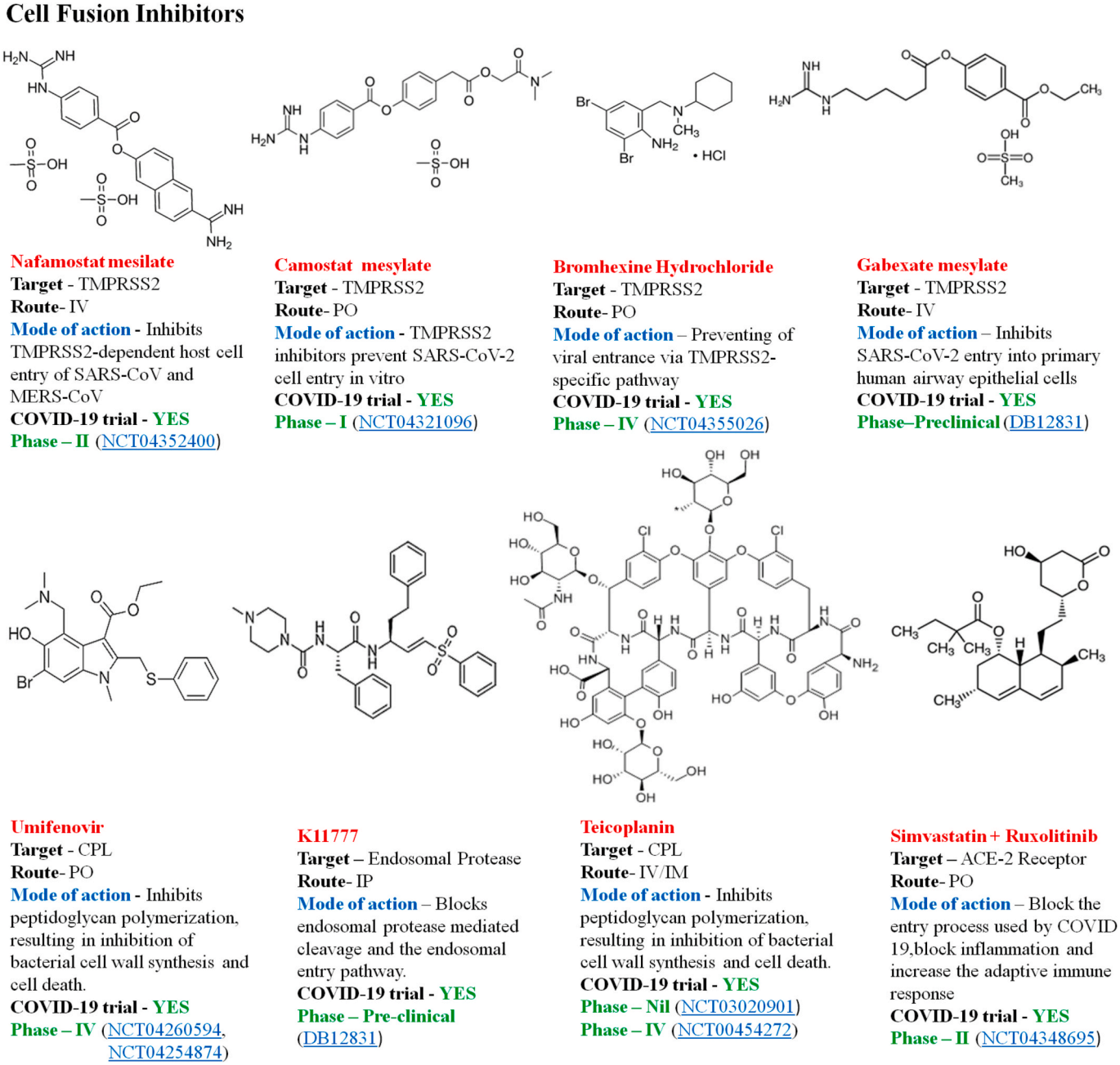


Fig. 8. Representative viral cell fusion inhibitors against COVID-19.

against SARS-CoV2.

4.3.3. Virus-cell fusion inhibitors

The Spike (S) protein of the SARS-CoV2 exposed to the surface, mediates the entry of the pathogen into the host cells, which is the crucial target of antibodies neutralization upon infection [92]. ACE-2 and TMPRSS2 are the receptors, which mediates the fusion of the S protein of the SARS-CoV2 to the host cell. The fusion of the S protein to the ACE-2 receptor is by cleavage through TMPRSS2, which is essential for viral entry and spread of infection [93]. The majority of coronaviruses enter their target cells via plasma membrane fusion, the endosomal endocytosis through the protease enzyme cathepsin L (CPL) that cleaves the S glycoprotein into two subunits S1 and S2, S2 fusion with the cell membrane is another entry mechanism [94]. Inhibitors of the TMPRSS2 and CPL activity may become a potential antiviral target thereby inhibiting the mechanism of cell-fusion and entry of the SARS-CoV2 into the cells. Fig. 8 illustrates some of the cell fusion antiviral drug molecules against SARS-CoV2.

4.3.4. Neuraminidase inhibitors

Neuraminidase inhibitors (NIs) are drug molecules targeting the category of influenza A and B viruses, which are currently in the therapeutic trial of COVID-19. NIs interact with the release of progeny influenza virus from contaminated host cells, a mechanism that protects new host cells from infection and thus avoids the spread of respiratory tract infection [95]. Fig. 9 illustrates the common neuraminidase inhibitors in trial against COVID-19.

4.4. Host-based Therapies

It include the host immune responses and host based drug targets. Immune response improves the effect of interferon reaction in the host factors used by SARS-CoV-2 for replication influencing host-signalling pathways [85]. Drug targets emphasizes on the receptors through which the virus binds to the cellular receptors (ACE-2 and TMPRSS2) on the surface and initiates the infection [91]. This includes the antimalarial drugs and the drugs of Janus-Kinase inhibitors.

4.4.1. Interferons

In clinical studies, synthetic recombinant interferon α has been shown to be successful in treating SARS patients linked with higher oxygen supply and greater detection of radiographic lung opacities than just systemic corticosteroids [71,96]. Relative to the glucocorticoid-treated community alone, the pulmonary X-ray irregular recovery period has shortened by 50% across the interferon-treated population, indicating to be an important MERS-CoV replication inhibitor [97]. Throughout the diagnosis of patients with SARS or MERS, different formulations of interferon alfa or interferon beta and other antivirals such as ribavirin and/or lopinavir – ritonavir is used [98]. Such results indicated interferon could be included in COVID-19 therapy. Table 3 illustrates some of the common interferon therapies in current clinical trials against COVID-19.

4.4.2. Antimalarial drugs

Chloroquine (CQ) and hydroxychloroquine (HCQ) are aminoquinolines and implemented for over 50 years for the prevention of malaria and autoimmune diseases [99]. It is reported to be successful in COVID-19-associated pneumonia, which prevents pneumonia exacerbation, faster conversion to negative viruses and shortens the period of the disease [100]. The SARS-CoV-2's primary target cells are enterocytes and pneumocytes when it enters into the body, which involves fusion of viral and cell membranes, and it binds to these cells with the aid of spike protein-host protein interaction [101]. Chloroquine prevents contact with the virus by elevating the endosomal pH necessary for virus/cell fusion as well as interacting with the glycosylation of virus cell receptors. Its anti-inflammatory and immunomodulative action may add to COVID-19's effectiveness [102]. Fig. 10 illustrates some antimalarial drugs in clinical trial against COVID-19.

4.4.3. Janus kinase inhibitors

Numb-associated kinase (NAK) target drugs in patients with COVID-19 pneumonia reduce systemic and alveolar inflammation by inhibiting important cytokine signals involved in immune-mediated inflammatory response [103]. Studies define COVID-19's cytokine profile as close to the one of hemophagocytic lymphohistiocytosis (sHLH). IL-2, IL-7, GCSF, INF-gamma, monocyte chemoattractant protein 1 (MCP1), macrophage inflammatory protein-1 (MIP-1) alpha, and TNF-alpha are distinguished by decreased sHLH. Inhibition of JAK may be a therapeutic choice [104]. Baricitinib is a small molecule inhibitor of Janus kinase subtype 1 and 2 (JAK1, JAK2) licensed for the treatment of TNFα-antagonist-resistant rheumatoid arthritis in the EU and USA. Regardless of its dual purpose, Baricitinib was identified as a potentially beneficial agent in COVID-19 patient in vitro anti-inflammatory and antiviral function [105]. Fig. 11 describes some of the JAK inhibitors currently in clinical trial against COVID-19.

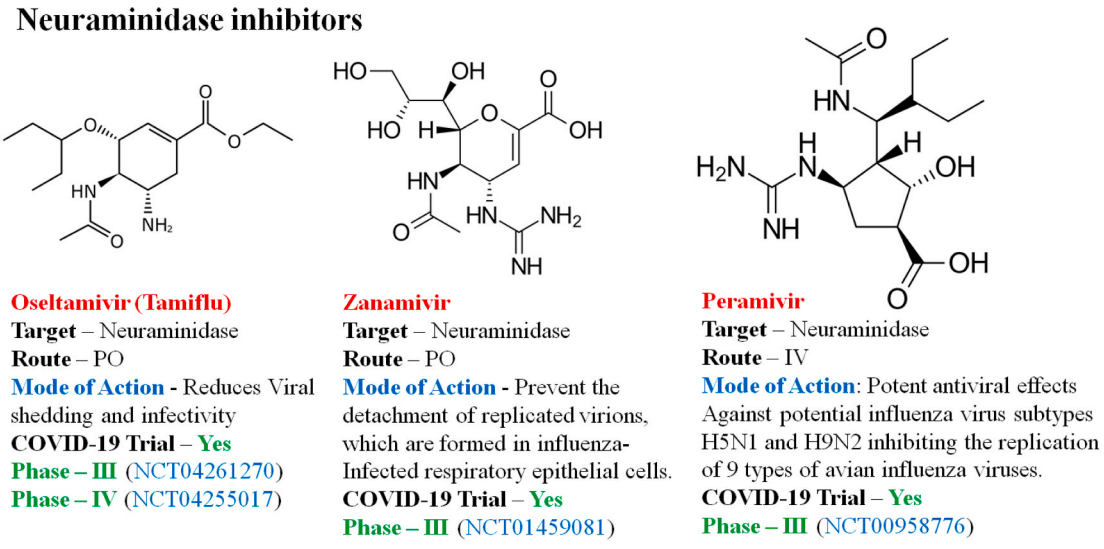


Fig. 9. Representative neuraminidase inhibitors against COVID-19.

Table 3
Some common interferons with the efficacy in the treatment in COVID-19. IFN- Interferon; IM-Intramuscular; IV-Intravenous; SC-Sub-cutaneous; PO-Oral; PFOR-Pyruvate: ferredoxin oxidoreductase; INH- Inhalation; PAR- Parenteral; IP- Intraperitoneal; IFN-α-Interferon alpha; IFN-β- Interferon beta; poly I:C- Polyinosinic-polycytidylic acid; peg–IFN–λ1a-Peginterferon lambda-1a.

Compound	Chemical Formula	Target	Route	Mechanism of action	COVID-19 Trial Status
IFN-β-1a	$C_{908}H_{1408}N_{246}O_{252}S_7$	IFN-β receptor 2	SC	Blocking of the key SARS-CoV-1 protease, which results in viral replication inhibition	Phase- 4 (NCT04350671, NCT02735707)
IFN-α-2b	$C_{16}H_{17}Cl_3I_2N_3NaO_5S$	IFN-α/β receptor 2	IM, SC, IV	Inhibition of protein synthesis, inactivation of viral RNA, and enhancement of phagocytic and cytotoxic mechanisms	Phase 1 (NCT04379518)
IFN-α-con-1	$C_{860}H_{1353}N_{227}O_{255}S_9$	IFN-α/β receptor 1/2	SC	Induces innate antiviral immune response.	Phase-1 (NCT01227798)
peg–IFN–λ1a	–	IFN-α/β receptor	SC, IV	Preventing virus infection by maintaining an antiviral condition	Phase-2 (NCT04331899)
Nitazoxanide	$C_{12}H_9N_3O_5S$	PFOR	PO	Antiprotozoal behaviour by interfering with the electron transfer reaction based on PFOR	Phase-2 (NCT04360356)
Novation (Recombinant)	–	IFN-α	INH	Interferon stimulants	Phase-4 (ChiCTR2000029496)
IFN-β-1b	$C_{908}H_{1408}N_{246}O_{253}S_6$	Leukocytes	SC	Modulates immune response by reducing antigen presence and increasing T-cells suppressors	Phase-2 (NCT04350281)
Calderon (IFN-α-n3)	–	IFN-α/β receptor 1	PO, PAR	Immunomodulating cytokine	Phase-2 (NCT00215826)
poly I:C	$C_{19}H_{27}N_7O_{16}P_2$	IFN-α	IM, IN, IV, IP	Produces antiviral effects by IFN induction and stimulation of macrophage phagocytosis	Phase- 4 (ChiCTR2000029776)

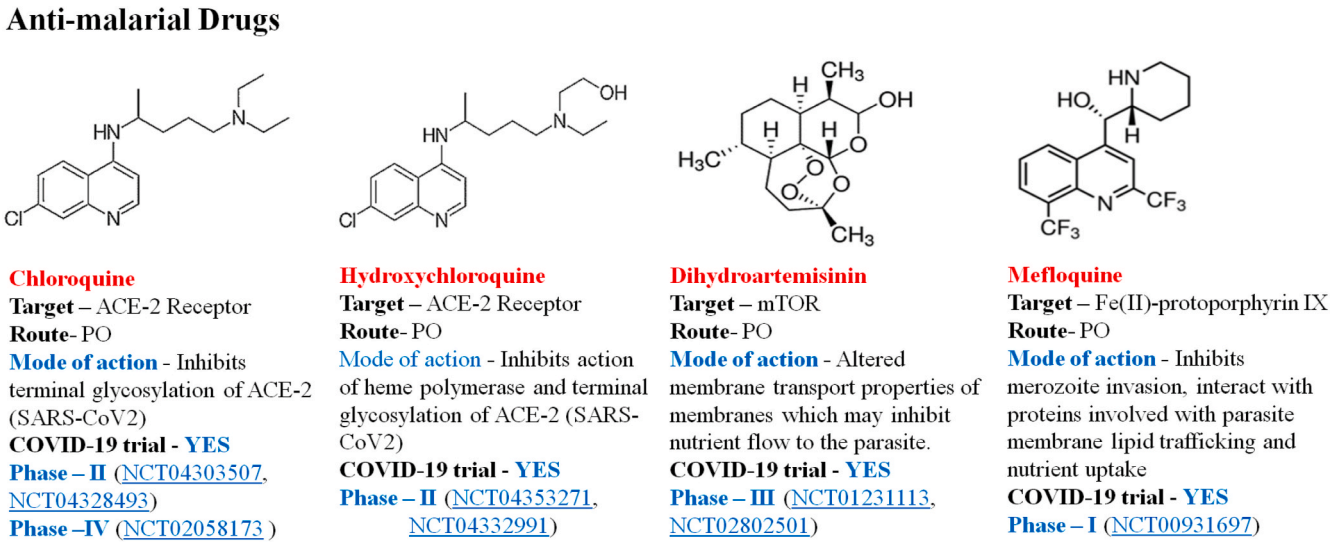


Fig. 10. Representative antimalarial drugs against COVID-19.

4.5. Immunotherapy

It acts through the mechanism of DNA synthesis interference, pulse depletion of immune cells, sequestration of leukocytes, immunomodulation, cytokine-targeted agents, complement inhibition, and blockage of intracellular signalling pathways, etc. [106].

4.5.1. Immunosuppressive therapies

Glucocorticoids possess strong anti-inflammatory and immunosuppressive effects; methylprednisolone is the major medicinal hormone which has a strong impact on the cytokine storm created by badly affected patients COVID-20 [95]. A cytokine profile close to that seen in the macrophage activation syndrome (MAS) identified in a subgroup of COVID-19 patients [71]. Anti-cytokine therapies may be helpful for managing this community of patients with COVID-19 who undergo such a cytokine-storm syndrome. However, selective inhibition of different cytokines during acute respiratory distress syndrome or sepsis can entail risks such as reactivation of viral infections and decreased bacterial infection susceptibility [107]. Host-directed therapies in patients with extreme COVID-19 and recurrent cytokine storms could be successful against SARS-CoV-2 infection [108] Therefore, treatments of immunosuppressant effectively employed against other viruses may be used with COVID-19. Fig. 12 describes the immunosuppressant drugs in clinical trial against COVID -19.

4.5.2. Immunoenhancing therapies

It includes the anti-inflammatory, antioxidant and antibody therapies. The disease's clinical characteristics include overproduction of reactive oxygen species that cause oxidative stress responses and lead to acute damage to the lung, which provides a new approach for the involvement of antioxidant therapy (NCT04466657). Vitamin C helps resist oxidative damage and increases immunity, improve antiviral ability and also avoid and manage acute lung infection and acute respiratory distress induced by certain respiratory viruses [95]. Fig. 13 illustrates some of the antioxidants and anti-inflammatory drugs in current scenario of COVID-19 clinical trials.

4.5.3. Antibody therapies

Other strategy of the Immunoenhancing therapy includes the plasma therapy (convalescent plasma) and the monoclonal antibody therapy. Studies suggest intervention of plasma therapy and immunoglobulin on patients infected with 2019-nCoV could improve clinical outcome

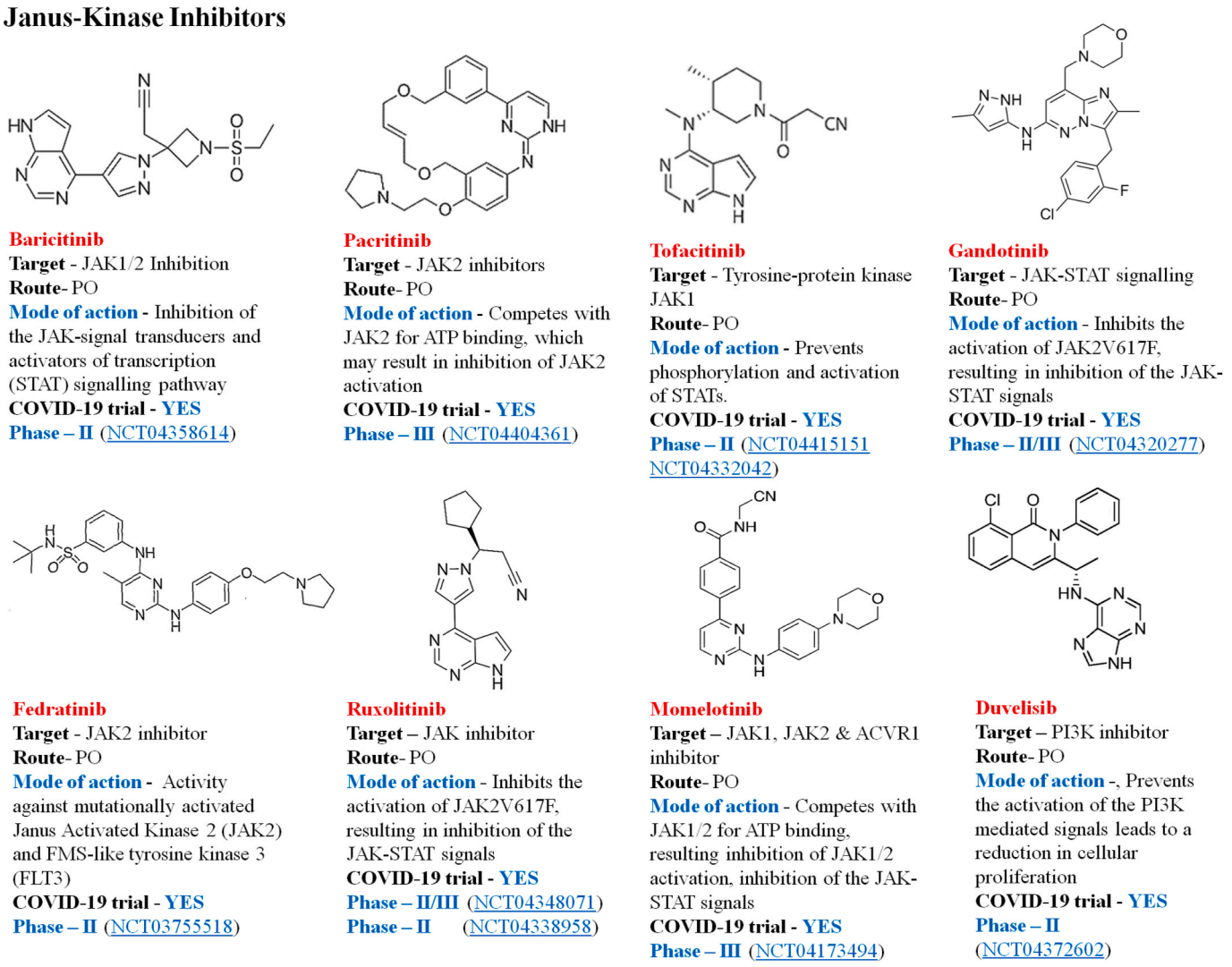


Fig. 11. JAKs/STAT signal inhibitors in current therapeutic trial against COVID-19.

[109]. Plasma therapy is a form of passive immunotherapy, with multivalent treatment wherein, different antibodies collected from recovered individual's

Serum to create convalescent blood products (CBPs), and administered into critically ill patients with SARS-CoV-2 infections [110]. Monoclonal antibody treatment applies to removing B-cells from patients in healing period, which then develop unique antiviral therapy antibodies administered to unrecovered patients. Monoclonal antibodies limit the amount of memory B cells that have neutralizing, and unique consequences produced by cloning the antibody genes [111]. Such antibodies may offer an effective solution for emergency prophylaxis and SARS-CoV-2 treatment, whereas vaccinations and experimental medications are undergoing alternate and more time intensive development [112]. Intravenous immunoglobulin can be the strongest long-term immunomodulator of all ages and can aid inhibit the release of proinflammatory cytokines and improve the production of anti-inflammatory mediators [113]. In fact, thymosin alpha-1 (Ta1) may be an immune aid for patients with SARS, successfully controlling epidemic transmission [114]. Therefore, intravenous immunoglobulin and Ta1 could be employed as COVID-19 therapies (Table 4).

4.6. Cellular therapy

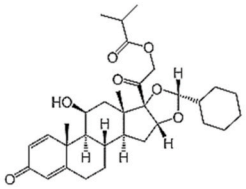
It implicates bone marrow mesenchymal stem cell engineering to release therapeutic factors that effectively reduce pulmonary inflammation and edema in ARDS [95]. Cell-based methods, mainly of mesenchymal stem (stromal) cells (MSCs), demonstrated protection and possible efficacy in patients with acute respiratory distress syndrome (ARDS), while not yet thoroughly established with ARDS caused by respiratory virus [115]. Table 5 explains the cellular therapy (stem cells) with the prolonged mechanism of action in different clinical trial against COVID-19 treatment.

4.7. Proteasome activator PA28γ-dependent degradation of COVID-19 (nucleocapsid protein)

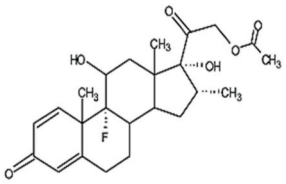
The SARS-CoV-2 nucleocapsid protein (from now on, alluded to as nCoV N) represents the biggest extent of viral structure proteins and is the most plentiful protein in infection contaminated cells. Its essential capacity is to bundle the viral RNA genome into a ribonucleoprotein complex, the capsid [116]. The nucleocapsid protein encoded by SARS-CoV-2 can go about as a viral inhibitory factor of RNA impedance in cells [117]. Besides, it has been demonstrated that the N protein of SARS-CoV can tweak the host cell hardware and it might serve in a regulatory job during the viral life cycle [118]. Subsequently, the nucleocapsid protein is a pivotal multifunctional protein, engaged with the procedure of infection disease, replication, and bundling [119].

An expanding number of studies have indicated that the proteasome

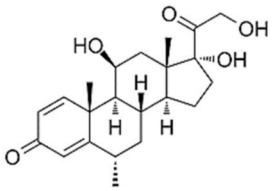
Immunosuppressants Drugs



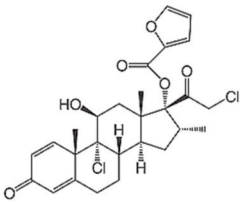
Ciclesonide
Target - Glucocorticoid receptor
Route- IN
Mode of action - In vitro activity against MERS-CoV and SARS-CoV-2. It selects for a mutation in the NSP-15 gene.
COVID-19 trial - YES
Phase – II (NCT04435795, NCT04381364)



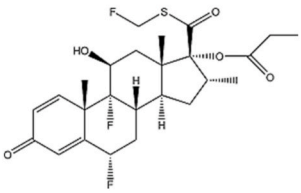
Dexamethasone
Target - Glucocorticoid receptor
Route- IN
Mode of action - Inhibits the enzyme phospholipase A2 and blocks the synthesis of the inflammatory mediators.
COVID-19 trial - YES
Phase – IV (NCT04325061)



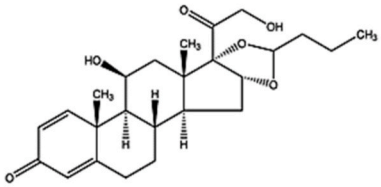
Methylprednisolone
Target - Glucocorticoid receptor
Route- IV/IM
Mode of action - Activates nuclear receptors, altered gene expression and inhibition of proinflammatory cytokine production.
COVID-19 trial - YES
Phase – II (NCT04244591)



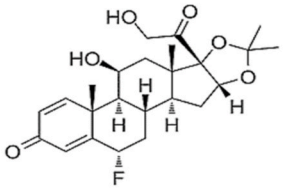
Mometasone
Target - Glucocorticoid receptor
Route- IN
Mode of action - IL-2 and other cytokine receptor-dependent signal transduction mechanisms, via action on mTOR, and thereby blocks activation of T and B cells
COVID-19 trial - YES
Phase – III (NCT01165424)



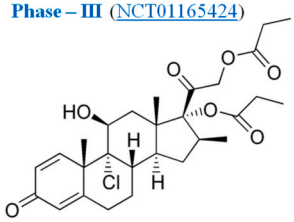
Fluticasone
Target - Glucocorticoid receptor
Route- IN
Mode of action - Affect the action of various cell types and mediators of inflammation
COVID-19 trial - YES
Phase – III (NCT04332978)



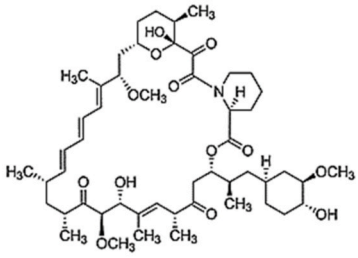
Budesonide
Target - Glucocorticoid receptor
Route- INH
Mode of action - Inhibit neutrophil apoptosis and demargination inhibit phospholipase A2, decreasing formation of arachidonic acid derivatives
COVID-19 trial - YES
Phase – IV (NCT04355637)



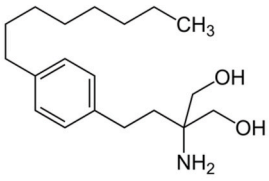
Flunisolide
Target - Glucocorticoid receptor
Route- INH
Mode of action - Anti-inflammatory actions of corticosteroids involving lipocortins, phospholipase A2 inhibitory proteins inhibition.
COVID-19 trial - YES
Phase – Nil (NCT02404103)



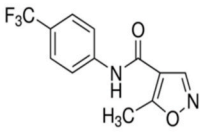
Beclometasone dipropionate
Target - Glucocorticoid receptor
Route- INH, IN
Mode of action - Altered gene expression and inhibition of proinflammatory cytokine production.
COVID-19 trial - YES
Phase – I (NCT03859414)



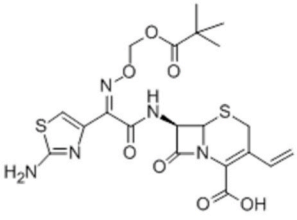
Sirolimus (Rapamycin)
Target - mTOR
Route- PO
Mode of action - IL-2 and other cytokine receptor-dependent signal transduction mechanisms, via action on mTOR, and thereby blocks activation of T and B cells
COVID-19 trial - YES
Phase – I/II (NCT04341675, NCT04371640)



Fingolimod
Target - Sphingosine-1-phosphate receptor
Route- PO
Mode of action - Binds and stimulates the receptor, which results in internalization and degradation of the receptor.
COVID-19 trial - YES
Phase – II (NCT04280588)



Leflunomide
Target - Dihydroorotate dehydrogenase , mitochondrial
Route- PO
Mode of action - Inhibiting dihydroorotate dehydrogenase and has anti-proliferative activity
COVID-19 trial - YES
Phase – I (NCT04361214)



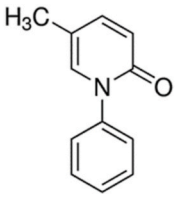
Anakinra
Target - Interleukin-1 (IL-1)
Route- SC
Mode of action - blocks the biologic activity of IL-1 alpha and beta by competitively inhibiting IL-1 binding to the interleukin-1 type I receptor (IL-1RI)
COVID-19 trial - YES
Phase – III (NCT04364009,

Fig. 12. Immunosuppressant's in current therapeutic trial against COVID-19.

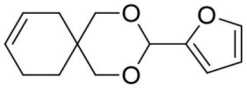
is related with viral disease, and there is proof that HCV core proteins can be corrupted through the PA28γ-20S framework. That is, the nuclear retention and stability of HCV core proteins are controlled by PA28γ-subordinate pathways with the end goal that the pathogenicity of HCV might be accomplished through this pathway [120]. Additionally, the human immunodeficiency infection 1 (HIV-1) Tat protein can repress the peptidase action of the 20S proteasome by contending with the 11 S/PA28 controller (REG) for connecting at the REG/Tat-proteasome-binding (RTP) site and meddling with antigen processing [121]. It has been indicated that the hepatitis B virus X protein-derived polypeptide, cultivating the α4 proteasome subunit restricting motif, debilitates the actuation of 20S proteasomes by PA28 [122]. The coxsackievirus infection can be improved by proteasome activator PA28γ advancing p53 corruption [123], like the system of debasement seen in the HBx infection [124]. Moreover, protein p30 connections with PA28γ may likewise influence ATM capacities and increment cell endurance [125].

On the contrary, PA28γ functions as a co-repressor of HTLV-1 p30 to

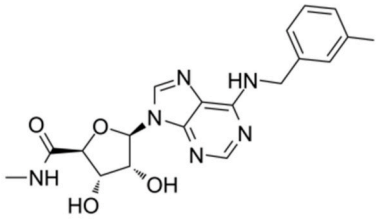
Immunoenhancing Drugs



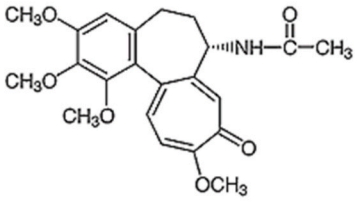
Pirfenidone
Target - TGF-beta2
Route- PO
Mode of action - Inhibits collagen synthesis, down-regulates profibrotic cytokines and decreases fibroblast proliferation.
COVID-19 trial - YES
Phase – III (NCT04282902)



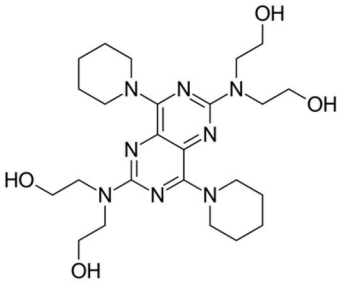
Ulinastatin
Target - TNF-alpha, IL-s
Route- IV
Mode of action - Inhibits inflammatory markers and the endotoxin-stimulated production of TNF alpha and interleukin 1, 8 and 6
COVID-19 trial - YES
Phase – III (NCT04393311)



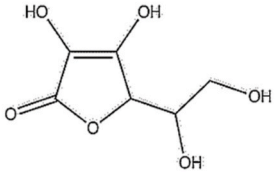
Piclidenoson
Target - Adenosine A3 receptor
Route- PO
Mode of action - Down-regulation of the NF-κB-TNF-α, inhibition of pro-inflammatory cytokine production and apoptosis of inflammatory cells.
COVID-19 trial - YES
Phase – II (NCT04333472)



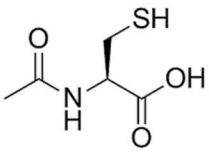
Colchicine
Target - Tubulin beta chain
Route- PO
Mode of action - Binds to tubulins, thereby blocking the assembly and polymerization of microtubules.
COVID-19 trial - YES
Phase – II//III (NCT04360980, NCT04350320)



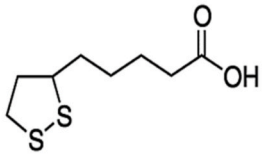
Dipyridamole
Target - PDE Inhibitor
Route- IV
Mode of action - blocks uptake and of adenosine by erythrocytes and vascular endothelial cells, reducing inflammation.
COVID-19 trial - YES
Phase – II (NCT04391179)



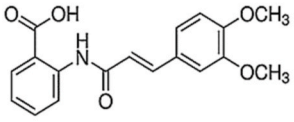
Vitamin C
Target - Peroxidase Inhibitor
Route- IV, P.O
Mode of action - Affects the development and maturation of T-lymphocytes, NK (natural Killer) cells involved in the immune response to viral agents.
COVID-19 trial - YES
Phase – II (NCT04264533, NCT04335084)



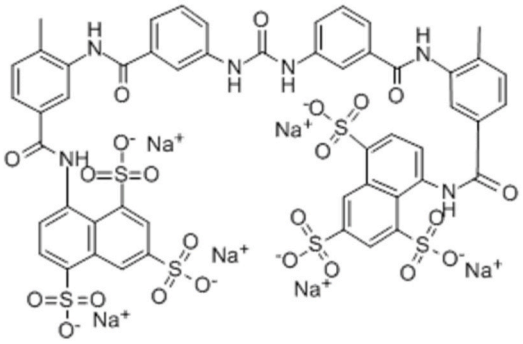
Acetyl cysteine
Target - Peroxidase Inhibitor
Route- IV, P.O, INH
Mode of action -. Loosen the thick mucus in the lungs of people with cystic fibrosis or chronic obstructive pulmonary disease (COPD)
COVID-19 trial - YES
Phase – II (NCT04419025, NCT04374461)



Alpha lipoic acid
Target - Lipoyltransferase 1, mitochondrial
Route- P.O
Mode of action -. Activates 5′-AMP-activated protein kinase (AMPK) and inhibits NF-κB, which in turn have a plethora of metabolic consequences
COVID-19 trial - YES
Phase – IV (ChiCTR2000029851)



Tranilast
Target - Hematopoietic prostaglandin D synthase inhibitor
Route- P.O
Mode of action - Inhibiting the release of histamine and prostaglandins from the mast cells,
COVID-19 trial - YES
Phase – IV (ChiCTR2000030002)



Suramin
Target - Hematopoietic prostaglandin D synthase inhibitor
Route- P.O
Mode of action - Blocks the binding of various growth factors, inhibiting endothelial cell proliferation and migration.
COVID-19 trial - YES
Phase – IV (ChiCTR2000030029)

Fig. 13. Antioxidant and anti-inflammatory drugs.

stifle viral replication and is imperative for the upkeep of control viral latency [126]. Hence, past investigations have indicated that PA28γ is firmly associated with the HTLV-1 virus and performs a permanent role in the development and dissemination of the virus. Furthermore, the capacity of PA28γ to advance viral protein debasement proposes its contribution in viral pathogenesis.

Studies additionally have exhibited that the novel coronavirus nucleocapsid protein (N) shares about 90% amino acid sequence affinity with SARS coronavirus. SARS coronavirus N protein antibodies can cross-respond with novel coronavirus, however, cannot give cross-resistance. Like SARS-CoV, nCoV N proteins can repress RNA impedance (RNAi) to beat the host protection [127]. Early examination uncovered the engagement of the ubiquitin-proteasome framework (UPS) in numerous stages of the coronavirus infection cycle and determined UPS as a prospective drug target to regulate the eminence of coronavirus infection [128].

Table 4
Antibody therapies with effectiveness in current trial activity against COVID-19. TNF- α - Tumor Necrosis Factor alpha; VEGF - Vascular Endothelial Growth Factor; IL-6- Interleukin 6; IL-17 –Interleukin 17; PD-L1/L2- Programmed death-ligand 1/ligand 2; CCR5- Chemokine Receptor type 5; GM–CSF–R -Granulocyte-Macrophage Colony-Stimulating Factor receptor; FCGR1A- High Affinity Immunoglobulin Gamma Fc receptor I; IV-Intravenous; SC-Sub-cutaneous; IVIG- Intravenous immunoglobulin.

Compound	Chemical Formula	Target	Route	Mechanism of action	COVID-19 Trial Status
Adalimumab	$C_{6428}H_{9912}N_{1694}O_{1987}S_{46}$	TNF- α	S·C	Inhibiting the interaction of TNF- α with the cell surface TNF receptors neutralizing TNF- α bioactivity.	Phase- 4 (ChiCTR2000030089)
Bevacizumab	$C_{6638}H_{10160}N_{1720}O_{2108}S_{44}$	VEGF	I·V	Binds and blocks VEGF	Phase 2 (NCT04275414)
Eculizumab	$C_{6442}H_{9910}N_{1694}O_{2034}S_{50}$	Complement C5	I·V	Inhibits terminal complement system including the development of membrane attack complex.	Phase- 2 (NCT04346797, NCT04288713)
Sarilumab	$C_{6388}H_{9918}N_{1718}O_{1998}S_{44}$	IL-6 receptor	I·V	Binds to receptor variants of IL-6, preventing IL-6 pro- and *trans*-inflammatory signalling cascades.	Phase-3 (NCT04345289) Phase-2 (NCT04315298)
Siltuximab	$C_{6450}H_{9932}N_{1688}O_{2016}S_{50}$	IL-6 receptor	I·V	Inhibits attachment to soluble and membrane-bound IL-6 receptors and thereby inhibits lymphocyte proliferation.	Phase-3 (NCT04330638) Completed (NCT04322188)
Ixekizumab	$C_{6492}H_{10012}N_{1728}O_{2028}S_{46}$	IL-17 receptor	S·C	Inhibit IL-17 A from connecting to receptor by attenuating an interleukin-mediated inflammatory response 17 A	Phase-3 (NCT02757352)
Tocilizumab	$C_{6428}H_{9976}N_{1720}O_{2018}S_{42}$	IL-6 receptor	I·V	Inhibits signal transduction by binding sIL-6R and mIL-6R	Phase- 2 (NCT04331808) Phase- 3 (NCT04320615)
Nivolumab	$C_{6362}H_{9862}N_{1712}O_{1995}S_{42}$	PD-L1/L2 receptor	I·V	Binds to PD-1, blocking PD-L1 and PD-L2 from inhibiting T-cell function, returning tumor-specific T-cell response to a patient	Phase- 2 (NCT04343144, NCT04413838)
Leronlimab	$C_{6534}H_{10036}N_{1720}O_{2040}S_{42}$	CCR5	S·C	Binds to several extracellular CCR5 receptor sites, inhibiting HIV from reaching the cell	Phase-2 (NCT04347239)
Lenzilumab	$C_{6474}H_{10024}N_{1748}O_{2010}S_{42}$	GM–CSF–R	I·V	Neutralizes GM-CSF binding to and blocking GM-CSF binding to its receptor, thus stopping GM–CSF–mediated signalling to myeloid progenitor cells	Phase-3 (NCT04351152)
Mavrilimumab	$C_{6706}H_{10438}N_{1762}O_{2104}S_{54}$	GM–CSF–R	S·C	Inhibits GM–CSF–R	Phase-2 (NCT04397497, NCT04399980)
Gimsilumab	$C_{6726}H_{10428}N_{1764}O_{2184}S_{38}$	GM–CSF–R	I·V	Inhibition by targeting GM-CSF itself or by targeting the GM-CSF receptor complex.	Phase-2 (NCT04351243)
IVIG	$C_{6332}H_{9826}N_{1692}O_{1980}S_{42}$	FCGR1A	IV	Reduce the inflammatory response to extreme SARS-CoV-2 infection, including the existence of autoreactive antibodies targeting cytokines or targeting to certain antibodies' vector domains	Phase-2/3 (NCT04261426)

An ongoing report displayed that a novel ubiquitination-independent pathway could administer the protein levels of nCoV N, and PA28γ could monitor the plethora of nCoV N by managing its endurance. Additionally, study results revealed that PA28γ connects with nCoV N and advances its intracellular degradation. SARS coronavirus nucleocapsid protein is a significant viral structural protein and an essential pointer in early prognosis owing to its multitude and high preservation in cells. Examining nucleocapsid protein structural function, how it takes part in transcription and translation, the molecular mechanism in virus tainted cells, and the management of gene expression will aid to fully comprehend SARS coronaviruses and find compelling strategies for curbing and management of related illnesses [116]. When SARS-CoV-2 attacks the human body, it elicits liaison with human immune cells, thereby enabling the immune cells to generate enormous IFN-γ, and IFN-γ can actuate PA28γ [127]. Therefore, invigorates proteasome action bringing about degradation of the coronavirus N protein. Therefore, virus production is obstructed, and multiplication and dissemination are enormously improved.

Conclusively, PA28γ could intercede with the degradation of nCoV N. These outcomes propose that the PA28γ interplay has a significant role in controlling 20 S proteasome activity and promotes our comprehension of the pathogenesis of 2019-nCoV. Continued work is important to find the precise zone of nCoV N synergy with PA28γ.

5. Progress in the development of vaccine of COVID-19

The emerging COVID-19 pandemic has inspired various medical agencies and companies to design candidates for vaccinations against this new disease. The coming months would undoubtedly see an ever-changing world as multiple applicants for the vaccine pass across the production process. As of June 22, 2020, there are 195 target vaccine candidates in the clinical trial processes across the world, as per the data obtained from Vaccine Center at the London School of Hygiene & Tropical Medicine. These target vaccine candidates categorized into different types, i.e., RNA, DNA, non-replicating viral vectors, replicating viral vectors, inactivated, live attenuated, protein subunit, other/unknown vaccines (Table 6).

6. Future directions

In the present scenario, prompt transmission of SARS-CoV-2 across various nations has linked to fierce illness that make it very serious public health risk. In various controversies of strong researches, officially substantiated effective therapy does not exist at the current level, thereby an urgent need for proven therapy for treatment as well as prophylaxis of COVID-19 patients. Recognizing the global public health threat of zoonotic diseases and to decrease the viral spread, wild animal trafficking must be prohibited with closing of live animal markets trading in wildlife. Further, decontaminating reagents and facilities for routine cleaning of hands should be arranged at the public services. Agents that can possibly serve as an alternative route of transmission like faecal and urine samples should be dealt with physical contact. Travel screenings and other prominent control measures to restrain the further attack of the virus should be implemented at global scale. A considerable number of significant unanswered questions must be addressed. Statistics on the frequency of testing, percentage of cases that

Table 5
Stem Cells Therapy in the effective clinical trial against COVID-19 treatment. TNF- α - Tumor Necrosis Factor alpha; VEGF - Vascular Endothelial Growth Factor; IL-6-Interleukin 6; IL-17 –Interleukin 17; PD-L1/L2- Programmed death-ligand 1/ligand 2; CCR5- Chemokine Receptor type 5; GM–CSF–R -Granulocyte-Macrophage Colony-Stimulating Factor receptor; FCGR1A- High Affinity Immunoglobulin Gamma Fc receptor I; IV-Intravenous; SC-Sub-cutaneous; IVIG- Intravenous immunoglobulin.

Stem Cells	Source	Route	Mechanism of action	COVID-19 Trial
UC-MSCs	Adipose Tissue, Umbilical cord, Placenta	IV	Preventing the stormy release of cytokines by the immune system and promoting endogenous repair by stem cell reparations.	Phase-1 (NCT04333368)
NestaCell®	Mesenchymal stem cells	IV	The release of anti-inflammatory, immunomodulatory, *anti*-fibrogenic and trophic functional biomolecules.	Phase-2 (NCT04315987)
Cord Blood Stem cells	Umbilical cord & Placenta	IV, IM	Initiate progenitor cell proliferation and tissue repair characterized by extracellular vesicle (EV) secretions and soluble factors	(NCT04393415)
MenSCs	Menstrual blood	IA, IV	Boost myocardial infarction owing to stimulation of lung-embolized cells to secrete anti-inflammatory protein	Phase-Pre-clinical (ChiCTR2000029606)
BM-Allo MSC	Bone Marrow	IV, IA, IM, I-OCUL	Found to have immunomodulatory effects, to reduce ARDS-related lung inflammation.	Phase-1 (NCT04397796)
WJ-MSCs	Umbilical cord	IV, IT, IM, IN	Pro-angiogenic activity mediator through the secretion of angiogenin, interleukin-8, protein-1 monocyte chemoattractant, and endothelial growth factor	Phase-1 (NCT04313322, NCT04390152)
UC-MSCs	Umbilical cord	IV	Preventing the stormy release of cytokines by the immune system and promoting endogenous repair by stem cell reparations	Phase-2 (NCT04288102)
PLX-PAD	Placenta	IM	Modulate the cytokine surge for immune system integrity and reduce tissue harm associated with SARS-CoV-2 ARDS	Phase-2 (NCT04389450)
CYNK-001	Placenta	IV, ITUMOR	Production of cytolytic perforin and granzyme molecules that may contribute to the killing of viral pathogens contaminated cells	Phase-1/2 (NCT04365101)
HB-adMSCs	Adipose Tissue	IV	Cell replacements	Phase-2 (NCT04348435; NCT04362189)
CAStem	Embryo	IV	Cellular replacement and organ regeneration	Phase-2 (NCT04331613)

turned positive should be checked to aware if the rate remains constant or variable. A small number of pediatric cases have been reported so far; either it accounts for scarcity of testing rates or a typical insufficiency of infection and/or susceptibility in them. How many populations have developed severe disease that have been tested so far, and how many confirmed cases have been found with asymptomatic condition? These central questions would provide a frame of reference to which a precise and rational public health measures would be conducted.

Presently, there is no approved treatment therapy for COVID-19 is available. However, virologists and frontline clinicians have been experimenting with virus based and host-based therapeutics since the outbreaks in the China. After a plethora of research search, we herein mention few pre-existing and novel therapeutic strategies for emerging scientists to discover drugs and/or vaccines to inhibit this viral outbreak that could assist in developing novel therapeutics for COVID-19 treatment.

1. For optimal outcomes, antiviral therapies like remdesivir, lopinavir/ritonavir and umifenovir could be initiated before the viral replication attains its peak level. Ribavarin is generally ineffective as a monotherapy and may be beneficial an add-on therapy.
2. The use of corticosteroids should be limited to indicating comorbidities. Owing to lack of data in COVID-19, IVIG is usually not recommended.
3. Due to the conflicting outcomes in coronavirus studies, the efficacy of interferon is still unclear.
4. Chloroquine and hydroxychloroquine demonstrated in vitro inhibition of SARS-CoV-2, and whether the benefits outweigh the risk of dysrhythmias remain inconclusive.
5. One of the great signs of COVID-19 is the so-called 'cytokine storm' due to attack of SARS-Cov-2 in the lungs. A cytokine family member Interleukin-6 (IL-6) inhibitors might be valuable for patients who developed cytokine discharge syndrome. Considering, mesenchymal stem cells (MSCs) therapy could contribute against SARS-CoV-2 viruses attack because of their immune modulatory, anti-inflammatory, and restorative ability linked to their stemness to the arsenal of treatments for COVID-19. For potential clinical recovery, remdesivir might be regarded early in the course of illness expeditiously before disease progression. Before concluding on efficacy, more well-designed RCTs are warranted in COVID-19 therapies.
6. Apart from mediating the virus entry, ACE2 also displays protective role in the pathophysiological process of virus-induced ALI but the sequential role of ACE2 still remains unclear in the whole disease process and high-quality clinical trials and real-world data are potentially required to answer the question.
7. Although, in view of its key role in disease pathogenesis and pathophysiology, ACE2 has inspired comprehensive interests and plan of action targeting ACE2 and its ligand-COVID-19 spike protein; this might render novel method in the prevention and management of COVID-19.
8. Vaccine development in progress by Oxford University and AstraZeneca's lead candidate AZD1222 is the most advanced one among all the samples currently in development is likely to enter the third phase of the trial in the upcoming week. On the other hand, Moderna/NIAID candidate, mRNA-1273 enters the final phase of the trial study in evaluating immunogenicity, dose levels and adverse effects towards the safer efficacy, as previous trials reported safer immune response in all the volunteers tested.
9. Researchers are attempting cellular therapies like monoclonal antibodies (Tocilizumab, Adalimumab, Siltuximab etc.) to create antibody dependent therapies to suppress and/or neutralize SARS-CoV-2. The virus structural and genetic similarity to SARS-CoV may assist in the creation of new approaches for COVID-19 therapy.
10. Numerous epidemiologic associations evidently advocate a rational hint that the MMR vaccine may grant protection to the COVID-19 virus as well. An immediate exploration of utilizing the already available MMR vaccine in controlled studies is urgently required to demonstrate a protective benefit. Epidemiologic research indicates its efficacy equivalent as a COVID-19 vaccine, and this could be set in motion within months, probably saving thousands of lives with an earlier deployment as compared to other vaccines under development.
11. As discussed above, study results have envisaged that the ubiquitin-proteasome framework performs a crucial role during several stages of the coronavirus disease. N protein of SARS-CoV-2 could be debased by PA28γ in vitro. This may show that PA28γ

Table 6
Pipeline of vaccines in clinical trials for the treatment of COVID-19 across the globe.

Country	Candidate	Type	Organization	Phase of Development
RNA vaccines				
United States	LUNAR-COV19	RNA	Arcturus Therapeutics & Duke- NUS	Pre-clinical development
Germany, China	BNT162	RNA	Biotech, Fosun Pharma Pfizer	Pre-clinical development Phase I/II (NCT04368728)
Germany	CVnCoV	RNA	CureVac	Pre-clinical development; Phase I
Belgium	mRNA TriMix vaccine	RNA	eTheRNA Immunotherapies	Pre-clinical development
United States	mRNA-1273	RNA	Moderna NIAID	Phase I (NCT04283461) Phase I/II (800057258) Phase III (700320962)
Japan	LNP-encapsulated mRNA vaccine	RNA	University of Tokyo Daiichi-Sankyo	Pre-clinical development
Belgium	ZIP-1642	RNA	Ziphius Therapeutics Ghent University	Pre-clinical development
United Kingdom	Self-amplifying RNA vaccine	RNA	Imperial College London	Pre-clinical development Phase I
Spain	RNA vaccine	RNA	Centro Nacional Biotecnología (CNB–CSIC)	Pre-clinical development
China	RNA vaccine (VLP)	RNA	Fudan University/Shanghai Jiao Tong University/ RNACure Biopharma (VLP)	Pre-clinical development
France	LNP-mRNA vaccine	RNA	Sanofi Pasteur, Translate Bio	Pre-clinical development
Russia	RNA vaccine	RNA	BIOCAD	Pre-clinical development
China	RNA vaccine	RNA	China CDC, Tongji University Stermina Therapeutics	Pre-clinical development
Thailand, United States	RNA vaccine	RNA	Chula VRC University of Pennsylvania	Pre-clinical development
United Kingdom, United States	RNA vaccine	RNA	Emergex Vaccines George Mason University	Pre-clinical development
Russia	RNA vaccine	RNA	FSRI SRC VB VECTOR, Rospotrebnadzor, Koltsovo	Pre-clinical development
China	RNA vaccine (RBD)	RNA	Fudan University/Shanghai Jiao Tong University RNACure Biopharma(RBD)	Pre-clinical development
Korea	RNA vaccine	RNA	GeneOne Life Science Houston Methodist	Pre-clinical development
United States	RNA vaccine	RNA	Greenlight Biosciences	Pre-clinical development
United States	RNA vaccine	RNA	HDT BioCorp	Pre-clinical development
Spain	mRNA vaccine	RNA	IDIBAPS-Hospital Clinic (RNA)	Pre-clinical development
Germany	RNA vaccine	RNA	Max Planck Institute of Colloids and Interfaces (RNA)	Pre-clinical development
United States	RNA vaccine	RNA	RNAimmune Inc.	Pre-clinical development
United States	RNA vaccine	RNA	Rochester Clinical Research	Pre-clinical development
DNA vaccines				
United States	DNA vaccine	DNA	Immunomic Therapeutics Epivax, PharmaJet	Pre-clinical development
United States	Fusogenix DNA vaccine	DNA	Entos Pharmaceuticals	Pre-clinical development
Korea	GX-19	DNA	Genexine Consortium	Pre-clinical development
United States	INO-4800	DNA	Inovio Pharmaceuticals	Pre-clinical development; Phase I (NCT04336410)
India	DNA-plasmid vaccine	DNA	Zydus Cadila	Pre-clinical development
Canada	bac-TRL-Spike	DNA	Symvivo Corporation	Phase I (NCT04334980)
Sweden, United Kingdom	DNA vaccine	DNA	Karolinska Institute Cobra Biologics	Pre-clinical development
Japan	DNA vaccine	DNA	Osaka University, AnGes Takara Bio	Pre-clinical development
United Kingdom United States	DNA vaccine	DNA	Scancell University of Nottingham	Pre-clinical development
Italy	DNA vaccine	DNA	Takis Biotech, Evvivax Applied DNA Sciences	Pre-clinical development
United Kingdom	DNA vaccine	DNA	University of Cambridge DIOSynVax	Pre-clinical development
Canada	DNA vaccine	DNA	University of Waterloo	Pre-clinical development
Non-replicating viral vector vaccines				
United States	T-COVID	Non-replicating viral vector	Altimmune	Pre-clinical development
United States	AdCOVID	Non-replicating viral vector	Altimmune; The University of Alabama at Birmingham	Pre-clinical development
China	Ad5-nCoV	Non-replicating viral vector	CanSino Biological Inc. Beijing Institute of Biotechnology	Pre-clinical development Phase I (NCT04313127) Phase II (NCT04341389)
Spain	Non-replicating viral vector vaccine	Non-replicating viral vector	CNB–CSIC (viral vector)	Pre-clinical development
Germany	MVA-S encoded vaccine	Non-replicating viral vector	DZIF - German Center for Infection Research	Pre-clinical development
Russia	Gam-COVID Vaccine	Non-replicating viral vector	Gamaleya Research Institute of Epidemiology and Microbiology	Pre-clinical development Phase I (NCT04436471) Phase II (NCT04437875)

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Table 6 (*continued*)

Country	Candidate	Type	Organization	Phase of Development
China	MVA-VLP vaccine	Non-replicating viral vector	GeoVax & BravoVax	Pre-clinical development
United States	Ad5 S (GREVAX)	Non-replicating viral vector	Greffex	Pre-clinical development
Spain	MVA-S vaccine	Non-replicating viral vector	IDIBAPS-Hospital Clinic (viral vector)	Pre-clinical development
United States	hAd5COVID19-Spike/ Nucleocapsid	Non-replicating viral vector	ImmunityBio NantKwest	Pre-clinical development
United States	Ad26 vaccine	Non-replicating viral vector	Johnson & Johnson BARDA	Pre-clinical development
United States	AAVCOVID	Non-replicating viral vector	Massachusetts Eye and Ear General Hospital	Pre-clinical development
United Kingdom	OraPro-COVID-19	Non-replicating viral vector	Stabilitech Biopharma Ltd	Pre-clinical development
United States	CORAVAX	Non-replicating viral vector	Thomas Jefferson University	Pre-clinical development
China	Adenovirus-vectored vaccine	Non-replicating viral vector	Tsinghua University	Pre-clinical development
Canada	Dendritic cell-based vaccine	Non-replicating viral vector	University of Manitoba	Pre-clinical development
United Kingdom	AZD1222/ChAdOx1-S	Non-replicating viral vector	University of Oxford AstraZeneca	Pre-clinical development Phase I (DB15656) Phase II (NCT04324606)
Finland	Pan-Corona	Non-replicating viral vector	Valo Therapeutics Ltd	Pre-clinical development
United States	Oral recombinant vaccine	Non-replicating viral vector	Vaxart Emergent Biosolutions	Pre-clinical development
Georgia	(PIV5)-based vaccine	Non-replicating viral vector	University of Georgia University of Iowa	Pre-clinical development
Replicating viral vector vaccines				
Russia, United States	Replicating viral vector vaccine	Replicating viral vector	BIOCAD IEM	Pre-clinical development
India, United States	CoroFlu (M2SR)	Replicating viral vector	FluGen Bharat Biotech UW-Madison	Pre-clinical development
Russia	Replicating viral vector vaccine	Replicating viral vector	FSRI SRC VB VECTOR, Rospotrebnadzor, Koltsovo	Pre-clinical development
United States, Germany	VSV vector vaccine	Replicating viral vector	IAVI Merck	Pre-clinical development
United States	TNX-1800	Replicating viral vector	Tonix Pharma/Southern Research	Pre-clinical development
Netherlands	NDV-SARS-CoV-2/Spike	Replicating viral vector	Intravacc Wageningen Bioveterinary Research Utrecht University	Pre-clinical development
Belgium	YF17D vector vaccine	Replicating viral vector	KU Leuven	Pre-clinical development
United Kingdom	APM vector vaccine	Replicating viral vector	Lancaster University	Pre-clinical development
Canada	VSV-S	Replicating viral vector	University of Western Ontario	Pre-clinical development
India	Replicating viral vector vaccine	Replicating viral vector	Zydus Cadila	Pre-clinical development
Inactivated vaccines				
China	CpG 1018	Inactivated	Sinovac/Dynavax	Phase I (700321277)
China	SCB-2019	Inactivated	Clover Biopharmaceuticals AUS Pty Ltd	Pre-clinical development Phase I (NCT04405908)
China	Inactivated vaccine	Inactivated	Beijing Minhai Biotechnology Co	Pre-clinical development
China	Inactivated vaccine	Inactivated	Institute of Medical Biology, Chinese Academy of Medical Sciences	Pre-clinical development Phase I/II
Japan	Inactivated vaccine	Inactivated	Osaka University BIKEN NIBIOHN	Pre-clinical development
Kazakhstan	Inactivated vaccine	Inactivated	Research Institute for Biological Safety Problems	Pre-clinical development
China	Inactivated + CpG 1018	Inactivated	Valneva/Dynavax	Pre-clinical development
Live-attenuated vaccines				
United States India	Deoptimized live attenuated vaccines	Live-attenuated	Codagenix Serum Institute of India	Pre-clinical development
Germany	Live attenuated, measles virus	Live-attenuated	DZIF - German Center for Infection Research	Pre-clinical development
India, Australia	Deoptimized live attenuated vaccines	Live-attenuated	Indian Immunologicals Ltd Griffith University	Pre-clinical development
Protein subunit vaccines				
Japan	Capsid like particle vaccine	Protein subunit	AdaptVac	Pre-clinical development
United States	D-Crypt™	Protein subunit	Akers Biosciences Premas Biotech	Pre-clinical development
China	RBD-Dimer vaccine	Protein subunit		Pre-clinical development

(*continued on next page*)

Table 6 (*continued*)

Country	Candidate	Type	Organization	Phase of Development
			Anhui Zhifei Longcom Biopharmaceutical	
			Institute of Microbiology,	
			Chinese Academy of Sciences	
Slovakia	Peptide vaccine	Protein subunit	Axon Neuroscience	Pre-clinical development
Thailand	Plant-based (RBD-Fc + Adjuvant)	Protein subunit	Baiya Phytopharm/Chula Vaccine Research Center	Pre-clinical development
Italy	OMV-based vaccine	Protein subunit	BiOMVis Srl	Pre-clinical development
			University of Trento	
United States	EPV-CoV-19	Protein subunit	EpiVax	Pre-clinical development
United States	NVX-CoV2373	Protein subunit	Novavax	Pre-clinical development
				Phase I (NCT04368988)
United States	PittCoVacc	Protein subunit	University of Pittsburgh	Pre-clinical development
United States	Linebacker and Equivir	Protein subunit	Impact BioMedical	Pre-clinical development
Israel	(IBV) Vaccine	Protein subunit	Migal Galilee Research Institute	Pre-clinical development
United States	Ii-Key peptide vaccine	Protein subunit	Generex & EpiVax	Pre-clinical development
United States	FlowVax™	Protein subunit	Flow Pharma	Pre-clinical development
Canada	VXL-301	Protein subunit	Vaxil BioTherapeutics	Pre-clinical development
	VXL-302			
	VXL-303			
United States	gp-96 vaccine	Protein subunit	Heat Biologics	Pre-clinical development
			University Of Miami	
Canada	DPX COVID-19	Protein subunit	IMV Inc.	Pre-clinical development
Switzerland	TaliCoVax19	Protein subunit	InnoMedica	Pre-clinical development
China, United Kingdom	COVID-19 XWG-03	Protein subunit	Innovax Biotech; Xiamen University; GSK	Pre-clinical development
India	Protein subunit (RBD)	Protein subunit	Biological E Ltd*	Pre-clinical development
United States	Protein subunit, nanoparticle vaccine	Protein subunit	LakePharma Inc.	Pre-clinical development
Netherlands, United States	OMV-peptide vaccine	Protein subunit	Intravacc	Pre-clinical development
			Epivax	
United States	PDS0203	Protein subunit	PDS Biotechnology	Pre-clinical development
	PDS0204			
Israel	RBD-based vaccine	Protein subunit	Neovii	Pre-clinical development
			Tel Aviv University	
United States	S–2P protein + CpG 1018	Protein subunit	Medigen Vaccine Biologics Corporation/NIAID/Dynavax	Pre-clinical development
United States	IC-BEVS	Protein subunit	Vabiotech	Pre-clinical development
Canada	Adjuvanted microsphere peptide	Protein subunit	VIDO-InterVac	Pre-clinical development
			University of Saskatchewan	
Australia, United States	Molecular clamp vaccine	Protein subunit	University of Queensland	Pre-clinical development
			GSK; Dynavax	
Japan	VLP recombinant protein vaccine	Protein subunit	Osaka University	Pre-clinical development
			BIKEN	
			NIBIOHN (subunit)	
Other vaccines				
United States	AVI-205	Other	AbVision, Inc.	Pre-clinical development
United States	AV-COVID-19	Other	Aivita Biomedical Inc	Pre-clinical development
				Phase I (NCT04386252)
Germany	VLP vaccine	Other	ARTES Biotechnology	Pre-clinical development
Australia	ERC SARS-Cov-2 vaccine	Other	ERC Worldwide	Pre-clinical development
Canada	Self-assembling vaccine	Other	HaloVax	Pre-clinical development
			Hoth Therapeutics	
United States	V-SARS plasma inactivated	Other	Immunitor Inc	Pre-clinical development
				Phase I (NCT04380532)
United Kingdom	AD Domer VLP vaccine	Other	Imophoron Ltd	Pre-clinical development
			Bristol University	
Sweden	ISR-50	Other	ISR Immune System Regulation	Pre-clinical development
United States	TerraCoV2	Other	Oragenics	Pre-clinical development
China	aAPC vaccine	Other	Shenzhen Geno-Immune Medical Institute (APC)	Pre-clinical development
				Phase I (NCT04299724)
China	LV-SMENP-DC	Other	Shenzhen Geno-Immune Medical Institute (D.C.)	Pre-clinical development
				Phase I (NCT04276896)
United States	1c-SApNP VLP vaccine	Other	Ufovax	Pre-clinical development
United States	rOMV vaccine	Other	Versatope	Pre-clinical development
			Umass (OMV)	
Canada	Nanoparticle vaccine	Other	University of Laval	Pre-clinical development

is a controller for SARS-CoV-2 N protein debasement. This stipulates some insight for understanding the earlier debatable physiological function of the proteasome-dependent debasement of the SARS-CoV-2 N protein during pathogenesis of COVID-19. Understanding the meticulous role of PA28γ may give us new shrewdness into virus-cell interplay and lead to a more noteworthy comprehension of the pathogenicity of 2019-nCoV infection.

12. Scientist should also work on investigating molecules that may target autophagy. Blocking of autophagy inhibits virus entry into cells, however, antigen presentation by macrophages blocks the activation of adaptive immunity on T cells as well as B cells. Consequently, the autophagy inhibitors would be best administered after achieving the adaptive immune response against the COVID-19, which often takes almost 5–6 days after the onset of disease.

13. Scientist should target human proteases involved in activation "Viral Spike protein". They may be transmembrane proteases, secreted proteases and intracellular endoplasmic reticulum (ER) proteases. Although the researches are conducting on exploration of human proteases that might activate and cleave SARS-CoV-2 Spike protein, the intracellular ER proteases can continue to activate Spike protein and induce viral membrane fusion after initial endocytosis activated by extracellular proteases. Few drugs having ability of blocking extracellular proteases (For instance; camostat, nafamostat, and cobicistat) are now in clinical trials.

7. Conclusion

The COVID-19 pandemic has emerged as the biggest public health threat with a potential to end up rivalling the 1918 influenza flu. This crisis has brought unprecedented challenges in the management of those who are afflicted, by overwhelming healthcare systems and causing great stress to the healthcare workforce. During such crises, generation of timely evidence for treatment options is crucial. Taking into consideration that in absence of any effective action and lack of effective therapeutic approach along with inadequate wide implementation of social distancing, the situation will remain same until 2022 with 90% of the global population affected with COVID-19 and evident mortality in over 40 million people. Consequently, it is rational to maintain methods and public health measures until potent and effective drugs/vaccines are discovered. An appropriate immunomodulatory diet, proper mental support, adherence to standards and combinatorial therapies will be effective in the long run against COVID-19. Moreover, future viral outbreaks resulting from pathogens of zoonotic origin are likely to continue, hence, comprehensive measures must be devised apart from curbing this outbreak. Special emphasis and endeavor to shield and decrease transmission should be employed in sensitive populations including children, health care providers, and elderly people. Owing to the weak immune system which permits rapid progression of viral infection, early mortality cases of COVID-19 outbreak were prominently seen in elderly people, Taking into account the rising incidence of CoV emergence in livestock animal populations and the identification of novel CoVs in reservoir species proves the high vulnerability of CoVs beyond public-health intervention strategies. Consequently, the design and development of vaccines for SARS-CoV-2 is equally crucial in addition to developing new drugs and clinical trials of old drugs. Experience from SARS-CoV and MERS-CoV indicates for significant emphasis on establishing animal models which can summarize various aspects of human disease and determinants of vaccine safety and efficacy.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cbi.2020.109298.

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