Approaches towards fighting the COVID-19 pandemic (Review)

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Abstract. The coronavirus disease 2019 (COVID-19) outbreak, which has caused >46 millions confirmed infections and >1.2 million coronavirus related deaths, is one of the most devastating worldwide crises in recent years. Infection with COVID-19 results in a fever, dry cough, general fatigue, respiratory symptoms, diarrhoea and a sore throat, similar to those of acute respiratory distress syndrome. The causative agent of COVID-19, SARS-CoV-2, is a novel coronavirus strain. To date, remdesivir has been granted emergency use authorization for use in the management of infection. Additionally, several efficient diagnostic tools are being actively developed, and novel drugs and vaccines are being evaluated for their efficacy as therapeutic agents against COVID-19, or in the prevention of infection. The present review highlights the prevalent clinical manifestations of COVID-19, characterizes the SARS-CoV-2 viral genome sequence and life cycle, highlights the optimal methods for preventing viral transmission, and discusses possible molecular pharmacological mechanisms and approaches in the development of anti-SARS-CoV-2 therapeutic agents. In addition, the use of traditional Chinese medicines for management of COVID-19 is discussed. It is expected that novel anti-viral agents, vaccines or an effective combination therapy for treatment/management of SARS-CoV-2 infection and spread therapy will be developed and implemented in 2021, and we would like to extend our best regards to the frontline health workers across the world in their fight against COVID-19.

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Key words: angiotensin-converting enzyme 2, acute respiratory distress syndrome, chloroquine, COVID-19, 3-chymotrypsin-like cysteine protease, hydroxychloroquine, traditional Chinese medicine, transmembrane protease serine 2

Contents

1. Introduction

The coronavirus disease 2019 (COVID-19) outbreak has spread worldwide with overwhelming speed, infecting >48.3 million individuals and causing >1.23 million deaths across ~200 countries as of 2nd of November, 2020 (1). COVID-19, caused by SARS-CoV-2 virus, hit China, the US and European countries considerably hard, with the aforementioned countries becoming the epicentres of the SARS-CoV-2 virus pandemic (2). Early prevention of transmission of SARS-CoV-2 via imposed lockdowns and social distancing have been the primary means of preventing the spread of COVID-19 (2,3).

Strategies aimed at interrupting interactions between the virus and host have been primarily utilised from the viewpoint of public epidemiology (4,5). To control the spread of the virus, several countries have limited or outright banned accesses to international flights, locked down the entire country or several cities, have instructed the public to follow social distancing measures, and made the wearing of masks either mandatory or recommended. Moreover, body temperatures are being measured wherever individuals congregate and social activities have been diminished in hopes of curbing peak prevalence and death (5-7). Remdesivir has received emergency use authorization by the US Food and Drug Administration (FDA) for the treatment of COVID-19 (8) for SARS-CoV-2 virus infections (1). However, the development of novel agents and vaccines against SARS-CoV-2 is now one of the most intensively researched subjects worldwide.

The current review summarises the clinical manifestations, SARS-CoV-2 viral genome structure and sequence, SARS-CoV-2 viral life cycle, diagnosis, preventative methods, and management measures of COVID-19. Finally, an overview is provided of the possible molecular pharmacological mechanisms of anti-SARS-CoV-2 agents and the effectiveness of remdesivir (GS-5734), chloroquine, hydroxychloroquine, steroids and anti-coagulant agents as well as traditional Chinese medicines (TCM) for management of COVID-19.

2. Clinical characteristics of COVID-19

According to the current literature, fever, dry cough and fatigue are the most common symptoms observed at the onset of COVID-19, with other symptoms including muscle pain, productive cough, headache, diarrhoea, dyspnoea and haemoptysis developing later (Fig. 1) (9). Symptoms generally appear ~5.2 days after COVID-19 (10). Although 50-75% of patients with COVID-19 remain asymptomatic, ~14% of infected individuals present with serious symptoms requiring hospitalisation and oxygen therapy, while 5% require intensive care. The median duration from symptom onset to intensive care unit admission is ~10 days, while the duration between symptom onset and death ranges from 2-8 weeks (10-13).

Laboratory findings include elevated lactate dehydrogenase and ferritin levels (14). Moreover, although while white blood cell counts can vary, leucopoenia and lymphopenia have been the most commonly observed in individuals infected with SARS-CoV-2 infection (15). Chest radiography and computed tomography (CT) findings are diverse and nonspecific, commonly presenting as multiple ground-glass opacity lesions, bilateral patchy shadowing or local patchy shadowing (16). Severe cases tend to yield more prominent radiological findings (17). However, a few cases have presented with no notable imaging abnormalities (17.9% of non-severe cases and 2.9% of severe cases) (9). As the disease progresses, multiple ground-glass opacity lesions may progress into consolidation or superimposed interlobular/intralobular septal thickening (for example, crazy-paving pattern), which may expand consolidation (18). Several similarities (fever, cough and fatigue) exist between COVID-19 symptoms and those caused by other atypical pathogens such as *Chlamydia*, *Legionella* and *Mycoplasma* (19,20). However, COVID-19 exhibits some distinctive clinical characteristics as well, including targeting of the lower respiratory tract instead of the upper respiratory tract, which produces symptoms like sneezing, rhinorrhoea and a sore throat (21). Moreover, chest radiographs and CT scans upon patient admission revealed an infiltrate in the upper lobe of the lung that was associated with increasing dyspnoea with hypoxemia (22). Certain patients with COVID-19 also developed gastrointestinal distress, such as diarrhoea, whereas only a low percentage of patients with Middle East respiratory syndrome coronavirus (MERS-CoV) or severe acute respiratory syndrome coronavirus (SARS-CoV) experienced these symptoms (23). Finally, the majority of the patients with COVID-19 exhibited leucopoenia and lymphopenia on admission. Tan *et al* (24) demonstrated that patients with blood lymphocyte percentage (LYM%) >20% are in the process of recovery. In contrast, those with between 5 and 20% LYM% are still at risk, and those with LYM% <5% become critically ill with high mortality rates and require intensive care. Lymphopenia seems to be an effective and reliable indicator of severity and hospitalisation amongst patients with COVID-19 (25). Table I presents the classification of the clinical manifestations of COVID-19 (26).

3. Structure, genome size and life cycle of SARS-CoV-2

Coronaviruses primarily cause respiratory and gastrointestinal tract infections and are genetically classified into four major genera: α-coronavirus, β-coronavirus, γ-coronavirus and δ-coronavirus (27). Six types of human coronaviruses have been previously identified, which include HCoV-NL63 and HCoV-229E belonging to the α-coronavirus genus and HCoV-OC43, HCoV-HKU1, SARS-CoV and MERS-CoV belonging to the β-coronavirus genus (27). Coronaviruses had not attracted worldwide attention until the 2003 SARS pandemic, followed by the 2012 MERS and, most recently, the COVID-19 outbreaks (27). Both SARS-CoV-2 and MERS-CoV have been considered highly pathogenic (28). Fig. 2 shows the schematic structure of SARS-CoV-2 (29,30).

SARS-CoV-2 possesses a genome length of ~30 kb. Accordingly, SARS-CoV-2 genome sequences from NCBI (30), covering between ~798 and 29,674 bases, include a variable number of open reading frames (ORFs) (Fig. 3). The first ORF, representing ~67% of the entire genome, encodes two large polyproteins, PP1a and PP1ab, which are proteolytically cleaved into 16 non-structural proteins (NSPs), including papain-like protease, 3-chymotrypsin-like cysteine protease (3CLpro), RNA-dependent RNA polymerase (RdRp), helicase and exonuclease (ExoN). The

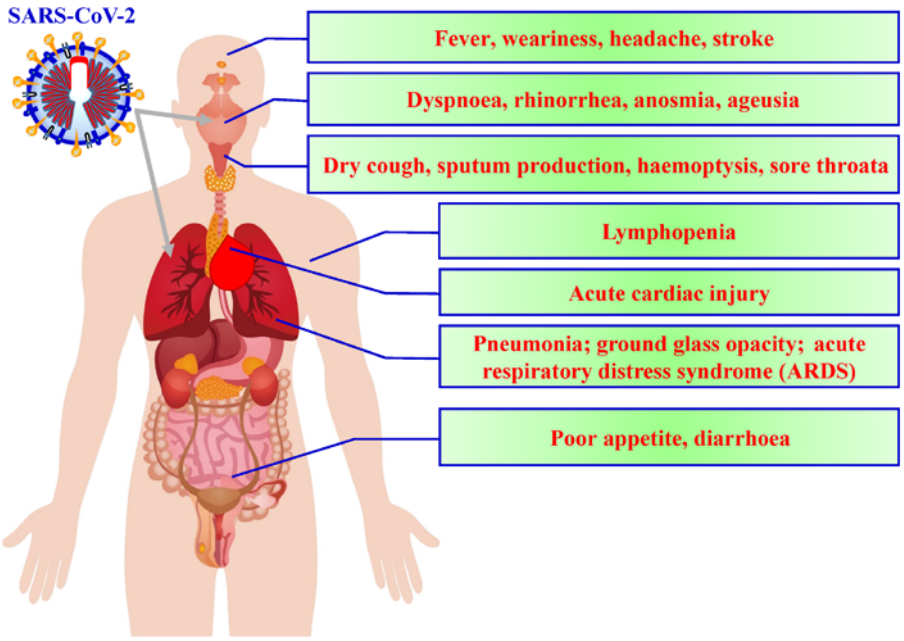

Figure 1. Symptoms of SARS-CoV-2. Symptoms of SARS-CoV-2 include fever, dyspnoea, cough and loss of taste or smell.

remaining ORFs encode accessory and structural proteins. The four major structural proteins include the spike surface glycoprotein (S) (31), envelope protein (E) (32), membrane (M) (33) and nucleocapsid protein (N) (34). Recent studies have revealed six major NSP subtypes, including nsp3 (35), nsp4 (36), nsp6 (37), nsp12 (38), nsp13 (39) and nsp14 (38) for SARS-CoV-2. Spike proteins of viruses bind to host cell receptors for entry. Accordingly, the spike proteins of SARS-CoV-2 and MERS-CoV bind to different host receptors through different receptor-binding domains. SARS-CoV-2 uses angiotensin-converting enzyme 2 (ACE2) as one of the main receptors with CD209L as an alternative receptor, whereas MERS-CoV uses dipeptidyl peptidase 4 (DPP4, also known as CD26) as its primary receptor (40-44). The cleavage of trimer S protein is initiated by the cell surface-associated transmembrane protease serine 2 (TMPRSS2) and cathepsin (45,46).

The life cycle of SARS-CoV-2 can be categorised into nine major steps (Fig. 4). Upon binding to ACE2 and TMPRSS2, SARS-CoV-2 enters host target cells through either fusion or endocytosis (step 1). In the endocytic pathway, the SARS-CoV-2 envelope fuses with the endosome membrane in the lysosomal acid environment, which promotes viral RNA genome release into the host cell cytoplasm (step 2). ORF1a/b encoding 3CLpro is then translated for the replication of genomic RNA (step 3). Thereafter, replicase polypeptide is cleaved (proteolysis), producing NSPs, such as RdRp and helicase (step 4). SARS-CoV-2 then undergoes viral RNA replication in the host cells (step 5). The viral sub-genome is transcribed (step 6). Viral N, M, E and S proteins are translated through the endoplasmic reticulum and Golgi apparatus (step 7). N protein and other structural proteins interact with viral genomic RNA to pack and form a novel virion (step 8). The assembled virion is then released via exocytosis into the extracellular compartment (step 9). The released viral particles are infectious and may begin a new life cycle (Fig. 4) (10,47).

4. Diagnostic methods for COVID-19

Two approaches have generally been utilised for the diagnostic screening of SARS-CoV-2: i) Reverse transcription-quantitative PCR (RT-qPCR) and, ii) rapid screening (48,49). Detection time and duration until COVID-19 diagnosis are detailed in Table II.

RT-qPCR. RT-qPCR assay utilises viral RNA extracted from patient samples (for example, material collected through nasopharyngeal and oropharyngeal swabs), synthesises of complementary DNA (cDNA) through the action of a reverse transcriptase enzyme, and amplifies the target sequences of the viral genome from the cDNA template. RT-qPCR can be interpreted semi-quantitatively, with the target amplification speed dependent on the concentration and quality of the viral RNA in the initial sample, thereby allowing the amplification rate to be used as a proxy for the sample viral load (49). The three target screening assays include E gene, RdRp gene and N assaying (Fig. 5) (50). For a routine workflow, the Taiwan Centers for Disease Control recommends the E gene assay as the first-line screening tool, followed by confirmatory testing with the RdRp gene assay. Utilising the RdRp gene assay with dual colour technology can discriminate between SARS-CoV-2 (both probes positive) and SARS-CoV RNA provided that the latter is used as a positive control. Alternatively, laboratories may choose to run the RdRp assay with only the SARS-CoV-2-specific probe. Despite also performing well, the N gene assay has not been subjected to further intensive validation given its slightly inferior sensitivity (51).

Rapid screening. To date, five antibody-based tests have been used for detecting the presence of IgG and IgM in body fluids, such as whole blood, serum or plasma. The BioMedomics rapid test and Surescreen rapid test cassette

Table I. Classification of clinical manifestation of COVID-19.

Symptoms of COVID-19	Clinical manifestation
Asymptomatic	25-50% of patients with SARS-CoV-2 infection are asymptomatic
Mild clinical manifestation without comorbidity	1. Common symptoms of upper respiratory tract infection include cough, fever, sore throat, running nose, headache, malaise and muscle pain 2. A few patients may have symptoms of diarrhea, nausea and vomiting
Pneumonia	Cough, dyspnea and chest images presented as pneumonia patch or multiple ground-glass opacities, without manifestation of severe pneumonia or requirement for oxygen supply
Severe pneumonia	Pneumonia with requirement of oxygen therapy, plus respiratory rate >30 breaths/min, severe respiratory distress or SpO_2 ≤93% on room air
ARDS	Chest images presented as pneumonia Oxygenation impairment: With the minimum level of PEEP 5 cm H_2O, PaO_2/FiO_2 ratio at ≤300 and >200 is defined as mild ARDS; PaO_2/FiO_2 ratio at 100-200 is defined as moderate ARDS; PaO_2/FiO_2 ratio at <100 is defined as severe ARDS

ARDS, Acute respiratory distress syndrome; PEEP, positive end-expiratory pressure; PaO_2, arterial oxygen tension; FiO_2, fraction of inspiration O_2; SpO_2, oxyhemoglobin saturation by pulse oximetry.

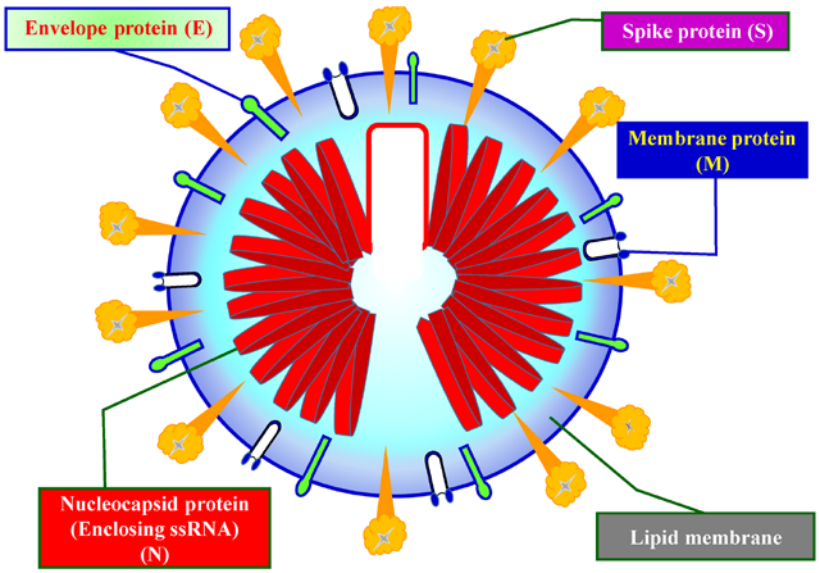

Figure 2. Schematic structure of SARS-CoV-2. SARS-CoV-2 encodes four major structural proteins, including the envelope protein, membrane protein, nucleocapsid protein and spike protein. ssRNA, single stranded RNA.

utilise lateral flow immunoassays, which are diagnostic devices used to examine antibodies (12,52-55). Moreover, Goldsite diagnostics has developed a time-resolved fluorescence immunoassay kit, while the Assay Genie rapid POC kit and VivaDiag COVID-19 IgG-IgM tests are colloidal gold-based immunoassays for detecting viral infection (56). To perform the assay, a few drops of blood obtained from the individual using a finger-stick or vein are applied onto the immunoassay. A few drops of buffer solution are then added onto the assay, after which the results are obtained within 10-15 min at room temperature. RT-qPCR testing is used as the reference standard to which immunoassays are compared. Amongst the five rapid screening tests, the BioMedomics IgM-IgG rapid test has been widely used for detecting antibody production in the human body (57).

The results by Wang (58) indicated that diagnostic sensitivity and specificity were 95.7% (antibody-based tests) and 98.7% (RT-qPCR), 92.2% (antibody-based tests) and 100% (RT-qPCR) by total antibody tests and RT-qPCR, respectively.

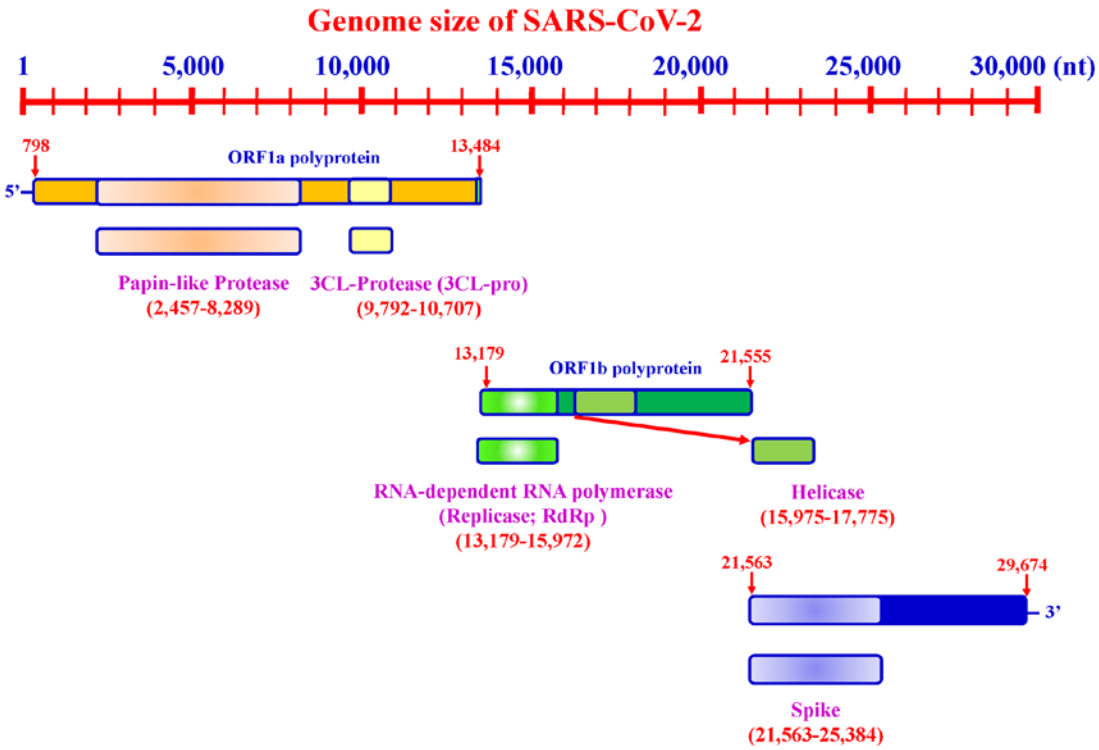

Figure 3. Genome size of SARS-CoV-2. The *length* of the SARS-CoV-2 *genome* is ~30 kb.

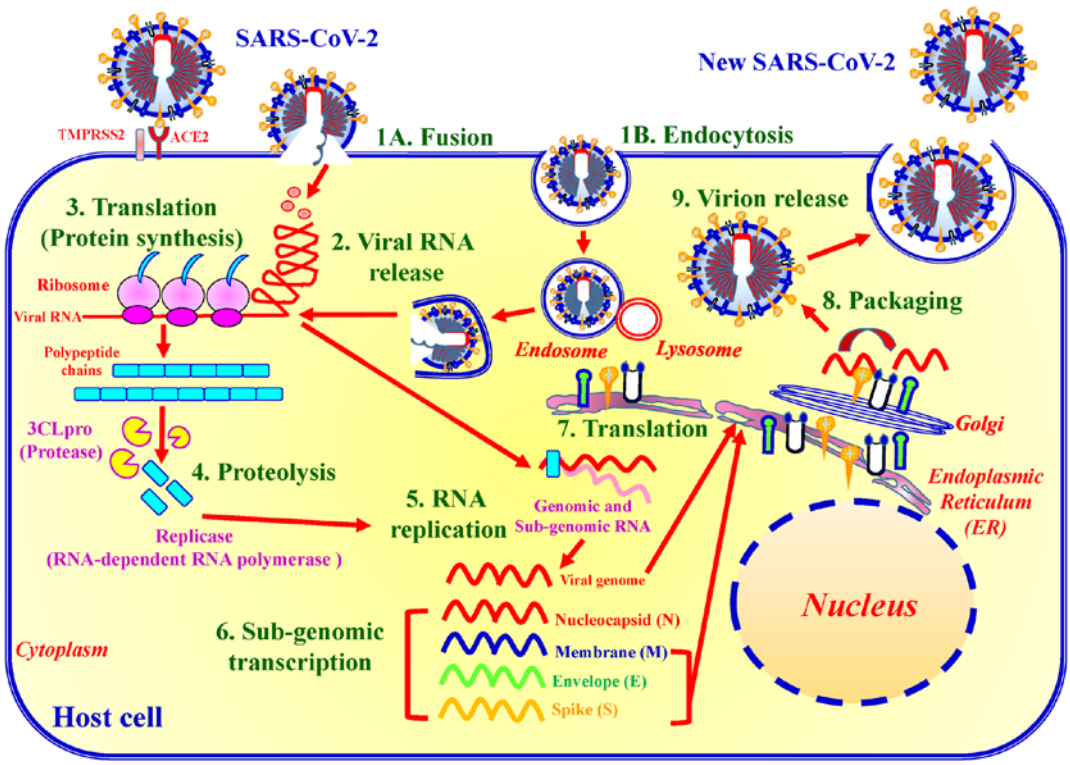

Figure 4. Life cycle of SARS-CoV-2. The SARS-CoV-2 life cycle consists of nine major stages: Step 1, virus entry either via fusion (1A) or endocytosis (1B); step 2, viral RNA release; step 3, translation of viral replication machinery protein; step 4, proteolysis; step 5, RNA replication; step 6, sub-genomic transcription; step 7, translation of viral structure protein; step 8, virion assembly; and step 9, virion release.

5. Methods to prevent COVID-19

SARS-CoV-2 possesses several problematic properties, such as transmission from asymptomatic individuals and nonspecific features of COVID-19, and utilises the ACE2 and TMPRSS2 receptors for attachment and transmission (31,59). Both ACE2 and TMPRSS2 proteins are expressed in <10% of human respiratory and gastrointestinal tract cells, including

Table II. Primary means of diagnosis of COVID-19, including use timing, detection time, specificity and sensitivity.

First author, year	Method	Use timing	Detection time	Specificity %	Sensitivity %	(Refs.)
Wang, 2020	RT-qPCR	Early stage of clinical manifestation	2-4 h	100	98.7	(58)
Porte, 2020	Antigen method (rapid screening)	Early stage of clinical manifestation. Peak period of SARS-CoV-2 infection	15 min	100	93.9	(161)
Wang, 2020	Antibody method (Rapid screening)	After 7-day clinical manifestation	15 min	92.2	95.7	(58)

Specificity, ratio of non-sick individuals who get a negative reaction; sensitivity, ratio of sick individuals who get a positive reaction; RT-qPCR, reverse transcription-quantitative polymerase chain reaction.

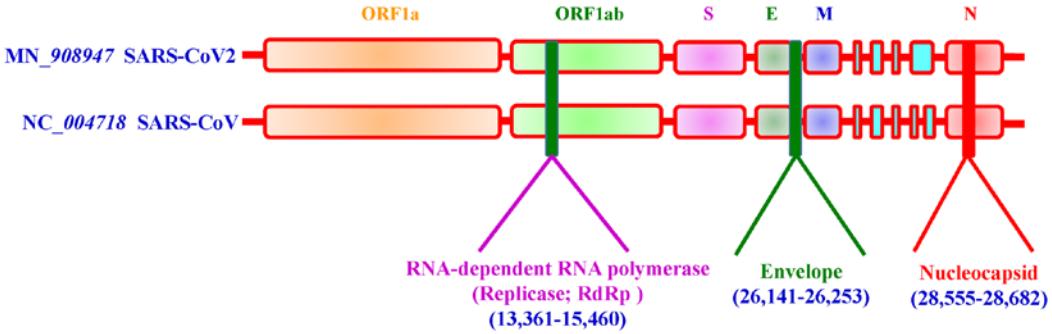

Figure 5. Three candidate diagnostic reverse transcription PCR assays for detection of infection with SARS-CoV-2. The relative genome positions of virions are used to assay for SARS-CoV-2. The three target screening assays include the E gene assay, RNA-dependent RNA polymerase gene assay and N gene assay. E, envelope protein; N, nucleocapsid protein; M, membrane protein.

nasal goblet secretory cells, lung type II pneumocytes and ileal absorptive enterocytes (60,61). At present, prevention of viral entry into the human body has been the best option for controlling viral spread. The TCDC has established technical guidelines for COVID-19 (1). The following are crucial steps for preventing viral spread: i) Stay at home, unless essential, the general public should avoid travelling to affected countries and regions, as well as avoiding contact with animals, dead or alive. The general public should make a habit of applying alcohol-based hand sanitisers after entering any public spaces. ii) Maintain decontamination: Rooms should be regularly decontaminated, preferably with 5 to 10% sodium hypochlorite. iii) Keep a safe social distance, the general public must avoid public gatherings. Individuals should preferably maintain a distance of at least 1.5 m (5 ft) between themselves and anyone who is coughing or sneezing indoors. Individuals should maintain a distance of at least 1 m (3 ft) distance between themselves and anyone else outdoors. iv) Regularly sanitize hands, individuals are advised to practice appropriate hygiene, such as frequently washing their hands with soap after sneezing or coughing. Avoid touching any secretions, such as stool or urine. In addition, individuals should refrain from touching their eyes, nose and mouth with unclean hands. v) Wear face masks, healthcare personnel must use personal protective equipment, such as medical masks (including surgical face masks and N95s), eye protection, gloves, gowns and protective gear. The general public must wear a face mask to help prevent viral transmission, particularly in public spaces. Given the supply shortages, each country has their own recommendations regarding wearing of face masks.

6. Current therapeutic modalities for COVID-19

Given the lack of clinical evidence supporting the efficacy of any existing anti-viral agents or the existence of vaccines which have completed Phase II clinical trials and have been approved by a regulatory body for COVID-19, supportive treatments for clinical conditions in the early stages is imperative. In addition, conservative fluid management should be employed among patients with COVID-19 when no evidence of shock is present. Details and targets of supportive treatments for clinical conditions are presented in Table III (26).

Several ongoing clinical trials have evaluated the following direct treatments for SARS-CoV-2: Chloroquine (Aralan®), hydroxychloroquine (Plaquenil®), arbidol (Umifenovir®), camostat mesylate (Foipan®), remdesivir (GS-5734), favipiravir (Avigan®), ribavirin (Rebetol®), lopinavir/ritonavir (Kaletra®) and interferon-α and interferon-β (47). The chemical structures of hydroxychloroquine (Plaquenil®), chloroquine (Aralan®), remdesivir (GS-5734), favipiravir (Avigan®), ribavirin (Rebetol®), lopinavir/ritonavir (Kaletra®), and camostat mesylate (Foipan®) are presented in Fig. 6. Table III and Fig. 7 summarise ongoing therapeutic agents being evaluated for management of COVID-19 and their molecular pharmacologic mechanisms. The mechanisms by which suitable therapeutic agents against SARS-CoV2 exhibit their effects are discussed below.

Table III. Summary of anti-viral agents against COVID-19.

Anti-viral agents for COVID-19	Chemical formula	Molecular weight, g/mol g·mol^{-1}	Drug targets	Pharmacologic mechanisms	Inhibits stage	(Refs.)
Chloroquine (Aralan®)	$C_{18}H_{26}ClN_3$	319.87	1. Endosomal acidification 2. Phosphatidylinositol binding clathrin assembly protein	1. A lysosomotropic base 2. Increases endosomal and lysosomal pH (Alkalinizes vacuolar pH) 3. Disrupts intracellular trafficking. 4. Inhibits phosphatidylinositol binding clathrin assembly protein 5. Downregulates IL-6	Inhibits viral fusion events	(70, 90-95)
Hydroxychloroquine (Plaquenil®)	$C_{18}H_{26}ClN_3O$	335.87	1. Endosomal acidification 2. Phosphatidylinositol binding clathrin assembly protein	1. A lysosomotropic base 2. Increases endosomal and lysosomal pH (Alkalinizes vacuolar pH) 3. Disrupts intracellular trafficking. 4. Inhibits phosphatidylinositol binding clathrin assembly protein 5. Downregulates IL-6	1. Inhibits viral fusion events	(70, 90-95)
Arbidol (Umifenovir®)	$C_{22}H_{25}BrN_2O_3S$	477.41	1. Interacts with aromatic residues within the viral hemagglutinin glycoprotein	1. Inhibition of viral entry and membrane fusion	1. Inhibits viral entry and membrane fusion	(66,67)
Camostat mesylate (Foipan®)	$C_{21}H_{26}N_4O_8S$	494.52	Transmembrane protease serine 2	1. Inhibits transmembrane protease serine 2	1. Blocks entry of SARS-Cov-2 into lung cells	(62,63)
Remdesivir (GS-5734)	$C_{27}H_{35}N_6O_8P$	602.58	RNA-dependent RNA polymerase	1. Inhibits RNA-dependent RNA polymerase 2. Evades proofreading by viral exoribonuclease (ExoN)	1. Inhibits viral replication 2. Delays RNA chain termination	(105, 106, 112)
Favipiravir (Avigan®)	$C_5H_4FN_3O_2$	157.10	RNA-dependent RNA polymerase	1. Inhibits RNA-dependent RNA polymerase	1. Inhibits viral replication	(70, 104)
Ribavirin (Rebetol®)	$C_7H_{10}N_4O_5$	230.18	RNA-dependent RNA polymerase	1. Inhibits RNA-dependent RNA polymerase	1. Inhibits viral RNA synthesis 2. Inhibits viral mRNA capping	(109, 116-118)

Table III. Continued.

Anti-viral agents for COVID-19	Chemical formula	Molecular weight, g/mol g·mol^{-1}	Drug targets	Pharmacologic mechanisms	Inhibits stage	(Refs.)
Lopinavir	$C_{37}H_{48}N_4O_5$	628.80	3C-like protease	1. Inhibits 3C-like protease	1. Inhibits protease by proteolysis	(68, 119, 120)
Ritonavir	$C_{37}H_{48}N_6O_5S_2$	720.94	3C-like protease	1. Inhibits 3C-like protease	1. Inhibits protease by proteolysis	(68, 119, 120)
Recombinant Interferon	Type 1 interferons (IFN-α; IFN-β)			1. Induces the phosphorylation of transcriptional factors such as STAT1 2. Activates interferon-stimulated genes	1. Immunomodulation 2. Activates both innate and adaptive immunity responses to against the virus	(103, 115, 121, 127, 128, 131, 162)

Blocking coronavirus-host interactions and attachments. Camostat mesylate (Foipan®) is a serine protease inhibitor that inhibits TMPRSS2 and blocks virus entry into lung cells (62,63). *In vitro* studies have shown that Foipan® inhibits TMPRSS2 and blocks SARS-CoV and human coronavirus NL63 infection of HeLa cells (62,63). Hoffmann *et al* demonstrated that SARS-CoV-2 exploits ACE-2 for entry and serine protease TMPRSS2 for S protein priming (31). Moreover, reports have shown that Foipan® blocks SARS-CoV-2 infection of Calu-3 lung cells *in vitro* (63). Accordingly, four clinical trials on camostat mesylate for COVID-19 are currently ongoing worldwide (NCT 04353284, NCT 04321096, NCT 04338906 and NCT 04355052) (64).

Arbidol (Umifenovir®) is a small indole-derivative agent used for the treatment of respiratory viral infections (65-68). *In vitro* and *in vivo* studies have demonstrated that Umifenovir® inhibits a number of enveloped or non-enveloped RNA or DNA viruses, including influenza viruses A, B and C, SARS-CoV, adenovirus, poliovirus, rhinovirus, coxsackievirus, Hantaan virus, Chikungunya virus and Hepatitis B and C viruses (68-70). Umifenovir® interacts with aromatic residues within the viral hemagglutinin glycoprotein and inhibits viral entry (71-73). A total of eight clinical trials (NCT 04350684, NCT 04286503, NCT 04260594, NCT 04323345, NCT 04273763, NCT 04306497, NCT 04261907 and NCT 04333589) on Umifenovir® for COVID-19 are ongoing worldwide (64).

Recently, ACE2 has been considered as a target for the treatment of COVID-19 (74). ACE2 is abundantly expressed on vascular endothelial cells of the lung (75), heart (42), nervous system (76), intestine (77), kidneys (51), blood vessels (78) and muscles (75) on the cell surface. ACE2 possesses *peptidyl dipeptidase* activity by catalyzing the cleavage of Angiotensin II into Angiotensin, and is one of the means by which blood pressure and cardiovascular functions are regulated (1-7). SARS-CoV-2 binds ACE2 for entry into the host (40-44). The ACE2 specific inhibitors, including MLN-4760 and Dx600 are not used clinically (79,80). It was reported that administration of excessive soluble ACE2 may slow the entry of SARS-CoV-2 into the host cells (74). Soluble forms of ACE2 include recombinant human ACE2 protein (rhACE2) (81) and recombinant bacterial ACE2 receptors-like enzyme of B38-CAP (rbd ACE2) (82). Studies have suggested rhACE2 (83) or rbd ACE2 (82) competitively bind with SARS-CoV-2, neutralizing the virus and also rescuing host cellular ACE2 activity and protecting the lungs from injury. The molecular pharmacological mechanisms of ACE-2 inhibitors are summarized in Fig. 8. A soluble form of ACE2 (rhACE2 and rbd ACE2) on COVID-19 therapy may exert dual functions: i) Slowing viral entry into host cells and inhibiting viral spread; ii) protecting the lung from injury (84). A total of four clinical trials (NCT 04375046, NCT 04382950, NCT 04287686 and NCT 04335136) on ACE-2 inhibitors for management of COVID-19 are ongoing worldwide (64).

Triggering lysosomal activation and disrupting intracellular trafficking. Chloroquine (Aralan®), a well-known anti-malarial and anti-autoimmune agent, has long been used to treat malaria (85) and autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis (86), Hydroxychloroquine (Plaquenil®) is synthesised by introducing

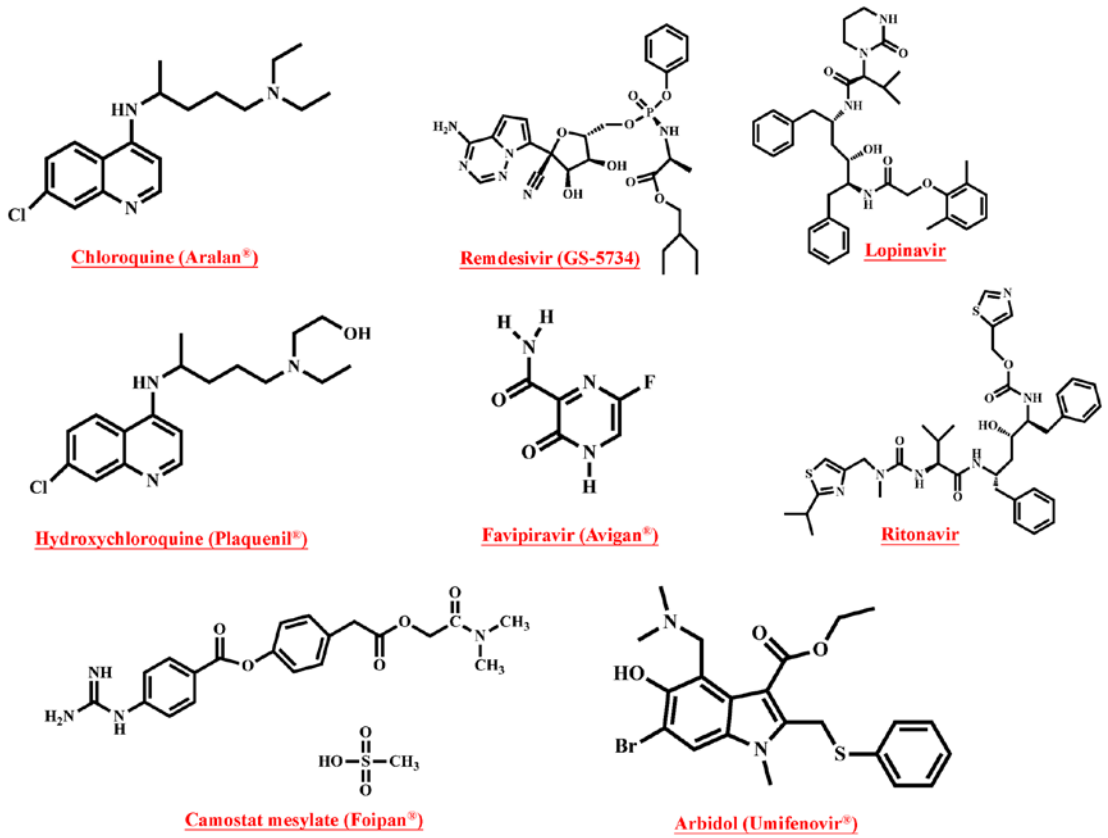

Figure 6. Chemical structures of hydroxychloroquine, chloroquine, remdesivir, favipiravir, ribavirin, lopinavir/ritonavir, arbidol and camostat mesylate.

a hydroxyl group into chloroquine. Animal studies have demonstrated that Plaquenil® is much less toxic than chloroquine (10,87-89).

Reports have shown that chloroquine and hydroxychloroquine increase endosomal and lysosomal pH (alkalinises vacuolar pH) and then disrupt intracellular trafficking (90-94). Recent studies have demonstrated that chloroquine reduces the expression of phosphatidylinositol binding clathrin assembly protein (PICALM), a cargo-selecting clathrin adaptor that senses and drives membrane curvature, which regulates endocytosis (95). *In vitro* studies have demonstrated that chloroquine significantly inhibits SARS-CoV-2 from infecting Vero E6 cells. One of the mechanisms for the chloroquine-mediated effects against SARS-CoV-2 is the decrease in the ability of cells to perform clathrin-mediated endocytosis of nanosized structures due to PICALM suppression (95).

Clinical investigations have shown that patients with COVID-19 had high concentrations of cytokines, such as IL-1β, IL-1β, IL-2, IL-6, IFNs and MCP-1 (96-98), in their plasma, subsequently causing a cytokine storm. In addition, hydroxychloroquine has been demonstrated to exhibit anti-inflammatory activity and can significantly decrease the IL-1, IL-6, TNF-α and TNF production through Toll-like receptor/NF-κB signalling (99,100).

The molecular pharmacological mechanisms of chloroquine and hydroxychloroquine are summarised in Fig. 9. A total of 52 clinical trials on chloroquine and 150 clinical trials on hydroxychloroquine for the treatment of COVID-19 are ongoing (64). Given that chloroquine and hydroxychloroquine are longstanding therapeutic agents widely used for disease treatment in hospitals, several ongoing clinical trials on COVID-19 have focused on both. However, it has more recently been reported that hydroxychloroquine does exhibit beneficial effects in the management of infection with COVID-19, and may in fact result in increased deaths due to its side-effects, resulting in the early halting an Oxford-based study (101).

Inhibiting RdRp. Remdesivir (GS-5734), favipiravir (Avigan®) (45,65,102-104). Remdesivir (GS-5734), a phosphoramidate prodrug of an adenine-derivative agent, was originally developed by Gilead Sciences (Gilead Sciences Inc.; patent holder) for the Ebola virus (105-108). Avigan®, a guanine-derived agent, has been approved for influenza for patients resistant to Tamiflu and Relenza treatment (10,109,110). Remdesivir and Avigan® are incorporated into nascent viral RNA and inhibit the RdRp (109,110). This results in the premature termination of the viral RNA chain and consequently halts the replication of the viral genome. Recent *in vitro* studies have reported that remdesivir and Avigan® possesses bioactive effects against SARS-CoV-2 (109,111,112). Our previous preliminary studies using Discovery Studio 2020 (DS 2020) software revealed that remdesivir and Avigan® exhibited strong binding potential to RdRp (Fig. 10 and Table SI). A total of 19 clinical trials on remdesivir and 12 clinical trials on Avigan® for the treatment of COVID-19 are ongoing (64). In April, 2020, a National Institutes of Health clinical trial reported that remdesivir accelerates recovery from COVID-19. On May 1, 2020, the US FDA issued an emergency authorisation for the use of investigational remdesivir in the treatment of suspected or laboratory-confirmed COVID-19 amongst adults

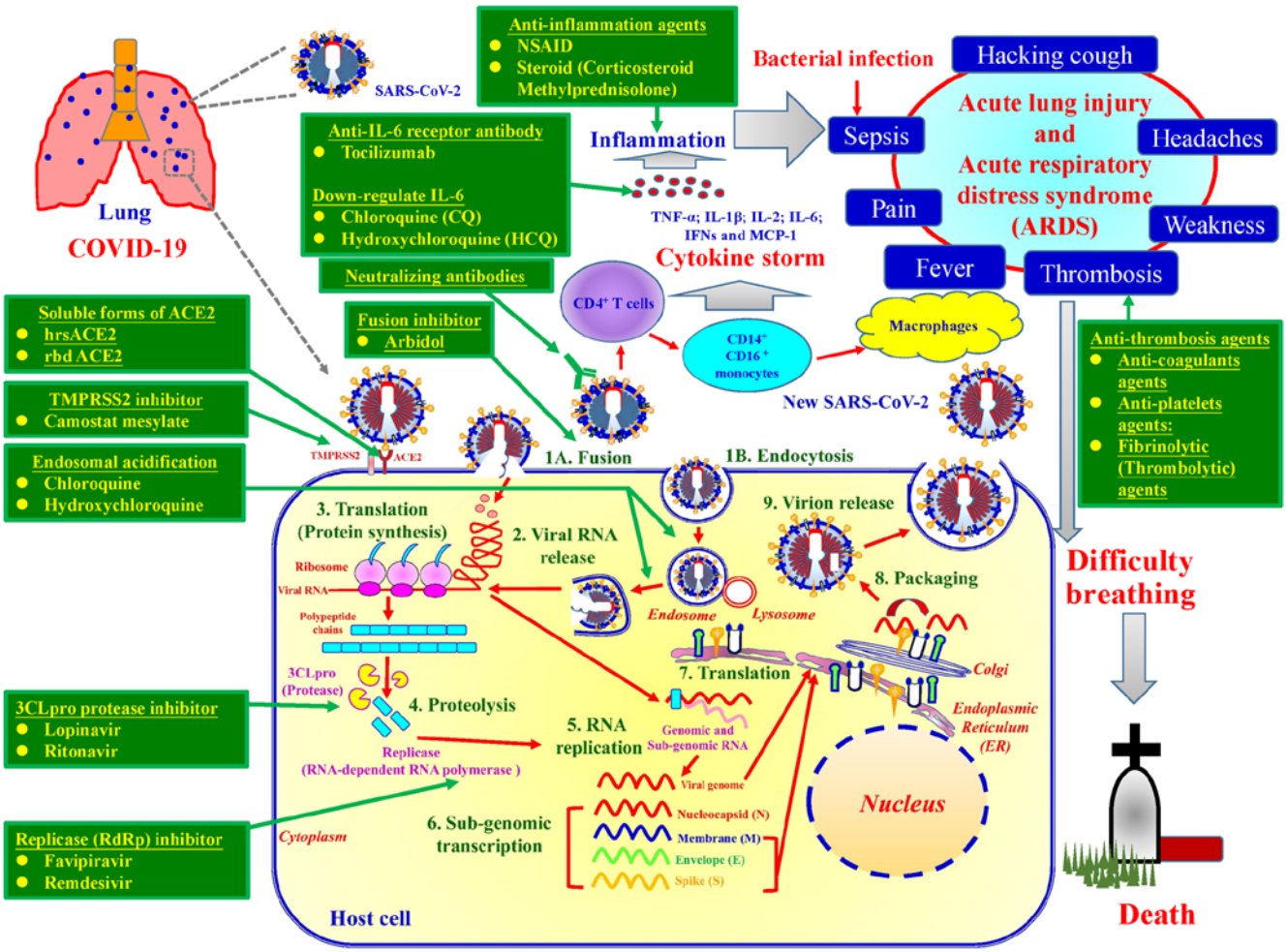

Figure 7. Molecular pharmacological mechanisms of ongoing potential therapeutic agents for management of COVID-19.

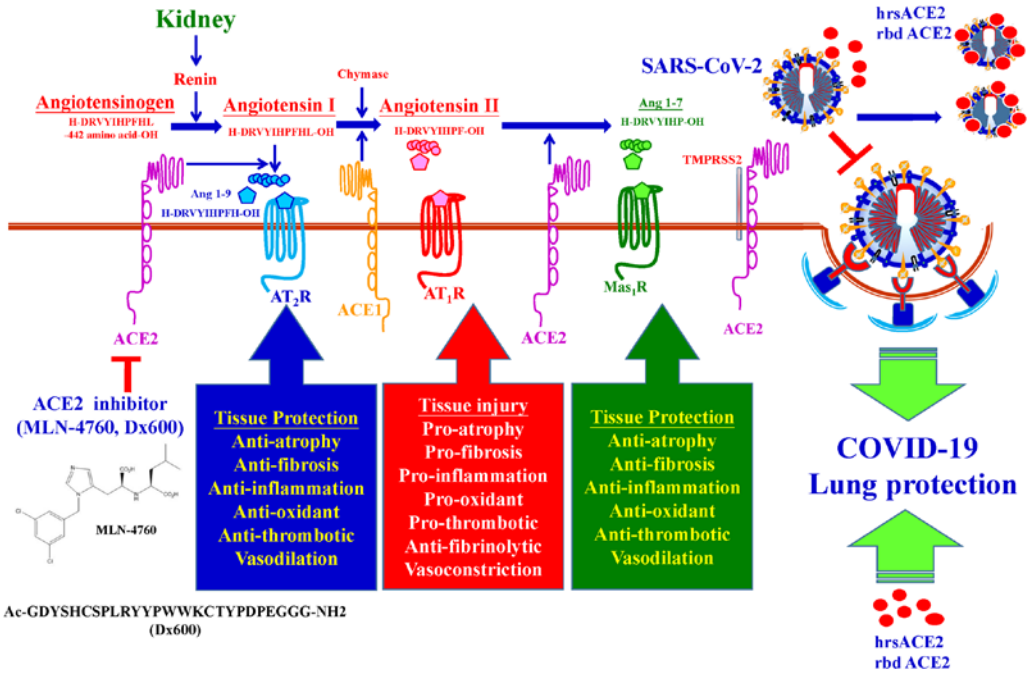

Figure 8. Molecular pharmacological mechanisms of ACE2 inhibitors and soluble forms of ACE2. ACE2 possesses *peptidyl dipeptidase* activity by catalyzing the cleavage of Angiotensin II into Angiotensin. The ACE2 specific inhibitors including MLN-4760 and Dx600, but are not used clinically. Soluble forms of ACE2, including rhACE2 protein and rbd ACE2, competitively bind with SARS-CoV-2 to neutralize the virus and also rescue the hosts cellular ACE2 activity and thus protect the lungs from injury. ACE2, angiotensin-converting enzyme 2; rhACE2, recombinant human ACE2; rbd, ACE2, recombinant bacterial ACE2 receptors-like enzyme of B38-CAP.

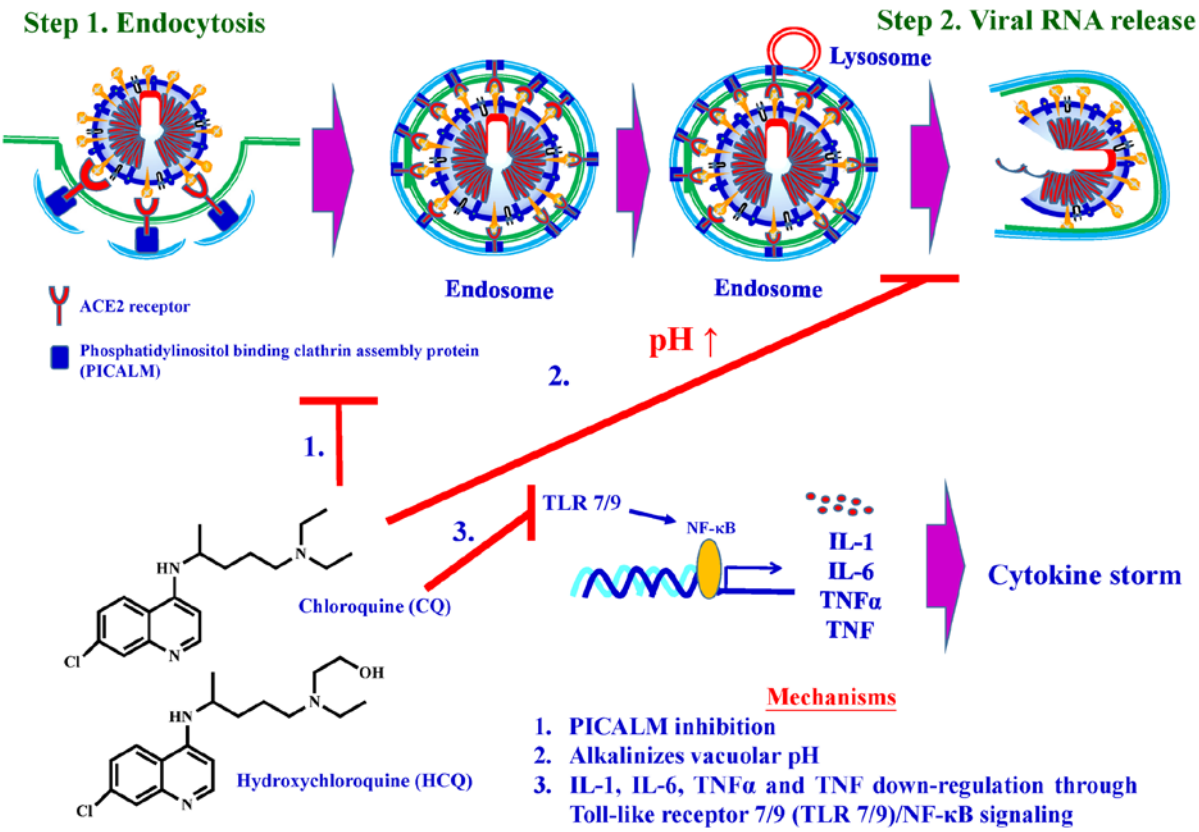

Figure 9. Molecular mechanisms of chloroquine and hydroxychloroquine.

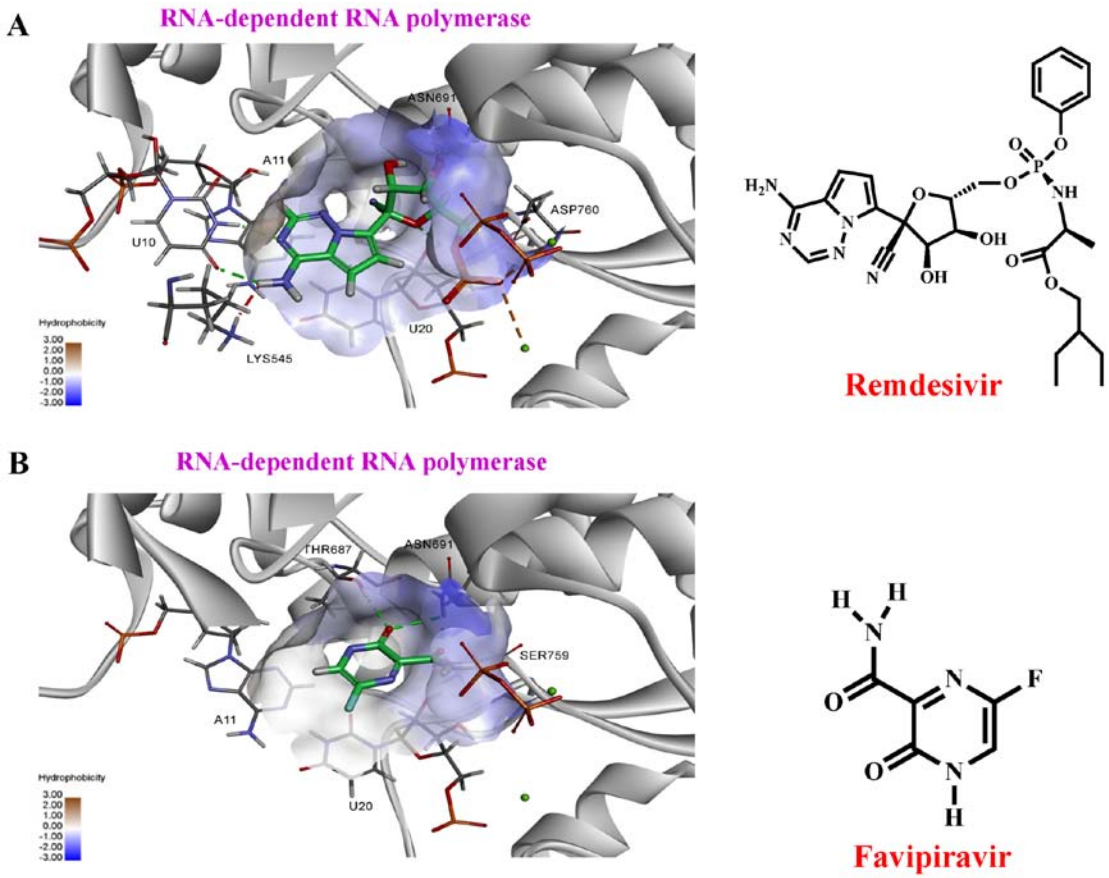

Figure 10. Molecular docking of remdesivir and favipiravir binding to RdRp. (A) The right panel shows the structure of remdesivir, the left panel shows molecular docking simulation using Discovery Studio 2020. (B) The right panel shows the structure of favipiravir, the left panel shows molecular docking simulation. The structures of the drugs are presented using a stick model. Carbon atoms are coloured green. RdRp, RNA-dependent RNA polymerase.

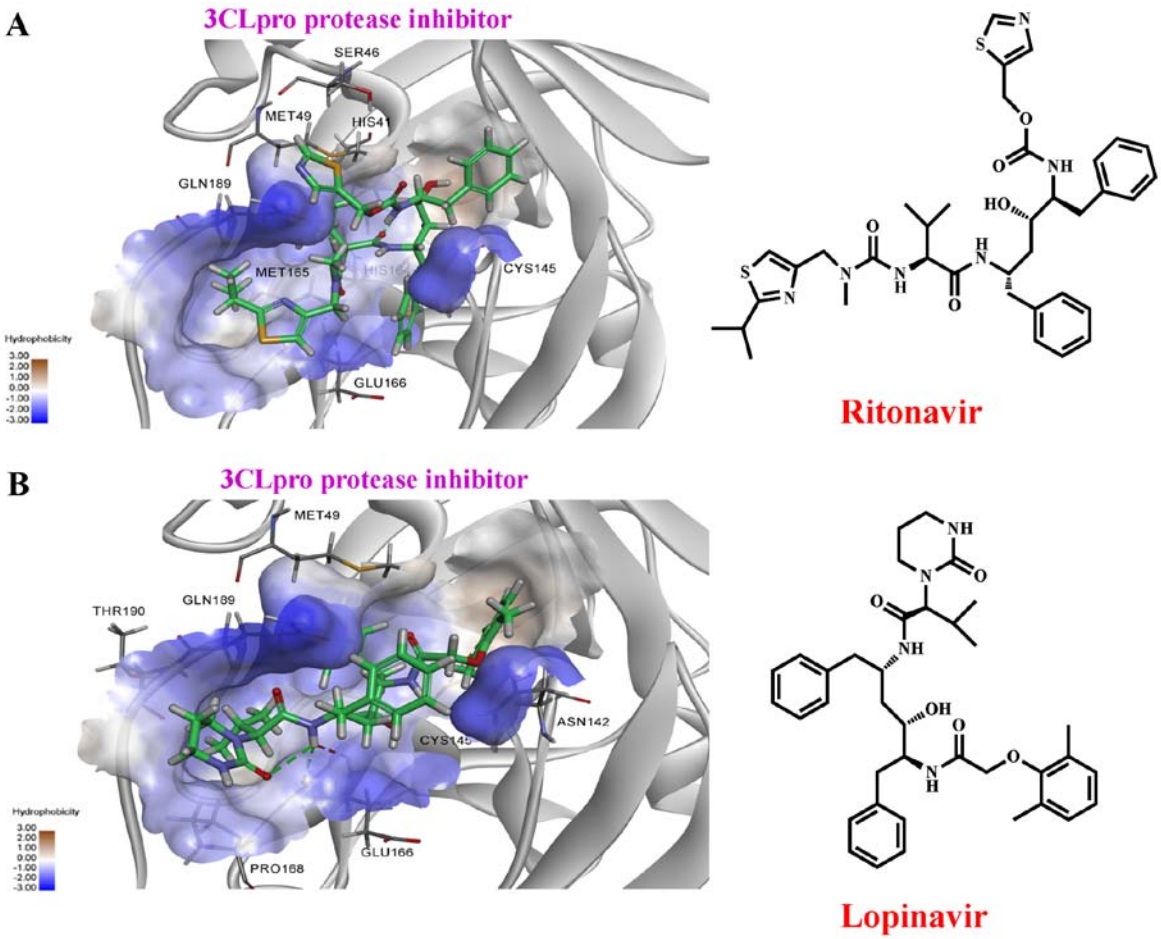

Figure 11. Molecular docking of ritonavir and lopinavir binding to the 3CLpro. (A) The right panel shows the structure of ritonavir, the left panel shows molecular docking simulation using Discovery Studio 2020. (B) The right panel is the structure of lopinavir, the left panel shows molecular docking simulation. The structures of the drugs are presented using a stick model. Carbon atoms are coloured green. 3CLpro, 3-chymotrypsin-like cysteine protease.

and children hospitalised with severe disease (113). The US FDA has approved remdesivir for the treatment of hospitalized COVID-19 patients on October 23, 2020 (8). This is positive and exciting news for the treatment of COVID-19.

Interfering with RNA metabolism required for viral replication. Ribavirin (Rebetol®) (109,114,115), a guanosine-derived agent, had been approved for the treatment of Hepatitis C viral infection. Recent studies have demonstrated that ribavirin can be used to treat respiratory syncytial virus and SARS-CoV by inhibiting viral RNA synthesis, viral mRNA capping and RdRp (109,116-118). To date, five clinical trials on Rebetol® for the treatment of COVID-19 are ongoing worldwide (64).

Inhibiting 3CLpro. Lopinavir/Ritonavir (Kaletra®) (103,111,115) are widely used for treating HIV infection. However, early studies have demonstrated that lopinavir and ritonavir are active against SARS-CoV and MERS by inhibiting 3CLpro via proteolysis in SARS-CoV (68,119,120). In contrast, Wu *et al* (27) demonstrated that Kaletra® did not shorten the duration of SARS-CoV-2 infection amongst patients with mild pneumonia in Taiwan. Our previous preliminary study using DS 2020 software showed that lopinavir and ritonavir exhibits strong binding potential to 3CLpro (Fig. 11 and Table SI). A total of 45 clinical trials on Kaletra® for the treatment of COVID-19 are ongoing worldwide (64).

Agents which exhibit immunotherapeutic properties. i) Type 1 IFN-α, pegylated IFNα-2a and α-2b and IFN-β (103,114,115,121); and ii) steroids (122,123). During viral infection, type I IFN synthesis is initially induced, which subsequently activates both the innate and adaptive immune response against the virus (124). The type I IFN family consists of IFN-α, IFN-β and other subtypes (121,125,126). When the virus infects target cells, RNA sensors induces IFN regulatory transcription factor translocation to the nucleus, which promotes type I IFN secretion. The secreted IFN interacts with IFN receptors on the cell membrane, which promotes phosphorylation of STAT1/2 transcriptional factors (127,128). The phosphorylated STAT1/2 localises to the nucleus, binds to IFN-stimulated response element responsible and activates IFN-stimulated genes, which then results in more production of type I IFN (129). Upon secretion of type I IFN, type I IFN-mediated innate immunity is initiated. Natural killer cells then become active and destroy infected cells. Type I IFN binds to the IFN receptors on cytotoxic T cells ($CD8^+$ T cells), subsequently killing infected cells through cellular immunity (130). In addition, type I IFN stimulates B cells and induces production of neutralising antibodies, which

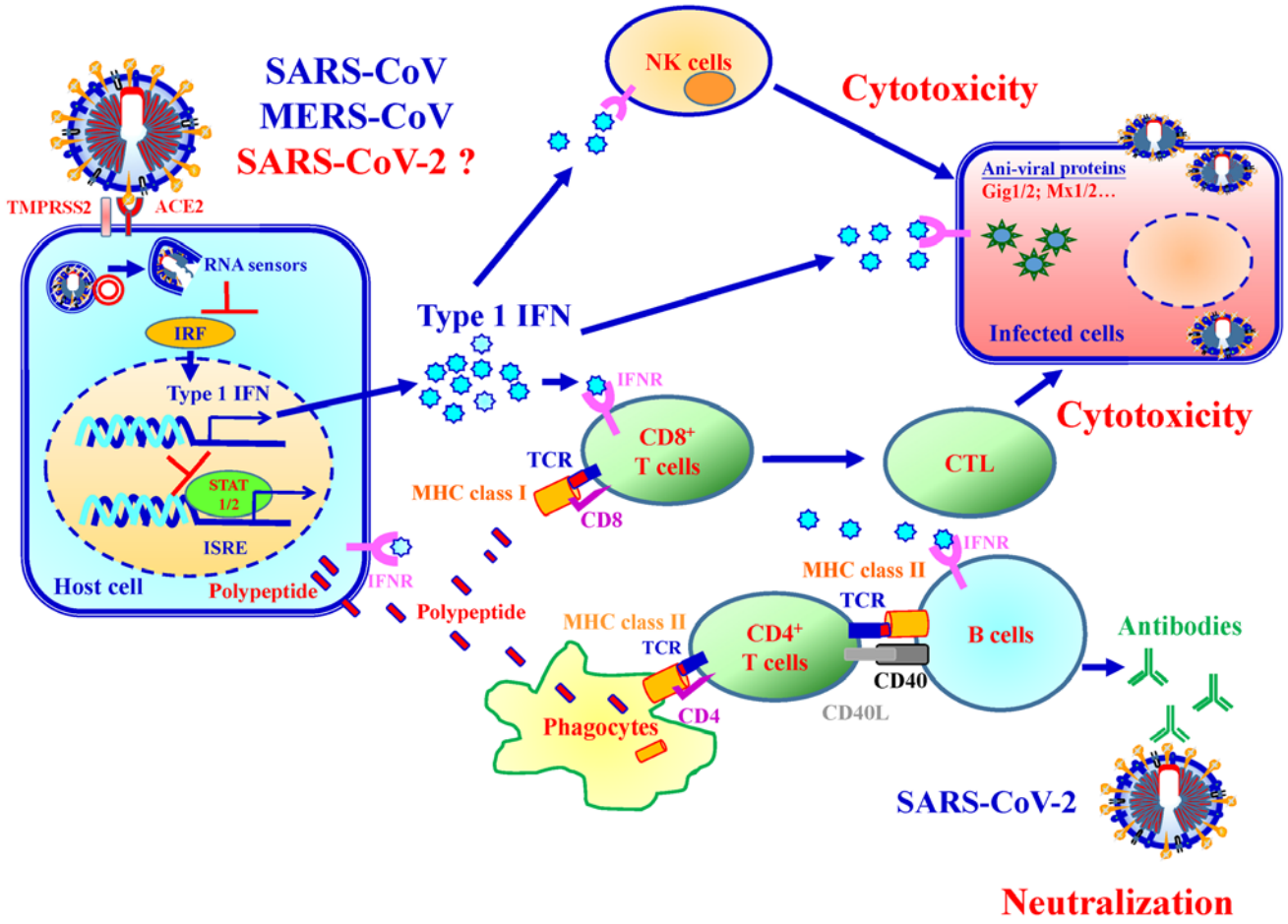

Figure 12. Schematic overview of type I interferon-mediated immune response mechanism for SARS-CoV, MERS-CoV and SARS-CoV-2. IRF, interferon regulatory transcription factor; type 1 IFN, type 1 interferon; ISRE, IFN-stimulated response element; IFNR, interferon receptor; MHC, major histocompatibility complex; TCR, T cell receptor; CTL, cytotoxic T lymphocyte; CD40L, CD40 ligand.

serves a protective role by limiting later-phase infections and preventing future re-infections (128). Treatment with IFN-α2b significantly reduced the duration of SARS-CoV-2 in the upper respiratory tract and reduced the levs of the inflammatory cytokines IL-6 and CRP in COVID-19 patients (131).

Cells infected with SARS-CoV and MERS-CoV exhibit reduced type I IFN. As such, it is hypothesized that SARS-CoV-2 may utilise a similar manner for type I IFN reduction. It has previously been shown that type I IFN treatments improve anti-SARS-CoV and anti-MERS-CoV activity amongst infected mice and exhibits synergistic effects with ribavirin against SARS-CoV *in vitro* (132). Immunocompromised patients are at higher risk for severe COVID-19 than the general public. Type I IFN treatments can thus be a safe and efficient approach to manage SARS-CoV-2 infection (121,133). A total of 37 clinical trials on IFN for COVID-19 are ongoing worldwide (64). Fig. 12 presents a schematic overview of the type I IFN-mediated immune response mechanism following SARS-CoV, MERS-CoV and SARS-CoV-2 infection.

Combining anti-viral and anti-inflammatory agents is another attractive therapeutic option for the prevention and *treatment* of *COVID-19*. Upon infection, innate immune cells including macrophages, natural killer cells, neutrophils and dendritic cells produce large amounts of pro-inflammatory cytokines (TNF, Type 1 IFN, IL-6 and IL-12). Previous clinical studies have demonstrated that steroids (corticosteroid and methylprednisolone) modulate inflammatory responses, reducing the incidence of treatment failure and reducing cytokine storms (123,134). The anti-inflammatory mechanisms of steroids is involved in the presence of steroid receptors and regulates down-stream gene transcription processes (135). Steroid receptor signaling mechanisms regulate down-stream gene expression via transactivation and trans-repression. i) In the process of transactivation, steroid receptors bind steroid hormones and form dimers. The ligand bound steroid receptor dimer complex binds to specific DNA sequences (steroid response elements; SREs), increasing anti-inflammatory gene transcription (such as Lipocortin 1 and IL-10). ii) In the process of trans-repression, the ligand bound steroid receptor tethers to SREs and inters pro-inflammatory transcription factors, which leads to a reduction of pro-inflammatory cytokines (136). SARS-CoV-2 infection induces pro-inflammatory cytokine production, resulting in local tissue inflammation and a systemic inflammatory response, termed a cytokine storm (137). Cytokine storm injures host cells and causes an increased risk of respiratory failure such as acute respiratory distress syndrome (ARDS) and eventually death. Fig. 13 presents a schematic diagram of the steroid-mediated immune response following SARS-CoV-2 infection.

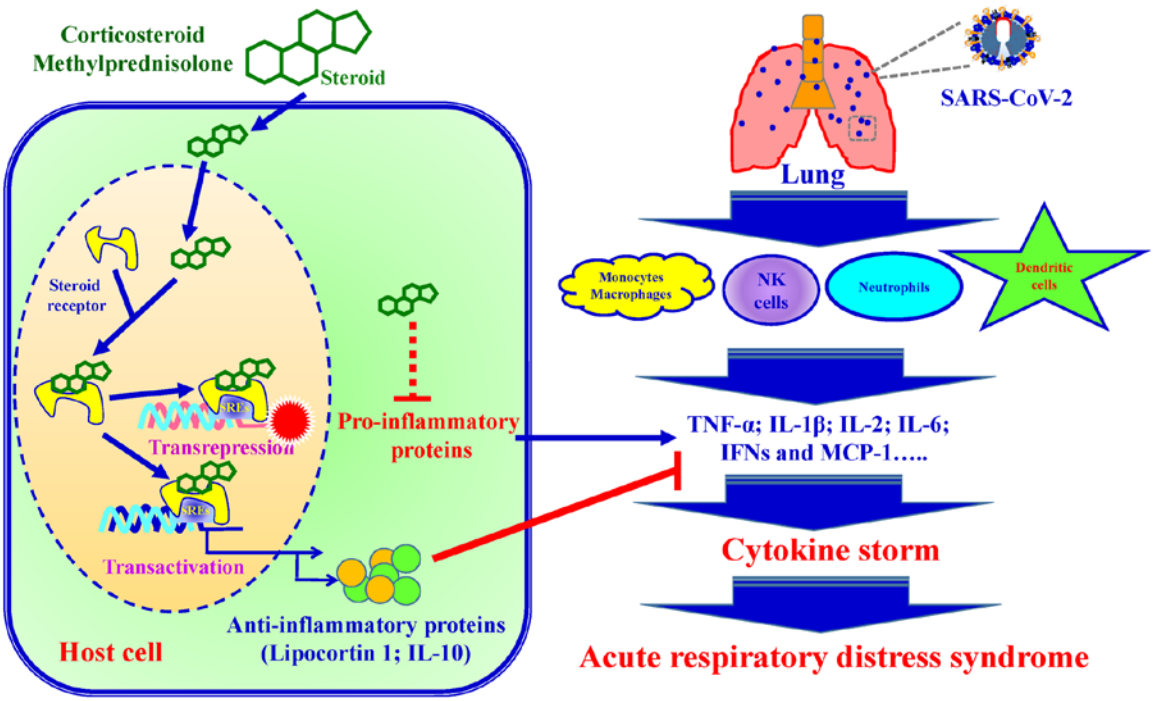

Figure 13. Schematic diagram of the steroid-mediated immune response following SARS-CoV-2 infection. Steroid receptor signaling mechanisms regulate down-stream gene expression via transactivation and transrepression. Steroids cause an increase in anti-inflammatory gene transcription and blocks pro-inflammatory cytokine production. SREs, steroid response elements.

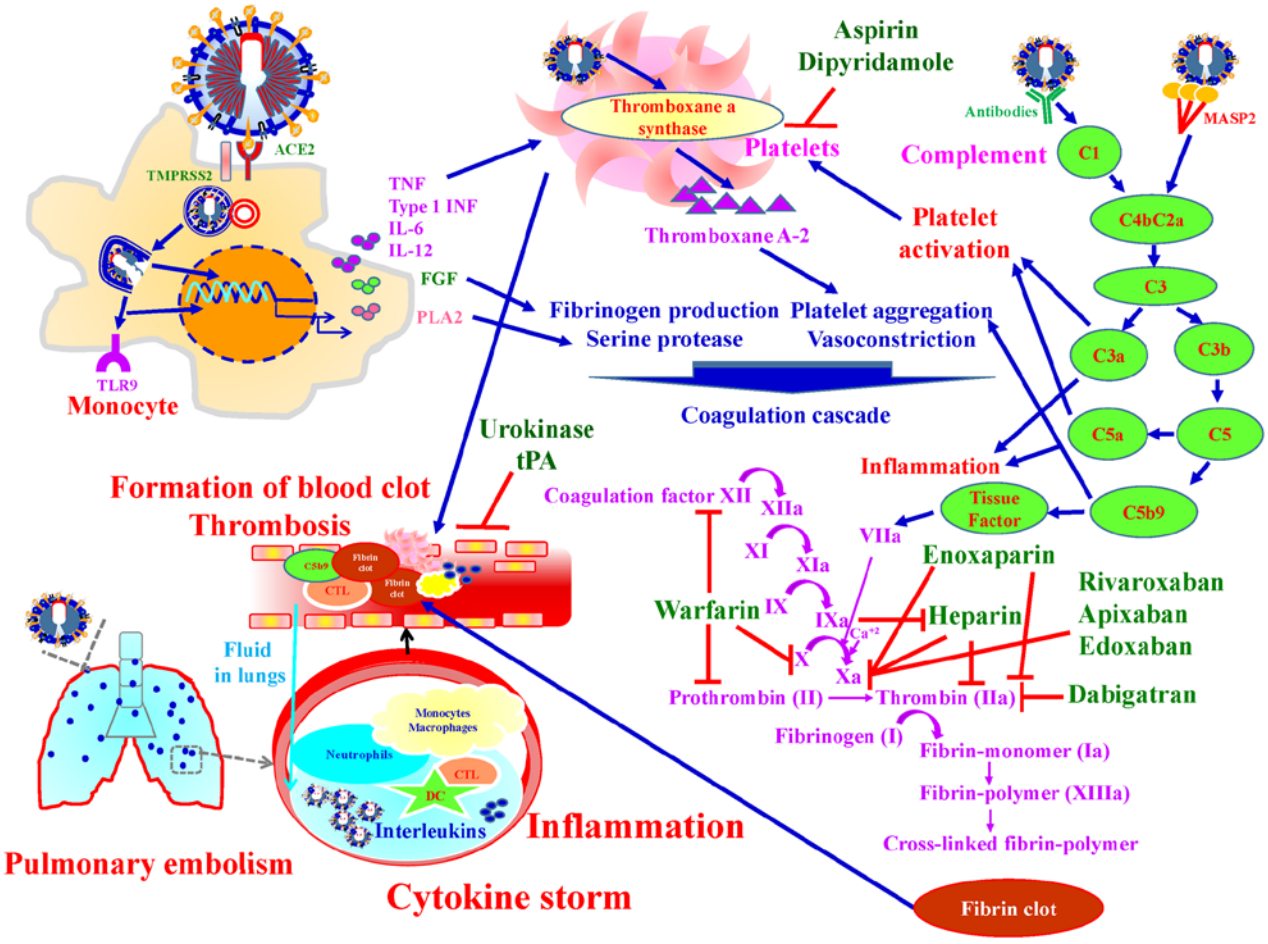

Figure 14. Schematic overview of the mechanisms of anti-thrombotic agents used for the treatment of SARS-CoV-2 infection. Anti-thrombotic agents include: i) Anti-coagulants: Unfractionated heparin, Enoxaparin, Danaparoid and warfarin; ii) anti-platelet agents: Aspirin and Dipyridamole; and iii) Fibrinolytic (Thrombolytic) agents: Urokinase, Streptokinase and tPA. tPA, tissue-type plasminogen activator.

7. Pharmacological agents targeting thrombosis

It was reported that SARS-CoV-2 infection increased the risk of thrombosis and up to 50% of severe COVID-19 patients developed coagulopathy (138). Coagulation and thrombosis are associated with pathogenesis of COVID-19 (139). SARS-CoV-2 results in direct injuries to the vascular endothelium cells or induces a cytokine storm, leading to systemic thrombus formation, thrombosis on pulmonary artery, and potentially lower limb arterial and cerebral infarction (138). Upon SARS-CoV-2 infection, the complement system, a bridge between innate and adaptive immune response, is activated and triggers inflammation. In addition, the complement system links the immune system with the coagulation system. C5a in the complement system induces tissue factor expression, and C5b-9 activates platelet (140) Tissue factor /factor VIIa complex converts prothrombin into thrombin. Thrombin catalyzes fibrinogen to fibrin and promotes fibrin formation by coagulation cascade activation and by activating platelets (140-144).

Pharmacological agents targeting thrombosis in COVID-19 are divided into three groups: i) Anti-coagulant agents; Unfractionated heparin, low-molecular-weight heparins (Enoxaparin), Danaparoid (a mixture of heparan sulfate, dermatan sulfate, and chondroitin sulfate) and Vitamin-K antagonists (warfarin). Heparin and Enoxaparin have strong anti-thrombotic activity, and anti-inflammatory properties via selectin blockade, bradykinin downregulation and thrombin generation. In addition, Heparins attenuate interactions between SARS-CoV-2 spike protein and ACE-2 (145). Enoxaparin is a first choice drug to prevent thromboembolic phenomena in COVID-19 patients (138). ii) Anti-platelets agents; Aspirin and Dipyridamole. Aspirin has been demonstrated with ARDS prevention and higher survival rates from acute lung injury in clinical studies (146,147). Dipyridamole is a phosphodiesterase inhibitor that inhibits platelet aggregation by increasing cyclic adenosine monophosphate concentrations. *In vitro* studies demonstrated that dipyridamole has anti-SARS-CoV-2 activity through binding with 3CLpro of SARS-CoV-2 (148). iii) Fibrinolytic (thrombolytic) agents; Urokinase, Streptokinase and Tissue-type plasminogen activator (tPA). The blood clots are broken down by plasmin call fibrinolysis. Fibrinolysis intermediate tPA and urokinase plasminogen activator convert plasminogen to plasmin. When tPA, a thrombolytic agent, is intravenously injected into the vasculature, increased fibrinolytic ability in the plasma and lyses of the thrombosis was observed in COVID-19 patients (149). Fig. 14 presents an overview of the mechanisms by which anti-thrombotic agents exert their effects in the treatment of SARS-CoV-2 infection.

8. Neutralizing antibodies and vaccines against SARS-CoV-2

Two promising countermeasures for controlling the current COVID-19 pandemic are recombinant neutralizing antibodies (150) and vaccines (151) directed against SARS-CoV-2. Recombinant human or humanized monoclonal antibodies are proving to be safe, effective, and highly specific in their ability to target an invading pathogen. More than 70 recombinant monoclonal antibodies have now been approved by the FDA for use in the treatment of infectious, autoimmune and inflammatory, malignant, or cardiovascular diseases (152). Thus, recombinant neutralizing antibodies isolated from those infected with SARS-CoV-2 are the most rapid and readily manufacturable immune intervention for passive administration that may be developed to either prevent or treat COVID-19 disease. Of note, US President Donald Trump, who recently suffered from infection with COVID-19 was treated with monoclonal antibodies generated by Regeneron.

Vaccines are a time-honored method for establishing long-lived immune memory for controlling infectious diseases, and technologies have been developed such that vaccines can now be developed faster than previously (151). Over 100 companies or academic institutions are working on COVID-19 vaccines with strategies that include recombinant vectors, mRNA in lipid nanoparticles, DNA, inactivated virus, live attenuated virus, virus-like particles and protein subunits (153). Three vaccine candidates have already advanced to Phase II testing that include an mRNA vaccine encoding the viral spike protein from Moderna, an Adeno-type 5 vector vaccine expressing the S protein from CanSino Biologicals, and a chimpanzee adenovirus encoding the spike protein from the Jenner Institute in Oxford, UK. There are several mRNA/LNP (for example, from Moderna/NIAID, BioNTech/Fosum, Pharma/Pfizer) or DNA (Inovio) vaccines as well as attenuated viruses, proteins, nanoparticles and viral vectors containing SARS-CoV-2 viral genes as vaccine candidates moving through safety and immunogenicity trials, and a smaller subset of vaccine candidates will be tested in Phase III or efficacy trials to better determine if they are safe, as well to determine their efficacy. In parallel now with Phase I and II trials, it is important to develop capacity for large-scale vaccine production, in the event of a successful efficacy trial (154). It is possible that genetic immunization strategies such as DNA or mRNA in LNPs can be manufactured more rapidly than proteins or viral vectors and can be more cost effective.

9. TCM and COVID-19

Based on >3,500 years of Chinese medical practice, TCM has spread to numerous countries worldwide, has profoundly influenced lives and has gradually merged with and complemented modern Western medicine and therapy (155). In recent decades, mounting evidence has suggested that TCM may be helpful in the prevention and treatment of human virus-related disorders, including influenza, liver diseases and acquired immune deficiency syndrome (114,156-158). Following the COVID-19 outbreak, TCM schemes have been included into the guidelines for the diagnosis and therapy of COVID-19 in China (114,159,160). Recently, *in silico* data showed that binding of curcuminoid derivatives to COVID-19 3CLpro is stronger than that of Lopinavir and curcumin (126). It is hypothesized that more convenient methods for the early detection of COVID-19 via genotyping will emerge in the near future. Even amongst severe/critical cases, TCMs can still serve as a complementary and integrative therapy to modern Western medicine to shorten the recovery period and relieve symptoms among patients with COVID-19.

10. Conclusions

This review describes several clinical manifestations of COVID-19, analyses the SARS-CoV-2 genome and outlines

the life cycle of SARS-CoV-2. Several methods have been used to examine SARS-CoV-2 infections. For example, RT-qPCR has been widely applied for RNA detection, whereas rapid screening has been used for antibody or virus detection. Despite the lack of medications for COVID-19, several clinical trials have been proposed for its treatment. In addition, several TCMs have been discussed for the readers' reference.

Global interaction and cooperation amongst several countries is expected to underlie the development of rapid and accurate screening assays, produce vaccines, design novel agents against SARS-CoV-2 and reduce the side effects of therapeutic TCMs, with the ultimate, long-term goal of eradication of COVID-19.

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Availability of data and materials

Not applicable.

Authors' contributions

SCT, FJT and JSY were involved in the conception of the study. CCL, DTB, YJC, YTY, YMH, CWF, SCK, YSL, HYC and YNJ were involved in the literature search and critical reviewing of the manuscript. SCT, CCL, DTB, YJC, YTY, YMH, SCK and JSY were involved in the preparation of the draft of the manuscript. SCT, FJT and JSY were involved in the revising and editing of the manuscript. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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