



Classification of the present pharmaceutical agents based on the possible effective mechanism on the COVID-19 infection

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Abstract

Objectives There are several types of research on the COVID-19 disease which have been conducting. It seems that prevailing over the pandemic would be achieved only by mastering over the virus pathophysiology. We tried to categorize the massive amount of available information for useful interpretation.

Evidence acquisition We searched databases with different keywords and search strategies that focus on virulence and pathophysiology of COVID-19. The present review has aimed to gather and categorize all implemented drugs based on the susceptible virulence mechanisms, and the pathophysiological events in the host cells, discussing and suggesting treatments.

Results As a result, the COVID-19 lifecycle were categorized as following steps: “Host Cell Attachment” which is mainly conducted with ACE₂ receptors and TMPRSS2 from the host cell and Spike (S) protein, “Endocytosis Pathway” which is performed mainly by clathrin-mediated endocytosis, and “Viral Replication” which contains translation and replication of RNA viral genome. The virus pathogenicity is continued by “Inflammatory Reactions” which mainly caused moderate to severe COVID-19 disease. Besides, the possible effective therapeutics’ mechanism and the pharmaceutical agents that had at least one experience as a preclinical or clinical study on COVID-19 were clearly defined.

Conclusion The treatment protocol would be occasional based on the stage of the infection and the patient situation. The cocktail of medicines, which could affect almost all mentioned stages of COVID-19 disease, might be vital for patients with severe phenomena.

Keywords Coronaviruses · COVID-19 · SARS-CoV-2 · Pandemic · Pharmaceutical agents · Possible treatments · Drug classification

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Introduction

CoVs (coronaviruses) are viruses with single-stranded RNA (30 kb genomes) and large enveloped particles (60–140 nm), which affect human and animal health [1–3]. Three remarkable ones cause respiratory and enteric disease with severe comorbidity and mortality in some cases [2, 4, 5]. SARS (severe acute respiratory syndrome) was the first one, which emerged in southern China and spread among 29 countries from November 2002 until July 2003 with 8098 patients, including 774 death. MERS (Middle East respiratory syndrome) was the second one, which appeared in Saudi Arabia and caused 2458 patients to be infected, leading to 848 death in 27 countries until July 2019 [2]. In Wuhan, Hubei province, China, there were reports of pneumonia emergent with unknown causes in December 2019 [6]. After that, the novel CoV (SARS-CoV-2,

known as COVID-19) was separated from pneumonia patients on January 7, 2020, as the third imperative and seventh known ones [2, 7]. COVID-19 infected 571 individuals in 25 provinces in China until January 22, 2020, which rapidly increased to 44,672 confirmed COVID-19 infection (62% of total 72,314 susceptible cases) through February 2020, reported by Chinese Center for Disease Control and Prevention [8, 9]. All the three notable CoVs are emerged by zoonotic transmission, likely from bats [9]. Contact with droplets, which dispersed from, infected patient's mouth and nose, is identified as the leading cause of person-to-person contamination [10]. World Health Organization (WHO) announced on March 11, 2020, that the occurrence of COVID-19 is considered a pandemic with more than 118,000 infected individuals, which led to 4292 deaths in 114 countries [11].

The main initial symptoms of an infected individual were fever (98.6%), fatigue (69.6%), dry cough (59.4%), myalgia (34.8%), and dyspnea (34.2%) in a report of 138 patients in the hospital in China [12]. Generally, children without underlying diseases appeared to have a mild disease [13]. Experts declare that the incubation period of COVID-19 is 14-day duration before the initial symptoms [14]. A Chest CT scan is a helpful tool for early diagnosis in susceptible individuals [15]. The ground-glass opacification with occasional consolidation is the main feature of patients' chest CT [16]. After confirmation of the diagnosis, treatment became the main challenge for clinicians. During the first days there was no strategy for treatment, so based on available drugs medication continued. On May 01, 2020, the U.S. Food and Drug Administration permits using Remdesivir antiviral drugs for the treatment of confirmed COVID-19 severe disease in adults and children [17, 18]. But this was not the end of the way. Remdesivir can decrease the stay in the hospital, on the other hand, the virus shows different manifestations that require various strategies for treatment.

Therefore, as finding an appropriate treatment protocol is the fundamental solution for overcoming the COVID-19, we searched databases with different keywords and search strategies that focus on virulence and pathophysiology of COVID-19. As a result, we explained the virus pathogenicity, the therapy mechanism, and the drug options. According to the tables, we gathered the pharmaceutical agents that had at least one experience as a preclinical or human clinical study on COVID-19. The drugs implemented in the clinic are reviewed in the text and drugs passing their human clinical trials are mentioned in the table. The mechanisms of all of the drugs are mentioned in the table, so this can give an insight to the researchers for choosing a good combination for therapy.

Method

An aimed literature review accomplished to classification of the present pharmaceutical agents on COVID-19. We

searched original articles published in the English language from Jan 2019 to April 2020, from the online databases and related websites as WHO and [ClinicalTrials.gov](https://www.clinicaltrials.gov), PubMed/MEDLINE, Google Scholar, Web of Science, along with assessing all the references of the articles retrieved. We used different keywords that focus on virulence, pathophysiology, and drugs implemented in COVID-19. The authors evaluated the relevance of the references firstly by reading the titles and the abstracts. Then the full papers of the selected articles and their relevant references were derived and read thoroughly. Also, it appears that there is a relationship between some drugs previously used against SARS-CoV and MERS-CoV and the COVID-19 life cycle. So, we searched studies published with in vitro and in vivo activity and clinical experiences to suggest possible treatment options for COVID-19. The searched terms were COVID-19 OR Coronavirus OR SARS-CoV-2 OR SARS-CoV OR MERS-CoV. For chosen drugs for the COVID-19 life cycle, clinical trials (including those recruiting, not yet recruiting, active, and completed) with searching on [ClinicalTrials.gov](https://www.clinicaltrials.gov) mentioned in the tables.

COVID-19 life cycle

It can be categorized as 1) "Host Cell Attachment" which is mainly conducted with ACE₂ (angiotensin-converting enzyme-2) receptors and TMPRSS2 (transmembrane protease serine-2) from the host cell and Spike (S) protein from the virus particle, 2) "Endocytosis Pathway" which is performed mainly by clathrin-mediated endocytosis, and 3) "Viral Replication" which contains translation and replication of RNA viral genome.

The virus particle includes a lipid envelope [19] structural proteins encompass envelope (E), membrane (M), surface glycoprotein projections called Spike (S) [20], and nucleocapsid (N) proteins. COVID-19 virus particles bind to the ACE₂ receptors on human cells via Spike proteins- homotrimer of S proteins with a high affinity comparing to SARS-CoV (10- to 20-fold higher) [21, 22] (Fig. 1) and mainly lead to endocytosis via "clathrin-mediated endocytosis" pathway [23, 24]. The virus particle endosome would be followed by either "Late endosome/Lysosome" formation or "Autophagy" via DMV (double-membrane vesicle) and Autolysosome creation, but there is some controversy about the Autophagy [25]. The lysosomal function needs acidic pH for injecting the viral genome into the host cell (Fig. 2). Nonstructural proteins contain polyproteins, nucleoproteins, RNA polymerase, 3CL (3-chymotrypsin-like) protease, PL (papain-like) protease, and helicase, which are produced after RNA genome expression in the host cell for forming the new virus particles and infecting other cells [26] (Fig. 3).

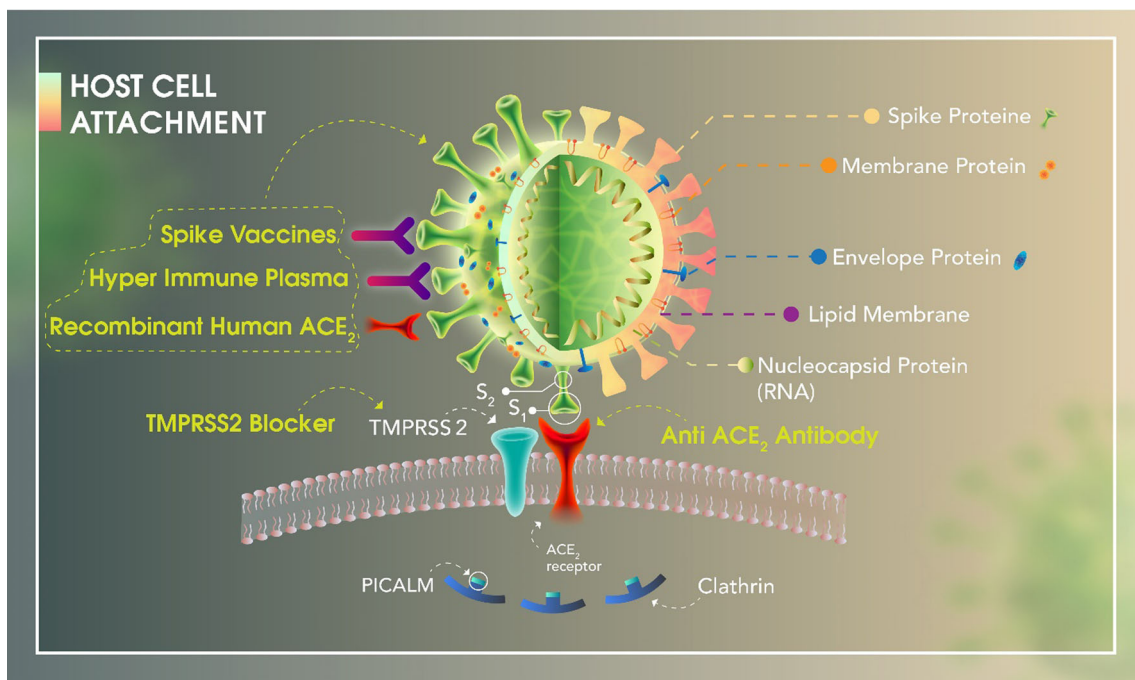


Fig. 1 Host Cell Attachment, The COVID-19 structural proteins include envelope (E), membrane (M), Spike (S), and nucleocapsid (N) proteins. S proteins bind the ACE₂ (angiotensin-converting enzyme-2) receptors with S₁ (subunit 1). The activity of proteases such as TMPRSS2 (transmembrane protease serine-2) has a crucial role in this step. The

clathrin proteins, PICALM (phosphatidylinositol binding clathrin assembly protein) and S₂ (subunit 2) would participate in the next stage of the virus life cycle. The pharmaceutical agents which could interrupt the COVID-19 binding to the host cell membrane are exhibited in yellow color based on the mechanism and the specific site of action

Host cell attachment

As it is briefly explained, COVID-19 virus particles target the ACE₂ receptors on human cells via S proteins for endocytosis and infecting the host cell [21, 24]. Also, it seems that COVID-19 might need the TMPRSS2 and other related proteases for host cell entry as it has a crucial role in S protein activation for membrane fusion [27, 28] (Fig. 1) and enhance the ACE₂ activity for viral entry [29]. Notably, all ACE₂-represented pulmonary cells are also TMPRSS2- positive [29], so the approved inhibitor might be a part of COVID-19 therapy [28]. We can categorize the “Host Cell Attachment” inhibitors as potential treatments into the following groups:

Spike protein blockers

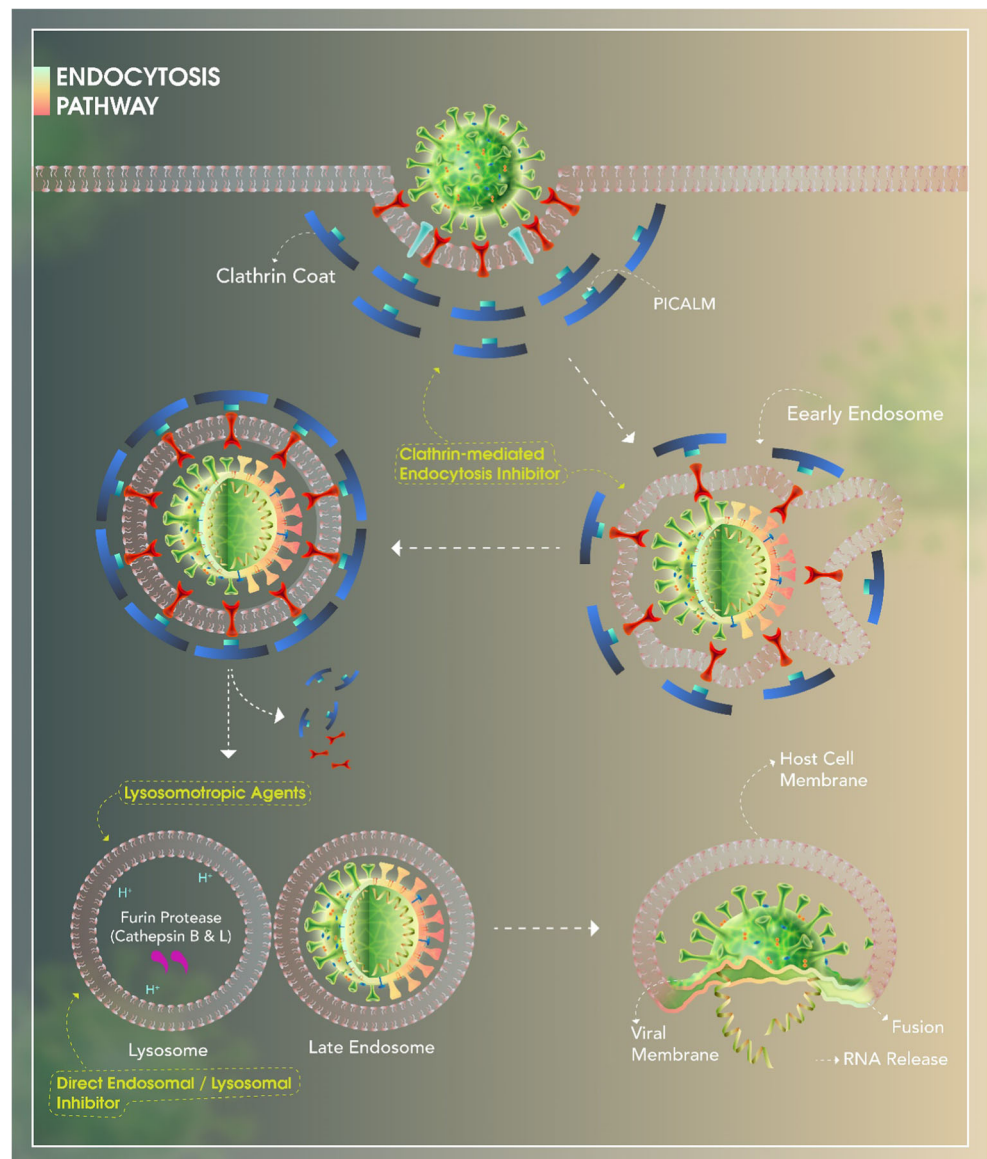
As the S proteins have a crucial role in initiating the pathogenicity, it can be neutralized by plasma antibodies from the cured COVID-19 patients (approved by the US Food and Drug Administration in severe cases) [30, 31], IVIG (intravenous immunoglobulin-passive immunity) [32], recombinant human ACE₂, or S protein-based vaccination (active immunity) [33]. Improvement in clinical status of 5 patients with severe COVID-19 disease and acute respiratory distress syndrome (ARDS), was reported in an uncontrolled case series after administration of neutralizing antibody from convalescent plasma [34]. The vaccine for COVID-19 should simulate

the exterior configuration of spike since it is responsible for virus-host cell interaction [8]. The development of an S₁ subunit protein-based vaccine may rely on the fact that ACE₂ is the COVID-19 receptor. Cell lines that facilitate viral replication in the presence of ACE₂ may be most efficient in large-scale vaccine production [33].

ACE₂ reversible blockers

There are several cells with high levels of ACE₂ expression, which could be a potential target for COVID-19 including AEC_{II} (alveolar epithelial type II cells) in the lung, esophagus upper and stratified epithelial cells, absorptive enterocytes from ileum and colon, cholangiocytes, myocardial cells, kidney proximal tubule cells, endothelial cells of the liver, and bladder urothelial cells [21, 35, 36]. Despite ACE₂ receptors are more significant in the heart, testis, bladder, kidney, gallbladder, adipose tissue, and intestine comparing to the lungs [22], lungs are a more susceptible target for the COVID-19. L Bao et al., study showed the histopathology of human-ACE₂ transgenic mice, which was infected by inhalation of COVID-19 virus particles, expressed the migration of remarkable amounts of monocytes and lymphocytes in the alveolar interstitial and macrophages accumulation in alveolar cavities causing interstitial pneumonia. Besides, there were no outstanding histopathologic finding in any other organs such as liver, myocardium, gallbladder kidney, intestine, and testis

Fig. 2 Endocytosis Pathway, This step initiates by viral particles clathrin-dependent endocytosis. The virus particles are now cargoes in the “Early Endosome.” Some proteins, like PICALM (phosphatidylinositol binding clathrin assembly protein), are essential for maturation of early endosome, especially its curvature and regulation of clathrin-dependent endocytosis rate. The “Late Endosome” is created by excluding the membrane receptors such as ACE₂ (angiotensin-converting enzyme-2) from the early endosome. Then lysosome is fused to late endosome for starting pH-dependent degradation. The lysosomal function needs acidic pH for injecting the viral genome into the host cell. FURIN proteases such as Cathepsin B & L are responsible for cutting Spike into S₁ and S₂ subunits from the FURIN cleavage site. After cutting the S₂ and revealing the S₁ subunit, the viral membrane could fuse the Late Endosome membrane and release the nucleocapsid protein into the host cell. The pharmaceutical agents which could interrupt the COVID-19 endocytosis pathway are exhibited in yellow color based on the mechanism and the specific site of action



[37]. Another animal model on murine, conducted with SARS-CoV infection, indicated the downregulation of ACE₂ receptors followed by angiotensin II accumulation, pulmonary vascular permeability, and finally, pulmonary edema [38]. This mechanism also suggested the occurrence of fulminant myocarditis [39]. As previously known, the downregulation of ACE₂ receptors indicated the severe lung injury in mice, which are infected by SARS-CoV [33]. Recombinant human ACE₂ can also prevent ACE₂ down-regulation [33].

Although Losartan, as an ACE₂ receptor antagonist, has the potential for mitigation of lung injury [38, 39], there is controversy regarding the use of RAS antagonists, including ACE inhibitors and ARBs in COVID-19 patients [38]. Clinical studies have been conducting to prove the efficacy of losartan (NCT04312009) and or to clarify the suspected risk factor of using RAAS (renin-angiotensin-aldosterone system)

antagonists in individuals with severe COVID-19 (NCT04318418) (Table 1).

The higher chronic expression of ACE₂ receptors explains this controversy, which could affect prone patients with a higher risk of severe COVID-19. There is a report regarding the beneficial use of ACE₂-modulating medicines (ACE inhibitors or ARBs) in patients with concomitant chronic disorders such as hypertension, or diabetes, who are receiving ACE₂-increasing drugs [40] like thiazolidinediones and ibuprofen, however, recent studies in clinics recommend ibuprofen usage if there is no alleviation after a full dose of acetaminophen [40]. Some experts have recommended avoiding the implementation of non-steroidal anti-inflammatory drugs (NSAIDs) in the early course of disease due to its negative impact on outcome [41]. Other ACE₂ activators are xanthone, which has

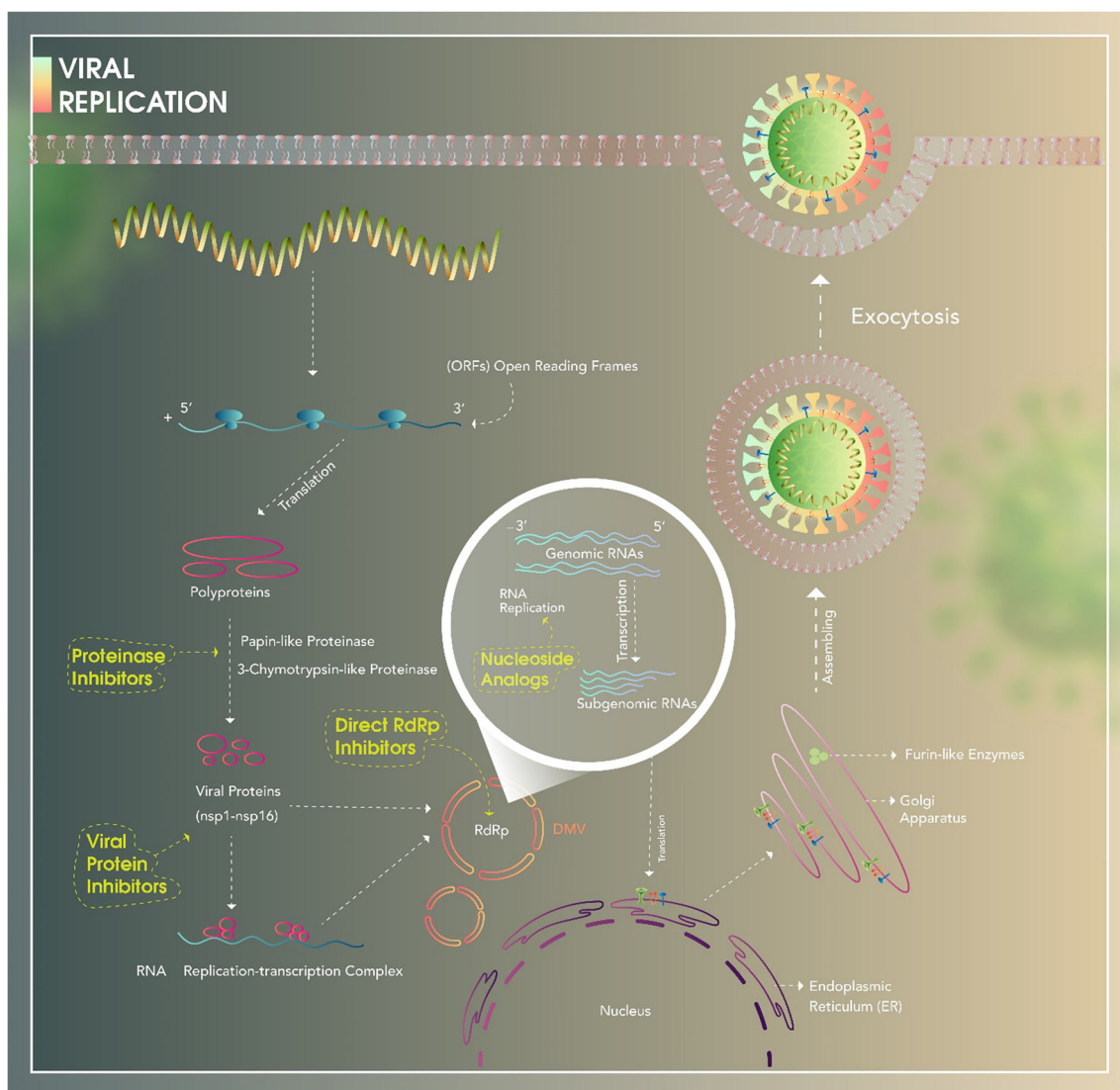


Fig. 3 Viral Replication, COVID-19 disassemble to release the RNA genome after the intra-cellular entrance. The genome which contains 5'-methylated caps and 3'-polyadenylated tails is arranged in the order of 5'. The open reading frames (ORFs) are translated into polyproteins in the cytoplasm. The produced polyproteins are cleaved by papain-like proteinase and 3C-like proteinase to produce sixteen non-structural proteins (NSP1-NSP16), which develop RNA Replication-Transcription Complex. The virus RNA replication is conducted by a viral enzyme called RNA-dependent RNA polymerase (RdRp) in the double-membrane vesicles (DMV) which is derived from the endoplasmic

reticulum (ER). Then the genomic RNAs are transcribed into subgenomic RNAs and translated. As a result, structural proteins are synthesized and assembled into the nucleocapsid and viral envelope with ER-Golgi coordination. FURIN-like enzymes form the bound between S₁ and S₂ subunit in the assembling stage in the Golgi. Finally, the new virions are released by exocytosis into the extracellular compartment. The pharmaceutical agents which could interrupt the COVID-19 replication are exhibited in yellow color based on the mechanism and the specific site of action. +: positive-stranded RNA, -: negative-stranded RNA

been studied in hypertensive rats [42]. However, the chronic use of ACE inhibitors and ARBs could up-regulate ACE₂ receptors [40], so it must be under consideration for COVID-19 treatment based on the stage of infection and the patient situation. According to animal observation, the pathogenicity of the virus by ACE₂ receptors would be responsible for the pulmonary damage in humans [37]. Reports show that respiratory failure alone and in concomitant with fulminant myocarditis was the leading identified cause of death among fatal cases, with about 53% and 33%

in one small clinical assessment in China, respectively. It is also notable that 7% were died only due to fulminant myocarditis [43]. However, Asian ethnicity is outstanding for the occurrence of high-degree AV block due to myocarditis in comparison with other populations (8.1% vs. 1%) [32]. We do not know the prevalence of fulminant myocarditis in other populations as a cause of death. Fortunately, some reports indicated that early use of IVIG before ECMO (extracorporeal membrane oxygenation) [32] and steroids could prevent mortality due to myocarditis [44].

Table 1 The definition of molecules that are assumed to be effective in the disruption of the COVID-19 Host Cell Attachment

Drug name	Category	Mechanism on COVID-19	Preclinical studies	Human clinical studies
Hyperimmune plasma	Immunoglobulin	Anti-infectious (passive immunity)	NR	NCT04344977, NCT04350580, NCT04333355, NCT04348656, NCT04343261, NCT04340050, NCT04343755
IVIG	Immunoglobulin	Anti-infectious (passive immunity) [32]	NR	NCT04261426, NCT04264858
Recombinant human ACE ₂	Soluble ACE ₂	<ul style="list-style-type: none"> • Virus particles neutralizing agent • ACE₂ down--regulation preventer 	in vitro [54]	In ARDS patients was safe (NCT04287686)
Losartan	RAAS inhibition	ACE ₂ reversible blocker	Murine model	Disagreement about use in human: NCT04312009, NCT04318418
Camostat Mesylate	Serine protease inhibitor	TMPRSS2 inhibitor	in vitro [28, 50, 51]	NCT04321096 NCT04338906

NR, Not Reported; IVIG, Intravenous Immunoglobulin; ACE₂, Angiotensin-converting Enzyme-2; RAAS, Renin Angiotensin Aldosterone System; TMPRSS2, Transmembrane Protease Serine-2

Although, there are some clinical observations regarding mostly ALT/AST abnormal rising, seldom bilirubin level elevation (with about 14.8% to 53%), and serum albumin increment in some severe cases. However, the causality between liver injury and COVID-19 remained unclear, since they had been taking lopinavir alone or plus ritonavir regimen that could damage the bile duct cells [35, 45]. Several studies discussed ACE gene polymorphism that it participates in risk elevation of related illnesses such as renal diseases, but its relationship remains uncertain for some other ones like diabetic nephropathy [46–48]. We reviewed literature about the role of ACE gene polymorphism in COVID-19 infection in European patients, which may influence the clinical manifestation [49].

Thus, theoretically, it seems that the respiratory damage would be the most critical implication of COVID-19, with about 86% incidence in cases of mortality [43]. There are some reasons for supporting these observations in the lung. First of all, the considerable surface area in alveoli, which makes it a vulnerable organ for inhaled virus particles. Secondly, the most ACE₂-expressed cells (83%) in the lungs are AEC_{II}, which can act as a reservoir for viral replication with significant levels of viral process-related genomes [33]. Therefore, experts recommend that pulmonary intervention in infected individuals would play a crucial role in the cocktail regimen treatment [33]. Table 1 shows some drugs that have the potential to be useful regarding the ACE₂ role in COVID-19 infectious.

TMRSS2 inhibitors

One of the potential drugs with TMPRSS2 inhibitory activity is camostat mesylate (serine protease inhibitor), used for chronic pancreatitis in Japan, which has prevented casualty in SARS-infected mice [25, 33]. Also, Nafamostat mesylate a drug like camostat mesylate in Japan has shown effectiveness in blocking COVID-19 entry into the host cells and particularly in lung cells in vitro, and the University of Tokyo is planning for clinical trials in April 2020 [50, 51].

There are some investigations regarding TMPRSS2 inhibition, such as Cbz (carboxybenzyl)-phosphono-Lys(OPh)₂, which could prevent its activity irreversibly [52]. The local pulmonary formulation of some serine protease inhibitors (Aprotinin) prescribed for influenza in Russia, but there is no evidence yet for its effectiveness in COVID-19 [53].

Endocytosis pathway

As briefly discussed previously, this step initiates by viral particles clathrin-dependent endocytosis. The virus particles are now cargoes in the “Early Endosome.” Some proteins, like PICALM (phosphatidylinositol binding clathrin assembly protein), are essential for maturation of early endosome, especially its curvature and regulation of clathrin-dependent endocytosis rate [3, 55] (Fig. 2). The “Late Endosome” is created by excluding the membrane receptors such as ACE₂ from the early endosome. Then lysosome is fused to late endosome for

starting pH-dependent degradation [25, 56]. FURIN proteases are one of the most imperative lysosomal cysteine proteases (such as Cathepsin B & L), which are responsible for cutting Spike into S₁ and S₂ subunits from the FURIN cleavage site [20, 57]. This cleavage is necessary for revealing the fusion peptide in S₂ [59], incorporation of virus and endosome/lysosome membrane, releasing the COVID-19 genome into the host cytoplasm, and infection [25, 58, 59] (Fig. 2). Some others believe that infection could emerge directly via this fusion between the virus particle and cell membrane without endocytosis [60]. However, it is not the primary mechanism. Also, we know that the FURIN cleavage site in COVID-19 might cause higher pathogenicity and human-transmission rates comparing to the other CoVs [23, 58]. The FURIN proteases are abundant in lung cells so that the virus would be more infectious for the respiratory system [61]. There is some evidence for FURIN proteases inhibitory function of folic acid, which might contribute to the COVID-19 treatment protocol [62] (Table 2). We can categorize the endocytosis pathway inhibitors as potential treatments into the three leading groups as below [25].

Clathrin-mediated endocytosis inhibitors

Studies show the effectiveness of some drugs against COVID-19, such as chloroquine (by reducing PICALM) [3]. Umifenovir is another drug that has shown the virus-cell entry and fusion by inhibiting the clathrin-mediated endocytosis in human studies in the combination of lopinavir/ritonavir and ribavirin [63, 64]. Besides, other studies show that ouabain and bufalin (cardio-tonic steroids- available drugs) and chlorpromazine have this effect on MERS-CoV, so they could have the same effect on COVID-19 and need additional studies [25]. Studies show that chloroquine (CQ) is more effective than chlorpromazine for inhibition of clathrin-mediated endocytosis [3]. Umifenovir and CQ have been added to the National Health Commission of the People's Republic of China guideline for COVID-19 treatment [65].

Lysosomotropic agents

Through the membrane permeability, weak bases could leak to acidic organelles and become protonated in the low pH, regarding their lipophilicity. After ionization, they catch up in the organelles (ion trapping) [66]. Agents with a viable function that accumulates in the Late Endosome/Lysosome vesicle with high concentration called "Lysosomotropism" [67]. Almost all of them shelter an amine group that makes them act as a weak base [66]. So they could diffuse into the endosome/lysosome vesicle, get trapped, and lead the protease inhibition by changing the pH and prevent the viral release for transcription [25, 68]. Some drugs such as CQ and hydroxychloroquine(HCQ) [69] act as lysosomotropic agent

so could trap the viral receptor ACE₂ within perinuclear vacuoles, prevent the transcription of the viral genome and interrupt the virus life cycle. An open-label non-randomized clinical trial revealed that HCQ could significantly reduce or vanish the viral load in COVID-19 patients, its effect strengthen by azithromycin [70]. Another clinical study on 62 patients with COVID-19 infection in Renmin Hospital of Wuhan University was showed that HCQ could improve pneumonia significantly (80.6%, 25 of 31) compared with the control group (54.8%, 17 of 31) [71]. Also, some other molecules like ammonium chloride (NH₄Cl) are known as lysosomotropic agents [72] (Table 2). They can enter in other acidic organelles such as Golgi vesicles, too. So, they also might prevent the virus life cycle in releasing the new virus particle outside the host cell [59] (replication step). The efficacy of HCQ and CQ against COVID-19 demonstrated in vitro and small, poorly controlled, or uncontrolled clinical studies [73]. Also, in vitro, studies show that HCQ is a more potent inhibitor of COVID-19 compare to CQ [74]. Some reports are suggesting the effectiveness of dapagliflozin in the severe disease of COVID-19 with inhibiting the cytosolic pH reduction and consequently reducing the viral load. [75]. There is no information regarding the exact mechanism but we can consider it in this stage of the virus life cycle. (NCT04350593) (NCT04393246).

Direct endosomal/lysosomal protease inhibitors

The antibiotic teicoplanin acts as a cathepsin L inhibitor in the late endosome so it could interrupt the COVID-19 life cycle by preventing the S protein cleavage and genome releasing to the host cell [74, 76]. According to Zhou et al., telavancin and teicoplanin were shown this mechanism on SARS-CoV and MERS-CoV, previously [77]. Some other investigational drugs (such as E64d [25] and vitamins (such as folic acid [62] have shown the inhibitory activity for FURIN like proteases. Another study declared that E64d indirectly reduced COVID-19 RNA levels [78].

Viral replication

The viral genome, with several open reading frames (ORFs) [81], is translated into polyproteins by changing in the ribosomal frame [58, 82]. The first produced polyprotein gets an auto-proteolytic process leading to Papain-like (PL) and 3-chymotrypsin-like (3CL) proteinases formation [58]. These viral proteinases have a crucial role in developing the 16 non-structural viral proteins (NSP 1 to 16) and, consequently, in the RNA replication-transcription complex [82]. PL proteinase plays a pathophysiological role in suppressing the innate immune response and inducing the cytokine expression by NSP3 activation [58]. The following steps of the replication-transcription complex occur in the viral-induced

Table 2 The definition of molecules which are assumed to be effective in the disruption of Endocytosis Pathway

Drug name	Category	Mechanism on COVID-19	Preclinical Study	Human clinical studies
Umifenovir	Broad-spectrum antiviral (in China and Russia)	Clathrin-mediated endocytosis inhibitor	in vitro [79]	NCT04260594, NCT04286503, ChiCTR2000030254
Chloroquine	Anti-malaria	Lysosomotropic agent <ul style="list-style-type: none"> • Increase endosomes' pH [25]→Protease inhibition [59] • Trap the viral receptor ACE₂ within perinuclear vacuoles [72] • Clathrin-mediated endocytosis inhibitor (by reducing PICALM) [3] • Autophagy inhibitor [80] 	in vitro [72–74]	Many trials including: NCT04342650, NCT04303507, NCT04328493, NCT04333628
Hydroxychloroquine	Anti-malaria	Lysosomotropic agent	in vitro [73, 74]	Many trials including: NCT04340544, NCT04328272, NCT04345692, NCT04351620, NCT04342221
NH ₄ Cl	Chemical Molecule	Lysosomotropic agent <ul style="list-style-type: none"> • Trap the viral receptor ACE₂ within perinuclear vacuoles 	in vitro [72]	NR
Bafilomycin A1	Macrolide Antibiotic	Lysosomotropic agent <ul style="list-style-type: none"> • Trap the viral receptor ACE₂ within perinuclear vacuoles Protease inhibitor • Endo/lysosomal V-ATPase inhibitor 	in vitro [72]	NR
Dapagliflozin	Antidiabetic agent	Increase endosomes' pH, reduce viral load	NR	NCT04350593, NCT04393246
Teicoplanin	Antibiotic (miscellaneous)	Cathepsin L inhibitor	in vitro [74]	NR
E64d	Cysteine-class proteases inhibitor	Cathepsin B/L inhibitor	in vitro [28, 78]	NR

NR, Not Reported; ACE₂, Angiotensin-converting Enzyme-2; PICALM, Phosphatidylinositol Binding Clathrin Assembly Protein; V-ATPase inhibitor, Vacuolar-Adenosine Triphosphatase inhibitor

DMVs [81]. 3CL proteinases promote the DMV creation by NSP4 activation. Generally, NSP 3, 4, and 6 contribute to DMV formation [58]. The DMV is the initial location for RNA replication [83]. The RNA virus replicates by a viral enzyme called RNA-dependent RNA polymerase (RdRp) or RNA-replicase, which locates in the NSP12 [84, 85] (Fig. 3). Some of ORFs are composed of the viral structural proteins encompass Spike, Membrane protein, Envelope protein, and Nucleocapsid protein [81]. FURIN-like enzymes form the bound between S₁ and S₂ subunit in the assembling stage in the Golgi [60, 86]. The internal interferon releasing by the infected cells shows the inhibition of the FURIN-like enzyme to prevent the viral expression [61]. Finally, the vesicle containing COVID-19 viruses is exported outside the infected host cell after assembling in the Golgi system [87] (Fig. 3). The envelope (E) protein and membrane protein (M) interact with each other in the budding compartment of the host cell. The M protein influence dominant cellular immunogenicity. Nucleoprotein (ORF9a) packages the positive-strand viral RNA genome into a helical ribonucleocapsid (RNP) during virion assembly via its interactions with the viral genome and membrane protein M. Nucleoprotein plays a critical role in enhancing the efficacy of sub-genomic viral RNA transcription during viral replication [58].

There is a mechanism that is discussed, particularly on the red blood cells (RBC). The envelope and ORF8 protein could attach the porphyrin in the RBCs [88]. Concomitantly some other ORFs (orf1ab, ORF3a, ORF10) could segregate the iron from heme and create porphyrin. So the active form of hemoglobin would be declined and affect the O₂/CO₂ transferring [89]. In conclusion, acute porphyria would occur. Also, the evidence of reducing hemoglobin levels exists in COVID-19 patients [90], and we can see the free iron chelator treatments (deferoxamine, NCT04333550, NCT04361032, NCT04389801) as a part of therapy for COVID-19 patients. CQ has been approved previously for the porphyria treatment [90].

We can categorize the potential treatments for viral replication into the main groups as below:

Proteinase inhibitors

We explained the crucial role of viral proteinases above. Regarding the importance of 3CL proteases in the COVID-19 life cycle, we assume that the target of treatment is preventing NSPs production [58]. It is worth mentioning that the CL proteases of COVID-19, HCV (hepatitis C virus), and HIV (human immunodeficiency virus) reveal structural and functional sameness. The combination of danoprevir and ritonavir in the clinical trial has shown effective therapy against COVID-19 [90] (Table 3). However, there is also some controversy about them, as we see many cocktail treatments indicated that the available RNA virus protease inhibitors might

have no sufficient efficacy alone in the treatment of COVID-19 [92, 93] (NCT04276688, NCT04254874, ChiCTR2000029308). Reports show that lopinavir/ritonavir alone does not affect almost all patients with COVID-19. There is an in vitro study which illustrates the effectiveness of nelfinavir in inhibition of COVID-19 replication as an anti-protease [94]. Besides, diarylheptanoids (natural product) and cinanserin (serotonin receptor antagonist), which shows the PL and 3CL proteases activity in SARS-CoV, respectively [95], could be potential choices for COVID-19. However, it needs further studies.

Direct RdRp inhibitors

They could interrupt the RNA replication, so the new virion particles cannot infect the other host cells. Beclabuvir and sofosbuvir, as HCV RNA polymerase inhibitors, are under clinical trial (Table 3) and could be used as therapy [96]. In the in vitro studies, it is cleared that zinc and zinc pyrithione could inhibit the RdRp function of SARS-CoV and block the replication [95, 97]. The clinical trials are mentioned in Table 3.

Nucleoside analogs

They could cause premature termination of RNA replication and indirectly inhibit the RdRp activity, including remdesivir [93, 98, 99], ribavirin [93], and clevidine (Table 3). However, some findings indicated that the use of ribavirin plus lopinavir/ritonavir in comparison to ribavirin alone is more effective for preventing ARDS in COVID-19 patients [93]. There is a suggestion that illustrates remdesivir may be the best potential drug for the treatment of COVID-19 [92]. An in vitro study demonstrated that lopinavir but not ritonavir blocks the COVID-19 replication [100]. Effectiveness of Remdesivir was reported in an uncontrolled cohort study on 68% of patients (36 of 53) with severe COVID-19 [101]. In a randomized clinical study which was conducted on 237 patients (158 to Remdesivir group = 158, placebo group = 79); there was no difference in time to clinical improvement between groups [102]. However, introductory results from the 1059 patients indicated that the Remdesivir group ($n = 538$) had a median recovery time of 11 days in comparison with 15 days in the placebo group ($n = 521$) [103].

Viral protein inhibitors

Daclatasvir is an HCV non-structural protein inhibitor and vitamin B12 (methylcobalamin form) as an NSP12 blocker could be in COVID-19 treatment consideration by interrupting the virus life cycle, also patients receiving the combination of sofosbuvir and daclatasvir showed a shorter hospital stay [84]. Regarding the role of COVID-19 on RBCs,

Table 3 The definition of molecules which are assumed to be effective in the disruption of the COVID-19 Replication

Drug name	Category	Mechanism on COVID-19	Preclinical studies	Human clinical studies
Danoprevir	Anti HCV(in China)	Chymotrypsin-like protease inhibitor [91]	in silico [109]	NCT04291729, NCT04345276
Ritonavir	Anti HIV	Chymotrypsin-like protease inhibitor [91]	in silico, in vitro, animal models [109]	NCT04291729, +Lopinavir: NCT04307693, NCT04330690, NCT04321174, NCT04276688, NCT04321993, NCT04315948
Lopinavir	Anti HIV	Protease inhibitor	in silico, in vitro, animal models [100, 109]	NCT04307693
Remdesivir	Nucleotide analog (investigational)	Rd Rp inhibitor, premature termination of RNA replication	in vitro [99]	NCT04292899 NCT04292730 NCT04280705 NCT04321616 NCT04302766
Clevudine	Anti HBV (in South Korea and the Philippines).	Rd Rp inhibitor, premature termination of RNA replication	NR	NCT04347915
Beclabuvir	Anti HCV	Rd Rp inhibitor [96]	in vitro [91]	NR
Sofosbuvir	Anti HCV	Rd Rp inhibitor	in silico [110]	IRCT20200128046294N2
Daclatasvir	Anti HCV	NSP inhibitor	in silico [109]	IRCT20200128046294N2
Zinc	Microelement	Rd Rp inhibitor	NR	NCT04335084, NCT04351490, NCT04342728, NCT04326725, NCT04334512
Ribavirin	Anti HCV (Nucleotide analog)	RdRp inhibitor, premature termination of RNA replication	in silico [110]	NCT04276688, NCT04293887, NCT04306497
Methylcobalamin	Vitamin B12	NSP12 blocker, RdRp inhibitor indirectly	in silico [84]	NCT04407572
Nelfinavir	Anti-HIV	Protease inhibitor	in vitro [111]	NR
Chloroquine	Anti-malaria	inhibit orf1ab, ORF3a, ORF10, ORF8 and envelope protein	in vitro [79]	(mentioned Table 2)
Hydroxychloroquine	Anti-malaria	Reduce replication	in vitro [79]	(mentioned Table 2)
Favipiravir	Anti-influenza (in Japan)	mRNA translation interruption [104], Envelope, and ORF7a protein inhibitor	in silico [109]	61.21% recovery after 7 days on COVID-19 (ChiCTR2000030254) [112] NCT04345419, NCT04349241
Ivermectin	Anthelmintic	Nucleocapsid protein inhibitor	in vitro [107]	NCT04343092, NCT04351347, NCT04345419,

NR, Not Reported; HCV, Hepatitis C Virus; HIV, Human Immunodeficiency Virus; RdRp, RNA-Dependent RNA Polymerase; HBV, Hepatitis B Virus; NSP, non-structural protein; ORF, Open Reading Frame

studies show that CQ could inhibit orf1ab, ORF3a, ORF10, ORF8, and envelope protein to affect the RBCs and effectively alleviate the symptoms of ARDS [89]. Favipiravir could block the envelope and ORF7a protein attaching the porphyrin, preventing the entrance to the host cells, and catching free porphyrins [89]. Also, it could reduce the viral load by interrupting the mRNA translation [104]. It is claimed that ORF-3a are codes for an ion-permeable channel in the SARS-CoV's infected cells, which could be related to the virus release [105]. So emodin or kaempferol derivatives-juglanin could potentially prevent the viral release from the infected cells by inhibition of the ion channel [106]. Besides, ivermectin could prevent SARS-CoV nucleocapsid protein

and interrupt the release of the viral genome into the host cell [107]. It also has shown efficacy on COVID-19 in vivo [108]. There is some evidence regarding the alleviation of ARDS in the severe cases of COVID-19 [108]. Table 3 shows the summary of drugs that could affect the COVID-19.

Inflammatory reactions

Besides the role of the virus life cycle in the pathophysiology of COVID-19, there is some strong evidence about the patient's inflammatory reaction, which mainly causes the morbidity and mortality in severe conditions [113], including lung, liver, heart, and kidney failure [114]. Interferons (IFNs),

a group of cytokines, have an important impact on the immune system against pathogens like CoVs [115]. There are various mechanisms for suppressing the immune system by CoVs [116]. First: CoVs could prevent the internal type-I IFN rapid production (such as IFN α and β), which could be related to severe symptoms and death [115, 116]. Second: STAT1, as the JAK-STAT (Janus kinase/signal transducers and activators of transcription) component, is blocked by CoVs, which lead to the prevention of type-I IFN signaling [115, 116]. Immune exhaustion is the third defensive mechanism of COVID-19, thereby exaggerates and prolongs IFN-1 production by plasmacytoid dendritic cells (pDCs) [116]. In conclusion, the hyperactive immune cells, including neutrophils, monocytes, the “cytokine storm” and IFN-1 induced T cell apoptosis to emerge in infected organs, especially the lung [116]. Besides, cytokines released from activated T helper (Th) cells contribute to autoimmune disorders [117]. The Th₁ cytokines encompass IL-2, IFN γ , and TNF- α (tumor necrosis factor-alpha) more involved for cellular immunity [117]. The other group, the Th₂ cytokines, including IL-4, IL-5, IL-6, IL-10, IL-11, and IL-13, have a role in B cell mediated humoral immunity [117, 118].

Data from plasma samples of patients admitted to ICU indicate various cytokines levels that are higher than usual, which are signs of “Cytokine Storm. These cytokines include: IFN- γ [113], IL-1 β , IL-2, IL-6, IL-7, IL-8, IL-9, IL-10, IL-17, G-CSF (granulocyte-colony stimulating factor), GM-CSF (granulocyte-macrophage-CSF), IP₁₀ (interferon- γ -inducible protein), MCP₁ (monocyte chemoattractant protein), MIP_{1 α} (macrophage inflammatory protein 1 alpha), MIP_{1 β} , and TNF- α [114, 119, 120]. Another common symptom in severe cases or mortalities are lymphopenias [121]. Some studies suggested that the IL-6 plasma level could aim to forecast lung complications in patients [118]. Some other worth mentioning feature is the CD₄ (cluster of differentiation-4) and CD₈ T cells reduction in number but with higher immune activities. Additionally, the concentrated pro-inflammatory cytokines, including IL-17 in CD₄ and cytotoxic granules in CD₈ T cells, exhibit the pathologic inflammatory reactions of T cells in COVID-19 patients. So it is demonstrated that the rise in Th₁₇ cells and the CD₈ cytotoxicity could contribute to severe damages in the infected organs [122]. Th₁₇ cells are CD₄ positive T cells that release the IL-22, IL-6, TNF- α , and exclusively IL-17 [123]. They can be differentiated easily into various types of Th cells to either enhance the immune system for body protection against microorganisms or regulate immunogenicity reactions with IL-10. However, studies show that Th₁₇ cells have a crucial role in autoimmune disorders [123, 124]. Generally, studies assume that the reduction of IL-6, IL-8, IL-17, TNF- α could prevent inflammatory-induced damages [125, 126]. Another worth mentioning topic is the role of oxidative stress in CoVs pathogenicity. Reactive oxygen species (ROS) are a series of by-products derived from molecular

oxygen (O₂) created in respiring cells during mitochondrial oxidative phosphorylation. Besides, ROS can come from extra-cellular origins such as smocking, metals, drugs, xenobiotics, radiation, and infection [127]. ROS produces continuously during viral infections. It could be effective for attacking the virus and also be harmful to normal cellular functions. When the balance is interrupted, the extra amount of ROS could lead to oxidative [128]. CoVs proteins affect mitochondrial integrity, proteasome function, and cause the generation of ROS [129]. It could be lead to the mitochondrial malfunction and aggregation of both host cell and viral proteins by affecting the proteasome (hamper cellular functions). Mortality of Patients by SARS-CoV and COVID-19 is related to inflammatory disorders. Patients with smoking, diabetes, cancer, and cardiovascular diseases almost have reduced-activity proteasome. Besides, proteasome activity could directly diminish by SARS-CoV proteins [129]. Smoking is responsible for proteasome inhibitory in pulmonary epithelial cells. Also, inflammatory disorders and obesity may increase cellular stress. Therefore, they could lead the infected cells incapable of getting rid of protein aggregates. Also, some believe that virally-induced ROS could trigger the STAT/IL-6 axis, cytokine formation, and infiltration of immune cells in the lung [129]. Some animal models of influenza and coxsackie viruses illustrated the changing in virus genome (the normal or mild pathogenic alter to the aggressive one) in host cells suffering the oxidative stress with ambiguous molecular mechanisms [128].

Thromboembolism mechanism in COVID-19

Another finding of COVID-19 pathophysiology is thromboembolism in bronchial arterioles [130] which could be defined by inflammatory mechanism lead to an interruption in procoagulant–anticoagulant balance and initiating the micro thrombosis, disseminated intravascular coagulation, and organ failure. The finding would be confirmed by the higher level of d-dimer in poor prognosis severe COVID-19 pneumonia and disseminated intravascular coagulation in expired patients [131]. So low molecular weight heparin (LMWH) for venous thromboembolism prevention or treatment in hospitalized patients with significantly high levels of d-dimer is recommended. Also, the anti-inflammatory effect of LMWH might play a beneficial role in COVID-19 management. Besides, the administration of antithrombin and anti-factor Xa direct oral anticoagulants as the well-established drugs in the prevention and treatment of venous thromboembolism might be useful [131]. Some findings suggested that the COVID-19 could suppress the production of pulmonary surfactant via binding the ACE₂ receptors on AEC_{II}. It might be responsible for ARDS presentation in severe cases. Therefore, the administration of pulmonary surfactants or stimulators of surfactant production would be useful as either treatment or

prevention [132]. Using anti-inflammatory treatments could prone the patient with secondary infections [133]. Based on almost all anti-inflammatory drug monographs, it is a noticeable warning about concomitant infection since they are suppressive agents for the innate immune system, too. It must be under consideration for use in the COVID-19 treatment protocol. However, we can categorize the possible drug which would affect the Inflammatory Reactions as below (Table 4).

Viral defense blockers

As it is clearly defined, the COVID-19 applied three main defensive mechanisms against the host immune system. Studies show that the percentage of CD₈ T cells with PD-1 (programmed cell death-1) is increased in COVID-19 ICU patients significantly comparing to both non-ICU and healthy individuals. The increment of PD-1 in T cells indicated T cell exhaustion [134]. Exhaustion of T cells indicated immunosuppression after the prolongation of some diseases like infection [134, 135] and might overcome by utilization of investigational PD-1 inhibitors (camrelizumab, Table 4) [136], especially at the end stage of the disease. Besides, one antiprotozoal drug (nitazoxanide) has exhibited the potential anti-viral activity, particularly on COVID-19 in vitro. The efficacy mechanism is assumed by blocking the COVID-19 defensive reaction to the internal IFNs [99], and it has been studying for hospitalized patients with moderate COVID-19 (Table 4).

Direct interleukin antagonists

According to the imperative role of interleukins information of cytokine storm in COVID-19 patients, we assume that they might alleviate the immune reaction and save the organ damage. Tocilizumab and sarilumab are IL-6 blockers, anakinra is IL-1 blocker, and dupilumab is IL-4, IL-13 antagonist is now under clinical trial for COVID-19 [137, 138]. This report shows that dupilumab could be beneficial for cytokine storm in older patients [138]. The latest update of the CDC on June 11, 2020, shows that earlier use of Tocilizumab decreases mortality and improves oxygenation. This report although shows that Anakinra improves respiratory distress but was stopped because of complications.

Pro-inflammatory inhibitors

Some drugs could interrupt the production of pro-inflammatory cytokines that would contribute to preventing the cytokine storm, such as CQ, HCQ [59, 69, 139], macrolide antibiotics like azithromycin (in vitro) [126] and corticosteroids like methylprednisolone [140]. A single centered, retrospective, observational study on 60 COVID-19 adult patients in Baqiyatallah Hospital, Tehran, Iran was showed that the short-term use of low-dose prednisolone in combination with

azithromycin, naproxen, and lopinavir/ritonavir, have a beneficial effect in oxygen saturation, serum level of c-reactive protein and shortening the average length hospitalization in comparison with meropenem, levofloxacin, vancomycin, HCQ, and oseltamivir [141]. However, the concern of QTc prolongation arrived from a study on 84 patients who were receiving HCQ and azithromycin for COVID-19 treatment [142].

Corticosteroids

As mentioned above cytokine storm lead to severe tissue damage especially organs rich in ACE₂ receptors like the lung. This damage causes ARDS that is the main cause of death. Corticosteroids can diminish this damage by reducing inflammatory cytokines like IL-1 and IL-6. They also increase the production of IL-10, an anti-inflammatory mediator. It is claimed that using methylprednisolone could reduce the mortality rate especially in severe cases of ARDS [143]. Although there was some controversy against using corticosteroids like dexamethasone in COVID-19 treatment [144], The National Institutes of Health on June 25, 2020, has recommended the administration of dexamethasone only in patients need either mechanical ventilation or supplemental oxygen [145].

Other pro-inflammatory inhibitors

Recombinant human ACE₂, which has studied in ARDS patients, indicated the reduction in the plasma level of inflammatory proteins like IL-6 and could be categorized as well [33]. Also, the cytokine storm theoretically could be treated by a single S1P (sphingosine 1 phosphate) agonist molecule [146]. Fingolimod, as an S1P, inhibits IL-6, skew IFN responses, and decreases pulmonary fibrosis [147]. Also, some investigational agents like S1P analog (FTY720) and all-trans retinoic acid or other analogs could block IL-17 and prevent the Th₂ differentiation [148]. Since etanercept was showed as a TNF blocker and IL-17/IL-22 modulator in psoriatic patients [124], it may be helpful for cytokine storm inhibition. Also, some drugs, including colchicine, thalidomide, emapalumab, atazanavir, and IVIG, are under clinical trial for COVID-19 with their previous pro-inflammatory inhibitory mechanism (Table 4).

JAK-STAT signaling inhibitors

Disruption in JAK-STAT signaling leads to a variety of immune-related diseases and cancers [149]. Patients with COVID-19 usually exhibit high levels of cytokines in the plasma so that the JAK-STAT signaling inhibitors might be useful in the treatment. Baricitinib, fedratinib, and ruxolitinib are JAK inhibitors and dominant anti-inflammatory drugs [113]. Baricitinib is on a clinical trial for COVID-19 besides

Table 4 The definition of molecules which are assumed to be effective in the treatment of COVID-19 by affecting the inflammatory reactions

Drug name	Category	Mechanism on COVID-19	Human clinical studies
Camrelizumab	Humanized monoclonal PD-1 antibody (oncology-investigational)	Viral Defense Blockers	ChiCTR2000029806 NCT04268537
Nitazoxanide	Anti-protozoal	Viral Defense Blockers	NCT04348409, NCT04343248, NCT04351347, NCT04341493, NCT04345419
Tocilizumab	Antirheumatic	IL-6 receptor antagonist, licensed for cytokine release syndrome [137]	ChiCTR2000029765, NCT04317092, NCT02097524, NCT04306705, NCT04332094, NCT04332913, NCT04339712, NCT04315480
Sarilumab	Antirheumatic	IL-6 receptor antagonist	NCT04315298, NCT04341870, NCT04327388, NCT04321993, NCT04345289
Dupilumab	Anti-Asthmatic	IL-4 and IL-13 receptor antagonist [138]	NCT04324866
Anakinra	Antirheumatic	IL-1 blocker	NCT04324021, NCT04339712, NCT04341584, NCT04330638, NCT02735707
Emapalumab	IFN γ Monoclonal Antibody	Pro-inflammatory inhibitor	NCT04324021
Recombinant human ACE ₂	Soluble ACE ₂	Pro-inflammatory inhibitor	NCT04287686, NCT04335136
Fingolimod	S1P receptor Modulator	Pro-inflammatory inhibitor	NCT04280588
Methylprednisolone	Corticosteroids	Pro-inflammatory inhibitor	Many trials including: NCT04263402, NCT04323592, NCT04244591, NCT04341038, NCT04345445, NCT04263402
Azithromycin	Macrolide antibiotics	Pro-inflammatory inhibitor	NCT04321278, NCT04329832, NCT04336332, NCT04345419, NCT04332107, NCT04334382
Infliximab	Antirheumatic	Pro-inflammatory inhibitor (TNF α blocker)	NCT04425538, NCT04344249
Baricitinib	Antirheumatic	JAK inhibitor	NCT04320277, NCT04346147, NCT04321993, NCT04345289
Ruxolitinib	Antineoplastic Agent	JAK inhibitor	NCT04348071, NCT04334044, NCT04338958, NCT04331665, NCT04337359
Tofacitinib	Antirheumatic	JAK inhibitor	NCT04412252, NCT04415151, NCT04390061, NCT04332042
Atazanavir	Anti HIV	Pro-inflammatory and viral replication inhibitor [156]	NCT04452565, NCT04459286
IVIG	Immunoglobulin	Anti-inflammatory, immunosuppressive [32]	NCT04350580, NCT04261426
Chloroquine	Anti-malaria	Blocking the pro-inflammatory genes transcription [59, 157]	(mentioned in Table 2)
Hydroxychloroquine	Anti-malaria	Blocking the transcription of the pro-inflammatory gene [59]	(mentioned in Table 2)
Colchicine	Antigout	Reducing the release of IL-1b and an array of other interleukins, including IL-6	NCT04322565, NCT04326790, NCT04328480, NCT04322682, NCT04350320
Thalidomide	Angiogenesis inhibitor	Anti-inflammatory, anti-fibrotic, and immune regulatory effects.	NCT04273529, NCT04273581
IFN α 1b	Interferon	Antiviral and anti-inflammatory activity	NCT04293887, NCT04320238
Peginterferon Lambda-1a	Interferon	Antiviral and anti-inflammatory activity	NCT04344600
IFN α 2b	Interferon	Antiviral and anti-inflammatory activity	NCT04254874, ChiCTR2000029308
IFN β 1	Interferon	CD ₇₃ induction, the release of the anti-inflammatory agents	NCT04343768
Vitamin C	Water-soluble vitamin	Oxidative stress inhibitor	NCT04347889, NCT04328961, NCT04323514, NCT04323228, NCT04335084, NCT04342728
Vitamin D	Fat-soluble vitamin	Oxidative stress inhibitor	NCT04335084, NCT04351490
Bromhexine	Mucolytic Agent	Surfactant replacement	NCT04405999, NCT04273763, NCT04355026, NCT04424134
Beractant	Pulmonary surfactant	Surfactant replacement	IRCT20091201002804N12

Table 4 (continued)

Drug name	Category	Mechanism on COVID-19	Human clinical studies
Bovine lipid extract surfactant	Pulmonary surfactant	Surfactant replacement	NCT04362059
Poractant alpha	Pulmonary surfactant	Surfactant replacement	NCT04384731

the antiviral treatment, which is conducted for the assessment of ICU admission reduction (Table 4). Tofacitinib, as a JAK inhibitor, has been shown to block interferon- α production in vitro [133],

Interferons

Due to the antiviral and anti-inflammatory activity of IFNs, some studies are going on. In one clinical study, the combination of inhalable IFN α and lopinavir/ritonavir are recommended as antiviral therapy for COVID-19 (NCT04251871) [93]. Some other studies evaluated, IFN α 2b, in combination with lopinavir/ritonavir and ribavirin (NCT04254874, 2/5/20, and ChiCTR2000029308, 1/23/20), but there is no published result regarding them. Also, the treatment effect of IFN α 1b is evaluated in another study in Wuhan (NCT04293887). The preventive effect of nasal IFN α (NCT04320238) and peginterferon lambda-1a (NCT04344600) on COVID-19 infection in the medical staff has also carried out. The results of a prospective single-arm clinical trial on 20 patients with severe COVID-19 disease revealed that the use of subcutaneous IFN β 1a in combination with HCQ and lopinavir/ritonavir would be beneficial in the management of COVID-19 [150]. Besides, a multicenter, prospective, open-label, randomized, phase 2 trial on 127 patients in Hong Kong Hospital suggested that antiviral therapy with IFN β 1a, lopinavir-ritonavir, and ribavirin were safe and superior to lopinavir-ritonavir alone in shortening virus shedding, alleviating symptoms and facilitating discharge of patients with mild to moderate COVID-19 (NCT04276688) [151]. when given within 7 days of symptom onset, is effective in suppressing the shedding of SARS-CoV-2, not just in a nasopharyngeal swab, but in all clinical specimens, compared with lopinavir-ritonavir alone. They hypothesized that a triple combination of modest antiviral drugs might rapidly suppress the high initial viral load, improve the clinical parameters, and reduce the risk of health-care workers by reducing the duration and quantity of virus shedding from these treated patients [151]. Eight of ten patients also had real-time RT-PCR-positive rectal swabs, suggesting potential fecal viral excretion, suggesting that the gastrointestinal tract may shed virus and fecal-oral

transmission may be possible [152]. All patients received antiviral therapy with α -interferon oral spray initiated from admission (8000 U, two sprays, three times a day). Viral RNA measurements suggest that viral shedding from the digestive system might be greater and last longer than that from the respiratory tract [152].

Also, it is assumed that IFN β 1 has a vital effect on the protection of pulmonary cells and the treatment of CoVs. IFN β 1 induced CD₇₃ in endothelial cells that lead to the release of the anti-inflammatory agents and keep the barrier capacity of endothelial cells. Therefore, a decrease in vascular leakage in ARDS patients treated with IFN β 1a might account for the defined mechanism. However, the death reduction in ARDS patients has not satisfied yet with clinical evidence. Generally, IFN β has more efficacy compare to IFN α in the suppression of CoVs [153]. The comparison of IFN β 1a and IFN β 1b is ongoing in a clinical study (NCT04343768).

Oxidative stress inhibitors

As almost all nutrition have an essential role in preventing oxidative stress, it seems that they could be effective in COVID-19 treatment. Vitamin E is an antioxidant and selenium via assisting a group of enzymes, which could contribute to preventing the ROS generation and cell damages [95]. Also, selenium deficiency leads the host cells to oxidative stress [128]. Besides, it seems that inhibition of neutrophil infiltration to the pulmonary cells by vitamin B₃ treatment, which is observed in patients with ventilator-induced lung damage, might be related to its antioxidant activity in addition to the known anti-inflammatory effects [95]. Also, studies show that the people infected by the virus might have vitamin D (a membrane antioxidant) deficiency [95]. Although the Iron insufficiency could suppress the immune system, the excess amount of it could induce oxidative stress [95]. Some studies suggested that using melatonin with the anti-inflammatory, anti-oxidant, and immune system modulatory effects could come in handy with COVID-19 patients [154].

Since the possibility of lowering the incidence of lower respiratory tract infection in particular circumstances had been reported previously [95], it seems that a moderated

dose of vitamin C might be preventing COVID-19 [155]. Among all nutrition's, intravenous vitamin C effect as a potent antioxidant for viral treatment is being assessed in clinical trials on patients with COVID-19 (Table 4).

Surfactant replacement

As discussed, some possible drugs could prevent ARDS. Ambroxol and bromhexine could induce the production of pulmonary surfactant by affecting the AEC_{II}. Also, it is claimed that bromhexine inhibits TMPRSS2 and inhibits viral entry [132]. Besides, the use of pulmonary surfactant might be effective in the treatment of ARDS due to the COVID-19 as there are some ongoing clinical trials (Table 4).

Discussion

There are several types of research on the COVID-19 which have been conducting. It seems that prevailing over the pandemic would be achieved only by mastering over the virus pathophysiology. We tried to categorize the massive amount of available information into two main parts, the “virus life cycle” and the “Inflammatory Reactions” for useful interpretation. According to the explained information, besides attempts for discovering a novel pharmaceutical agent, we would find the effective ones more quickly through the present drugs. As a conclusion for the present review, we suggested that the treatment protocol would be occasional based on the stage of the infection and the patient situation. It is worth mentioning that the prescription of off-label medicine in clinical practice may provide the opportunity for COVID-19 treatment; although there are some ethical issues to be regarded [158].

Conclusion

Presently there is no effective drug for COVID-19, so based on the affected organ and severity of the disease, the cocktail of medicines, which mainly consists, antivirals and immunomodulators can affect almost all mentioned stages of COVID-19 disease, might be vital for patients.

Compliance with ethical standards

Conflict of interest The authors have no conflict of interest to be declared.

Abbreviation CoVs, Coronaviruses; SARS, Severe acute respiratory syndrome; MERS, Middle East respiratory syndrome; ACE₂, Angiotensin-converting enzyme-2; CME, Clathrin-mediated endocytosis; AEC_{II}, Alveolar epithelial type II cells; IVIG, Intravenous immunoglobulin; ECMO, Extracorporeal membrane oxygenation; RAAS, Renin

angiotensin aldosterone system; TMPRSS2, Transmembrane protease serine 2; DMV, Double Membrane Vesicle; PICALM, Phosphatidylinositol binding clathrin assembly protein; HIV, Human immunodeficiency virus; HCV, Hepatitis C virus; RCT, Randomized clinical trial; TNF- α , Tumor necrosis factor-alpha; G-CSF, Granulocyte-colony stimulating factor; GM-CSF, Granulocyte-macrophage colony-stimulating factor; IP₁₀, Interferon- γ -inducible protein; MCP₁, Monocyte chemoattractant protein; MIP_{1 α} , Macrophage inflammatory protein 1 alpha; MIP_{1 β} , Macrophage inflammatory protein 1 beta; SIP, Sphingosine 1 phosphate; PD-1, Programmed cell death 1; JAK-STAT, The Janus kinase/signal transducers and activators of transcription; CD, Cluster of differentiation; NSP, Non structural protein; ARDS, Acute respiratory distress syndrome

Glossary

- ACE₂ receptors: The typical type I integral membrane protein which the basis domain placed extracellularly [159].
- Clathrin-mediated endocytosis: The primary mechanism of transferring cargo molecules into the cell [160].
- Human-ACE₂ transgenic mice: Transgenic mice with overexpression of the human receptor ACE₂ for investigational purposes [161].
- Fulminant myocarditis: Acute heart failure and myocardium inflammation are due to inflammatory events mostly triggered by viral infections [162].
- Autophagy: The process of gathering the defected organelles and aged proteins in a DMV to link with lysosomes for recycling [80].
- Proteasome: A large protein complex that contributes to the degradation of intracellular energy-dependent proteins [163].
- Acute porphyria: The life-threatening attack occur when there is an interruption (including inherited, drug-induced, hormonal changes) during the heme biosynthetic pathway [164].
- Cellular immunity: The system is in charge of detecting the body cells from the stranger by recognition and elimination of intracellular pathogens and infected cells with microorganisms [165, 166].
- Humoral immunity: The response, which is mediated by antibodies, supports the body against extracellular pathogens and toxins [165, 166].
- Cytokines: The small proteins including pro-inflammatory (IL-1 β , IL-6, TNF- α) and anti-inflammatory cytokines with a crucial role in interaction and communication among cells, which are mainly released by helper T cells (Th) and macrophages [167].

JAK-STAT signaling: The major chain of events with a crucial role in the regulation of division, differentiation, and death of mammal cells [149].

Oxidative stress: The proteins, nucleic acids, and cell membranes damaging events caused by exposure to reactive oxygen intermediates, such as superoxide anion ($O^{\cdot-}$), hydrogen peroxide (H_2O_2), and hydroxyl radical ($HO\cdot$) [168].

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