REVIEW

Potential therapeutic and pharmacological strategies for SARS-CoV2

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Abstract

Background At the end of 2019, the new Coronavirus disease 2019 (COVID-19) strain causing severe acute respiratory syndrome swept the world. From November 2019 till February 2021, this virus infected nearly 104 million, with more than two million deaths and about 25 million active cases. This has prompted scientists to discover effective drugs to combat this pandemic.

Area covered Drug repurposing is the magic bullet for treating severe acute respiratory syndrome coronavirus 2 (SARS-CoV2). Therefore, several drugs have been investigated in silico, in vitro, as well as through human trials such as anti-SARS-CoV2 agents, or to prevent the complications resulting from the virus. In this review, the mechanisms of action of different therapeutic strategies are summarized. According to the WHO, different classes of drugs can be used, including anti-malarial, antiviral, anti-inflammatory, and anti-coagulant drugs, as well as angiotensin-converting enzyme inhibitors, antibiotics, vitamins, zinc, neutralizing antibodies, and convalescent plasma therapy. Recently, there are some vaccines which are approved against SARS-CoV2.

Expert opinion A complete understanding of the structure and function of all viral proteins that play a fundamental role in viral infection, which contribute to the therapeutic intervention and the development of vaccine in order to reduce the mortality rate.

Keywords COVID-19 · Hydroxychloroquine · Indomethacin · Tocilizumab · Teicoplanin · Camostat

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Introduction

The outbreak of Coronavirus disease 2019 (COVID-19) or severe acute respiratory syndrome coronavirus 2 (SARS-CoV2), has resulted in more than 1,139,608 deaths and 9,533,058 confirmed positive cases despite herd immunity until October 22, 2020. Unfortunately, it is observed that the recovered patients have a recurrent infection rate, without any symptoms, that can be considered an indicator of the rate of virus infection, disease severity and the possibility of sudden death. Therefore, the recovered patients should undergo regular diagnostic examinations (Zheng et al. 2020). The virus is transmitted by close contact and aerosol transmission routes. Several researchers have proven that COVID-19 not only affects the lungs, but also the digestive tract, as it is detected in stool, gastrointestinal tract, saliva, as well as urine (Xu et al. 2020b). Moreover, it is detected in the secretions of the conjunctiva and the tears of patients (Wang et al. 2020). In addition, Wang et al. (2020) reported that SARS-CoV2 also infects T lymphocytes.

Laboratory examination revealed that patients could have lymphopenia, thrombocytopenia, leukopenia with high levels of C-reactive protein, lactate dehydrogenase, ferritin, troponin, D-dimer and creatinine kinase (Guan et al. 2019; Yao et al. 2020). Cytokine release syndrome is a vital factor that aggravates disease progression. Higher levels of IL-6 and IL-10 and lower levels of CD4 + T and CD8 + T were observed in COVID-19 patients, along with disease severity (Tufan et al. 2020).

Likewise, SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV), SARS-CoV2 belongs to the genus betacoronavirus (β-coronavirus). The coronavirus particle consists of four structural proteins, namely the nucleocapsid, envelope, membrane, and spike, as shown in Fig. 1. In addition, the viral genome also encodes several nonstructural proteins, including RNA-dependent RNA polymerase (RdRp), the main coronavirus protease (3-chymotrypsin-like protease, 3CL^{pro}), and papain-like protease (PL^{pro}). Hoffmann et al. (2020a) demonstrated that the spike (S) protein receptor-binding domain (RBD) binds with angiotensin-converting enzyme 2 (ACE2), as SARS-CoV. Moreover, protein S can bind to CD26, ezrin, cyclophilins, and other cell adhesion factors important for cellular adhesion as well as virulence. Furthermore, it is well known that the glycosylated part of protein S can bind to sinusoidal endothelial cell C-type lectin (LSEC-tin), which is expressed in high levels of dendritic cells, lymph nodes, and liver and is co-expressed with dendritic cell-specific intercellular adhesion molecule-3 grabbing non-integrin (DC-SIGN). These receptors promote SARS-CoV-induced protein S infection and increase viral pathogens in the liver and lymph nodes (Gramberg et al. 2005; Vankadari and Wilce 2020; Liu et al. 2004).

The virus invades cells by binding to ACE2, which is a carboxypeptidase and leads to spike protein conformational changes. However, this may require additional triggers such as pH acidification or proteolytic activation like transmembrane protease/serine sub-family (TMPRSS211) (Simmons et al. 2013). On entering the host cells, the viral genome is released as a single-stranded positive RNA as shown in Fig. 1. Subsequently, it is converted into viral polyproteins using host cell protein translation machinery, which are then cleaved into effector proteins by the viral proteinases 3CL^{pro} and PL^{pro} (Fehr and Perlman 2015). PL^{pro} also acts as a deubiquitinate that may deubiquinate certain host cell proteins, including interferon factor 3 and nuclear factor κB, resulting in immune suppression. Furthermore, RdRp synthesizes a full-length negative-strand RNA template, to be used by RdRp to produce more viral genomic RNA (te Velthuis et al. 2010).

The viral protein along with other structures plays a major role in viral invasion. Wilson et al. (2004) illustrated that the envelope protein(E), forms ion channels that are more permeable to monovalent cations than monovalent anions, creating an acidic pH environment required for binding the S protein. Moreover, protein E affects virus morphogenesis, budding, assembly, intracellular trafficking, and virulence. Protein E is responsible for the uncontrolled induction of pro-inflammatory cytokines in the lung parenchyma that cause edema accumulation, leading to acute respiratory distress syndrome (ARDS), and very often to the death of infected animal models or human patients. Furthermore, Xiong et al. (2020) found that viral infection regulates apoptosis, autophagy, and p53 pathways in PBMC. Wenzhong and Hualan (2020) reported that COVID-19 attacks heme on the 1-beta chain of hemoglobin to dissociate iron and capture the porphyrin, leading to intense lung inflammation and symptoms of respiratory distress, due to the inability to exchange carbon dioxide and oxygen frequently.

Currently, there are no effective drugs targeting SARS-CoV2. Drug repurposing, which is an effective drug discovery strategy from existing drugs, such as anti-inflammatory agents, immunosuppressant or antineoplastic agents, selective estrogen receptor modulators, antiviral drugs, and anti-malaria agents, can shorten the time and reduce costs, compared to de novo drug discovery, according to WHO reports.

Consequently, different treatment protocols for COVID-19 infection are designed to eliminate the virus directly, in addition to protecting the human body and increasing its resistance against the viral effect. However, the aim of this review was to shed light on the different drug categories used in the treatment of COVID-19, and to understand their mechanisms of action (Table 1).
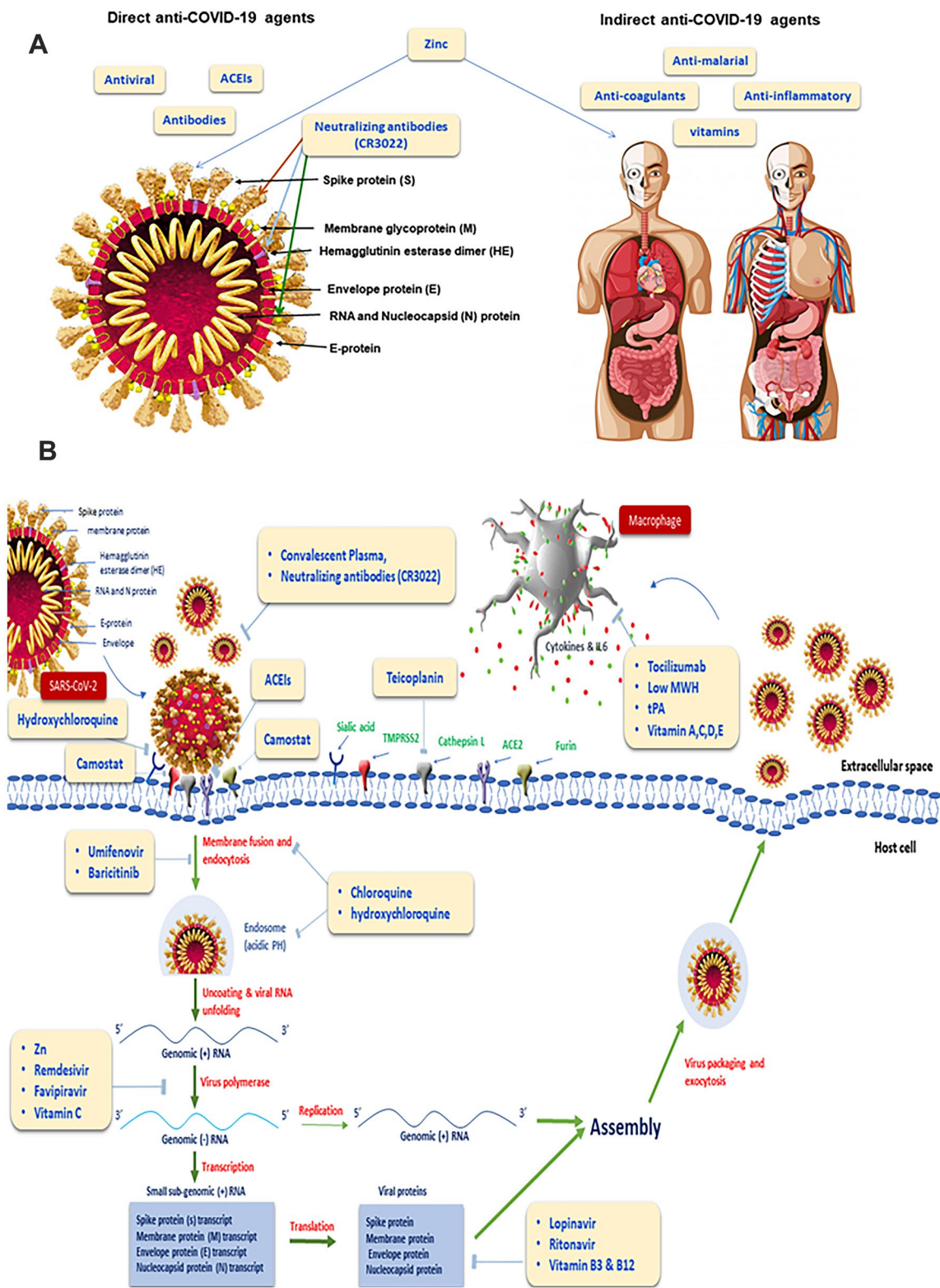
Fig. 1 The proposed scheme of **a** COVID 19 structure, direct and indirect anti-COVID 19 agents. **b** Coronavirus life cycle illustrating potential target sites and their inhibitors

Table 1 The mechanism of action of the different drug classes

		Classical Use	COVID 19 Targets	References
Antiviral drugs	*Camostat*	Chronic pancreatitis, postoperative reflux esophagitis, and liver fibrosis	Inhibit TMPRSS2	Ueda et al. (2015), Roomi and Khan (2020)
	Umifenovir	Influenza virus	The interaction of the SARS-CoV2-S protein with ACE2, inhibits membrane fusion of the viral envelope	Sanders et al. (2020)
	Lopinavir/ritonavir	HIV/AIDS	Inhibit 3CL^{pro}	Choy et al. (2020)
	Favipiravir	Influenza in Japan	Viral RdRp inhibitor	Furuta et al. (2017)
Anti-inflammatory	*Indomethacin*	Cyclopentone- cyclooxygenase (COX 1 and 2) inhibitor	Inhibits virus replication and protects host cells from virus-induced damage	Amici et al. (2006)
	Tocilizumab	Anti-IL-6 antibody, commonly used in rheumatic diseases and rheumatoid arthritis	Prevents cytokine storm Increases oxygenation Removes lung lesion opacity	Sheppard et al. (2017)
	Baricitinib	Active-and-selective-adaptor-protein-2-associated protein kinase 1 (AAK1) inhibitor	Inhibits INF-α	Richardson et al. (2020)
	Ruxolitinib	Selective JAK 1 and 2 inhibitors, with selectivity against tyrosine kinase (TYK) 2 and JAK3, resulting in a powerful anti-inflammatory activity	Reduce the hyperinflammatory status, that causes ARDS Reduce intubation rates and ultimately improve patient outcomes	Gozzetti et al. (2020)
Anti-coagulants	Low-molecular-weight heparin	Anti-coagulant	Anti-coagulant and an anti-inflammatory medication	Magro et al. (2020), Thachil et al. (2020)
	Urokinase and Streptokinase	Efficient clot lysis ability	Reduce the mortality rate for patients with ARDS	Hardaway et al. (2001)
	Plasminogen activators		Increase the arterial pO2 Decrease the arterial pCO$_2$	Moore et al. (2020)
Angiotensin-converting enzyme inhibitors (ACEIs)	ACEIs and ARBs	Hypotensive drugs	Reduce lung, renal, and cardiac damage resulted from RAS hyperactivation	Guo et al. (2020)
Antibiotics	Teicoplanin	Treating infections caused by gram-positive bacteria	Inhibitors for cathepsin L-dependent viruses	Jean et al. (2020)

Table 1 (continued)

		Classical Use	COVID 19 Targets	References
Vitamins	*Vitamin D*	For bone disease treatment	It plays an essential role in stimulating the maturation of many cells, including immune cells. Inducing cathelicidins and defensins, reducing pro-inflammatory cytokines, along with elevating anti-inflammatory cytokines	Chen et al. (2020b), Grant et al. (2020)
	Vitamin E	Antioxidants	Antioxidants	Moriguchi and Muraga, (2000), Meydani et al. (2004)
	Vitamin A	Antioxidants and anti-infective vitamin	Regulate the elements of the innate immune response	Chen et al. (2020b)
	Vitamin C	Antioxidants and weak antihistamine	Change cellular pH and in silico data reported its ability to bind to spike protein	Rosa and Santos (2020), Quiles et al. (2020)
	Vitamin B	Coenzymes and increases the host's immune response	In silico data proved that vitamin B inhibits COVID-Mpro	Kandeel and Al-Nazawi (2020)
Zinc	*Zinc oxide*	Food supplement with antimicrobial and antiviral properties	Antioxidant and anti-inflammatory activities. In vitro data proved that it inhibits the SARS-CoV RdRp. Zinc ions can decrease ACE2 activity	Zhang et al. (2020a), te Velthuis et al. (2010)
Anti-malarial drugs	Chloroquine and hydroxychloroquine	Antiprotozoal and anti-inflammatory drugs	In silico data proved that it binds with spike protein. Alkalinization of endosome compartments	Kupferschmidt and Cohen (2020), Fantini et al. (2020)
Neutralizing antibodies	CR3022		Antibodies against the RBD within the S1 unit	Tian et al. (2020)
Convalescent plasma therapy	Increased oxyhemoglobin saturation, lymphocyte counts, and decreased C-reactive protein which can rapidly reduce viremia			Roback and Guarner, (2020), Shen et al. (2020)

1. Antiviral drugs

Several antiviral compounds can be used to treat COVID-19 such as camostat, umifenovir, lopinavir, ritonavir, pleconaril, and favipiravir. Antiviral compounds are mainly used to reduce disease duration and infection index. There are multiple different mechanisms through which antivirus can work, yet they all have one thing in common preventing viral replication (Munir et al. 2020).

Camostat is a serine protease inhibitor with anticarcinogenic and antiviral effects. Camostat is used to treat chronic pancreatitis, postoperative reflux esophagitis, and liver fibrosis (Ueda et al. 2015). Camostat is a specific inhibitor of TMPRSS2 enzyme (Roomi and Khan 2020). The mortality rate of mice infected with SARS-CoV was reported to have decreased from 100 to 35% after treatment with a therapeutic dose of camostat mesylate as well as reduced lung cell infection Calu-3 caused by SARS-CoV2 (Medicine 2020).

Umifenovir (arbidol), which is used to treat influenza infection, inhibits the membrane fusion of the influenza virus, and prevents the virus from entering the host cell. Umifenovir prevents contact between virus and target host cells, and stimulates the immune response (Amarelle et al. 2017). In silico data proved that umifenovir targets the interaction of the SARS-CoV2-S protein with ACE2, and inhibits membrane fusion of the viral envelope (Sanders et al. 2020). Results obtained from clinical trial indicated that umifenovir reduces the viral load of COVID-19 by preventing the development of lung lesions and preventing transmission of the virus (Munir et al. 2020).

Lopinavir/ritonavir is a protease inhibitor and was the first combination of lopinavir with a low dose of ritonavir for use in the treatment and prevention of HIV/AIDS (Chandwani and Shuter 2008). It can inhibit 3CL^{pro}, which is essential for viral RNA treatment. Recently, lopinavir has proven to have anti-SARS-CoV2 activity in vitro (Choy et al. 2020). Treating severe COVID-19 patients with **Lopinavir/ritonavir** did not reduce the viral load; however, it induced huge adverse effect (Munir et al. 2020) as this drug can lead to multiple side effects such as gastrointestinal disturbance, dyslipidemia, hyperglycemia, and organ inflammation (Chandwani and Shuter 2008).

Favipiravir (T-705; 6-fluoro-3-hydroxy-2-pyrazinecarboxamide) is a viral selective inhibitor of RdRp (Furuta et al. 2017). Favipiravir is a prodrug that transforms inside the cell to active favipiravir-ribofuranosyl-5′-triphosphate (favipiravir-RTP). Favipiravir inhibits the replication of the viral genome by pressing with purine nucleosides. A prospective open-label, randomized clinical experiment on 236 adult infected patients indicated that treatment with favipiravir improved recovery time, nonetheless several side effects were detected in approximately 71% of patients (Chen et al. 2020a).

2. Anti-inflammatory drugs

Due to the presence of a cytokine storm during a COVID-19 infection, the use of anti-inflammatory drugs may be helpful in preventing tissue injury. Moreover, these drugs can also affect the cytokines necessary for fighting the virus. Therefore, it is very important to define the time window for anti-inflammatory therapies (Chen et al. 2020b).

Indomethacin (INDO) is a cyclopentone-cyclooxygenase (COX 1 and 2) inhibitor that blocks prostaglandin synthesis and has a potent anti-inflammatory and analgesic properties (Vane and Botting 1998).

Furthermore, INDO has been found to have a potent antiviral response against canine coronavirus and SARS-CoV, as it inhibits virus replication and protects the host cells from virus-induced damage. Moreover, INDO rapidly and effectively initializes the antiviral cellular defense mechanism by activating protein kinase R (PKR) in an interferon- and dsRNA-independent manner (Rossen et al. 2004; Amici et al. 2006). PKR serves as a virus replication sensor (García et al. 2006) and triggers eukaryotic initiation factor 2 (eIF2α) phosphorylation as well as blocking protein synthesis in virus-infected cells (Dabo and Meurs 2012). Xu et al. (2020a) reported that INDO is also highly effective against human SARS-CoV in vitro.

Tocilizumab (TCZ) is a recombinant human monoclonal anti-IL-6 antibody, commonly used in rheumatic diseases and rheumatoid arthritis. Through its mechanism of binding to soluble and membrane-bound IL-6 receptors, IL-6 signaling is blocked, which alleviates inflammatory responses (Sheppard et al. 2017). A retrospective analysis observing the efficacy of tocilizumab in treating severe or urgent COVID-19 patients was performed by Xu et al. (2020b). Moreover, when TCZ was administered at 400 mg once through an intravenous drip, the fever returned to normal within a few days and other symptoms improved dramatically in several patients where oxygenation increased by 75%. Lung lesion opacity, as shown by CT scans, was removed in 90.5% of patients, and the number of peripheral lymphocytes returned to normal in 52.6% of patients (Xu et al. 2020b). Several clinical trials have been reported on the safety and efficacy of TCZ in treating serious COVID-19 pneumonia in adult patients (Chen et al. 2020b).

JAK inhibitors were approved for treating rheumatoid arthritis and myelofibrosis as active-and-selective-adaptor-protein-2-associated protein kinase 1 (AAK1) inhibitors (Vainchenker et al. 2018). These inhibitors act on the JAK-STAT signaling pathways observed in COVID-19 patients. In addition, the virus invades the cell by endocytosis, where AAK1 is one of the endocytosis regulators. Therefore, AAK1 inhibitors can disrupt virus entry into the cell and prevent viral infection (Stebbing et al. 2020). **Baricitinib**, which has the highest affinity for AAK1, a variety of

inflammatory cytokines, including INF-α that plays a significant role in combating virus development, were inhibited at a dose of 2 or 4 mg/day (Richardson et al. 2020).

Ruxolitinib, which is a selective inhibitor of JAK 1 and 2, has proven to be quite promising with a short-term high dose schedule, in rapidly improving COVID-19-related severe ARDS (Gozzetti et al. 2020).

3. Anti-coagulants and drugs boosting platelet formation

Thrombocytopenia has been observed in some COVID-19 patients in intensive care units (ICUs) (Lippi et al. 2020; Mattiuzzi and Lippi 2020). The platelet count in the case of thrombocytopenia was found to be $< 100 * 10^9/L$ in some cases and $< 150 * 10^9/L$ in others (Guan et al. 2019; Yao et al. 2020; Chen et al. 2020b). In a study by Lippi et al. it was suggested that the platelet count could be considered a discriminating parameter to differentiate between mildly- and severely-infected COVID-19 patients (Lippi et al. 2020). Therefore, based on the stage of disease in hospitalized patients, they can receive either anti-coagulants or the usual thrombocytopenia management drugs. Typical treatment options for thrombocytopenia include oral corticosteroids such as prednisone, injection of immune globulin, or medications like romiplostim that stimulate platelet production by the bone marrow. Care should be taken as the latter category may put the patient at risk of blood clot formation. Therefore, the blood platelet count should be monitored during treatment (Neunert et al. 2019).

It is noteworthy that even patients with low platelet levels can develop a blood clot (Wang et al. 2019). For this reason, coagulation factors that promote bleeding and clotting must be balanced. In the case of an imbalance or if the COVID-19 patient develops a pulmonary embolism (PE), anti-coagulants can play an essential role in saving their lives, especially those of critically ill patients. It was reported that hospitalized patients showed elevated levels of D-dimer, which means that these patients had thrombi that were further broken down, increasing the fibrin degradation products. In a study performed in China, 46.4% of patients tested had elevated levels of D-dimer, and this was considered one of the main predictors for mortality (Guan et al. 2019; Thachil et al. 2020). The patient's prothrombin time (PT) and platelet count were also measured, and it was found that the patients requiring the ICU had elevated PT up to 15.5 s. Moreover, it has been discovered that microvascular pulmonary thrombosis is the main pathophysiological condition for the high mortality rate observed in the case of COVID-19 patients. Tissue trauma was followed by the release of several mediators that in turn stimulated many humoral processes such as coagulation and fibrinolysis. This is usually followed by modifications in the patient's

hemostatic mechanisms so that changes were observed in neutrophils, macrophages, platelets, and other cellular elements. Based on these studies, anti-coagulants should be added to the COVID-19 management protocol. One of the most used anti-coagulants is low-molecular-weight heparin (low MWH), which has an additional benefit of acting as an anti-inflammatory medication, and thus contributes to mitigate disease progression. The decrease in MWH lead to anti-inflammatory effect by reducing IL-6 activity (Magro et al. 2020). This effect was also suggested by Thachil et al. (2020), where the increase in the percentage of lymphocytes in a group of COVID-19 patients treated with low MWH in a hospital in China, was attributed to low MWH's anti-inflammatory action (Thachil et al. 2020). The medical team must monitor patients well to avoid the risk of bleeding, especially since the majority of severely- infected COVID-19 patients are elderly and have underlying risk factors such as liver or renal impairments. Thachil et al. suggested a prophylactic dose of low MWH should be given to all hospitalized patients with COVID-19, and not only those who are in the ICU. Patients who experience active bleeding or have a low platelet count should be excluded. Subsequent monitoring should follow this prophylactic dose, especially in patients with renal impairments (Thachil et al. 2020).

Disseminated intravascular coagulation (DIC) was observed by a team at Tongji Hospital in Wuhan, China, in most of the deceased patients with COVID-19 (Tang et al. 2020a, b). With regard to deaths, they explained that DIC could due to sepsis, which is common in viral infections, and leads to organ dysfunction. DIC can progress upon activation of monocytes and endothelial cells that further trigger cytokine release due to tissue injury. Accordingly, free thrombin will diffuse uncontrolled by natural anti-coagulants, and this can activate platelets in addition to having a stimulatory effect on fibrinolysis. The deceased patients had elevated levels of the fibrin-related marker D-dimer, which permitted the activation of coagulation and indicated a secondary hyperfibrinolysis condition observed in these patients (Kitchens 2009, Tang et al. 2020b). Thus, anti-coagulants must be involved in the treatment regimen. Heparin is primarily used in most hospitals, however it is not the only option. Other anti-coagulants such as urokinase and streptokinase may be used as well, as both found to reduce mortality in patients with ARDS, without causing bleeding (Hardaway et al. 2001). Furthermore, a study by Moore et al. discussed the use of plasminogen activators to handle ARDS and studied its effect on reducing the number of deaths related to ARDS (Moore et al. 2020). Tissue-type plasminogen activator (tPA), has been reported to have effective clot lysis ability, which has been observed to increase the arterial pO_2, which also helps to reduce arterial pCO_2. The intravenous route was proposed for administration of tPA at a maximum total dose of 0.9 mg/kg, with an initial

dose of 25 mg over the course of two hours. Therefore, it is recommended to follow an infusion that delivers a 25 mg dose over a 22-h period (Moore et al. 2020).

4. Angiotensin-converting enzyme inhibitors (ACEIs)

ACE2 has been shown to be a functional receptor through which SARS-CoV2 helps enter the target host cells. Given that angiotensin receptor blockers (ARBs) and ACEIs were found to regulate ACE2 expression in animal studies, concerns may arise regarding whether ARBs and ACEIs will increase SARS-CoV2 infection and the severity of COVID-19 in patients with hypertension and cardiovascular diseases that receive these drugs (Kai and Kai 2020).

The angiotensin-converting enzyme (ACE) cleaves angiotensin I (Ang I) to the active octapeptide Ang-II where ACE2 cleaves Ang II to form Ang 1–7. Ang 1–7 activates both angiotensin II type 2 receptor (AT2R) and ACE2/Ang-(1–7)-Mas receptor axis, which improves lung function and oxygenation (Wang et al. 2019). Furthermore, Ang 1–7 negatively regulates the ACE/Ang-II angiotensin II type 1 receptor (AT1R) axis, which promotes activation and recruitment of inflammatory cells, apoptosis, and leads to increased microvascular permeability and pulmonary fibrosis (Kai and Kai 2020; Wang et al. 2019). Therefore, the ACE2 counteracts the effect of the ACE by inhibiting the renin-angiotensin system (RAS). Thus, it decreases the incidence of lung injury (Imai et al. 2006). Unexpectedly, the use of ACEIs can reduce epithelial apoptosis, interstitial fibrosis, and collagen deposition (Imai et al. 2006).

Moreover, many COVID-19 patients have cardiac injuries (Chen et al. 2020b; Guan et al. 2020) and renal dysfunction (Chen et al. 2020b). These patients are characterized by low cardiac ACE2 activity, low oxygen supply, lung failure, and a cytokine storm (Guo et al. 2020). In addition, Seltzer (2020) demonstrated that Ang II increases in COVID-19 patients with pneumonia. Consequently, the uses of ACEIs and ARBs can reduce lung, renal, and cardiac damage arising from RAS hyperactivation (Guo et al. 2020). ACEI was found to diminish the formation of Ang II, resulting in decreased concentrations of Ang II in the lungs, as well as decreased AT1R in the heart. The reduction in AT1R prevented inflammation, fibrosis, and proliferation pathways, which resulted in the reduction of cardiac fibrosis, thrombosis, and ARDS development. Furthermore, ARBs were proved to inhibit the binding of Ang II to AT1R, and upregulate ACE2 expression (Guo et al. 2020; Zhang et al. 2020b).

Nonetheless, the safety of ACEIs is questionable in viral respiratory infections such as COVID-19 due to their most common side effect, which is dry cough. Moreover, ACE inhibition is known to reduce the activity of kininase II, substance P and prostaglandins accumulation induces the dry cough reflex (Overlack 1996). Moreover, ACEIs were found

to increase bronchial reactivity in asthmatic patients (Overlack 1996). A clinical trial illustrated that the continued use of ACEi/ARB in COVID-19 hypertensive patients, leads to better clinical outcomes (Lam et al. 2020).

5. Antibiotics

Not only might bacteria compete, but also this battle could extend to multiple viruses, including the main killer bacteria, bacteriophage. Therefore, the possibility that bacteria may have developed antivirals in conjunction with antibiotics remains a valid hypothesis (Colson and Raoult 2016).

A specific class of antibiotics known as glycopeptide antibiotics, that are commonly used to treat infections caused by gram-positive bacteria via inhibiting the biosynthesis of the bacterial cell wall, has also shown potential antiviral activity (Balzarini et al. 2003). Glycopeptide antibiotics, along with several semisynthetic derivatives, have indicated significant potential antiviral activities with selective anti-coronavirus activities, including feline (FIPV) and human (SARS) coronavirus (Balzarini et al. 2006).

More recently, Zhou et al. (2016) identified cathepsin L, which is a protease involved in Ebola virus, MERS-CoV, and SARS-CoV cell invasion, as a target for a glycopeptide antibiotic known as **teicoplanin**. Apart from such activities in previous coronaviruses, the effect of teicoplanin and its derivatives (dalbavancin, oritavancin, and telavancin) in vitro to inhibit COVID-19 infection, has been estimated It was found that they can be considered as novel inhibitors for cathepsin L-dependent viruses (Jean et al. 2020), and serve as potential alternatives to treating COVID-19 (Baron et al. 2020).

6. Vitamins

Vitamin *D*, a fat-soluble vitamin, is not only a nutrient but also a hormone. It plays an essential role in stimulating the maturation of many cells, including immune cells. A large proportion of healthy adults are reported to have vitamin D deficiency, especially towards the end of winter (Chen et al. 2020b). Since the start of the COVID-19 pandemic, the role of vitamin D in the treatment and prevention of the virus as well as the relation of the virus to its deficiencies have become a point of concern. Evidence supports the relationship between low levels of vitamin D and viral infection, besides case-fatality rates increase with lower concentrations of 25-hydroxyvitamin D that occur with aging and some chronic diseases. Finally, vitamin D deficiency also contributes to ARDS (Grant et al. 2020). Vitamin D helps protect against COVID-19 infection by inducing cathelicidins and defensins, reducing pro-inflammatory cytokines along with elevating anti-inflammatory cytokines (Grant et al. 2020). McCartney and Byrne (2020) recommended that all

vulnerable groups should receive 20–50 μg/d of vitamin D to enhance their ability to resist COVID-19.

Vitamin E, another fat-soluble vitamin with potent antioxidant properties, can modulate immune functions of the host. Its deficiency is known to impair both humoral and cellular immunity (Moriguchi and Muraga 2000). On the contrary, and based on the research findings, vitamin E showed protective abilities against upper respiratory infections at a dose of 200 IU per day, nonetheless, it had no significant effect on lower respiratory infections in elderly residents in the nursing home (Meydani et al. 2004). Moreover, it showed anti-HBV properities (Andreone et al. 2001), as well as anti-bovine viral diarrhea virus (strain BVDV2-1373), which is a bovine coronavirus (Nonnecke et al. 2014).

Vitamin A, a fat-soluble vitamin with three active forms in the body namely, retinol, retinal, and retinoic acid, is known as the anti-infective vitamin (Chen et al. 2020b). It is involved in the development of the immune system with regulatory roles in cellular and humoral immune processes (Huang et al. 2018). It was reported that infections caused by the infectious bronchitis virus (IBV, one of the coronaviruses), were more pronounced in chickens that received a diet lacking vitamin A, compared to those that received an adequate diet at the same time. In addition, vitamin A may be a promising treatment option for COVID-19 due to its ability to regulate elements of the innate immune response (Chen et al. 2020b).

Vitamin C is a water-soluble vitamin that has several biological actions such as antioxidant and weak antihistamine immune function supporting properties (Chen et al. 2020b). It is reported that low vitamin C levels increase the risk of developing pneumonia (Hemilä and Louhiala 2007). Recently, intravenous administration of vitamin C (10–20 g/day, over a period of 8–10 h), has been successful in treating 50 patients with COVID-19 in China, with cases ranging from moderate to severe disease levels (Rosa and Santos 2020).

Vitamin B, which is a water-soluble vitamin, works as part of coenzymes and increases the immune response of the host. Therefore, B vitamins could be chosen as the primary treatment option for COVID-19 (Chen et al. 2020b). Virtual screening showed that vitamin B12 and nicotinamide (vitamin B3) act as inhibitors of the main protease of COVID-19 (COVID-Mpro) (Kandeel and Al-Nazawi 2020). In addition, vitamin B3 protects the lungs against bleomycin-induced lung injuries. Therefore, it may be prudent to provide vitamin B3 to COVID-19 patients once the cough begins (Derbyshire and Delange 2020).

7. Zinc

Zinc is considered as a 'gatekeeper' to immune function and plays a central role in several biological processes such as cell division, macromolecules biosynthesis, and immune function, being as a cofactor for more than 300 enzymes and transcription factors (Derbyshire and Delange 2020). Several studies have demonstrated the antimicrobial potential of zinc oxide (ZnO) nanoparticles against gram-positive and gram-negative bacteria as well as fungus (Yang et al. 2018), that reverted to their ability to destabilize the microbial membranes, enhance cellular permeability (Maleki et al. 2015), interact with nucleic acids, and deactivate respiratory system enzymes (Fang et al. 2006). Moreover, zinc acts as an antiviral metal against the H1N1 influenza virus (Ghaffari et al. 2019). In herpes simplex viruses 1 and 2 (Farouk 2019; Mishra et al. 2011), it serves as a second intracellular messenger, triggers apoptosis, and decreases viral protein synthesis (Lazarczyk and Favre 2008).

Zinc has been found to be essential for respiratory epithelium and can be used against COVID-19 due to its antioxidant and anti-inflammatory activities. Moreover, it improves cilia morphology and increases the ciliary beat frequency, which are impaired by the COVID-19 infection. Consequently, this enhances the viral clearance as well as the regulation of tight junction proteins ZO-1 and Claudin-1, thus increasing barrier functions (Skalny et al. 2020). Moreover, zinc was found to inhibit the SARS-CoV RdRp template binding and elongation in Vero-E6 cells, and thereby blocking viral RNA replication (te Velthuis et al. 2010). In addition, it has been reported that zinc ions can decrease ACE2 activity (Zhang et al. 2020a). Zinc ions upregulate IFNα-induced JAK1/STAT1 signaling and antiviral proteins (RNaseL and PKR), which are known to degrade viral RNA and inhibit its translation. Further, zinc ions have anti-inflammatory properties via the inhibition of IKK activity and modulation of regulatory T-cell functions (Skalny et al. 2020). Therefore, zinc has a significant impact on viral infections through anti-inflammatory and antioxidant activities, modulation of viral particle entry, and fusion, replication, and translation of viral protein. Thus, zinc can be used in a strategy to inhibit COVID-19 infection.

8. Anti-malarial drugs (chloroquine and hydroxychloroquine)

Despite the WHO recommendation to eliminate antimalaria drugs from COVID therapeutic protocol, many countries have used them in the treatment protocol such as Egypt for a short treatment period and at dose of 200 mg/day for a maximum period of 10 days. Chloroquine and hydroxychloroquine are 4-aminoquinoline derivatives that are primarily utilized as antiprotozoal drugs for the treatment of malaria via inhibiting biocrystallization of hemozoin that facilitates the aggregation of cytotoxic heme while the free cytotoxic heme accumulates in the parasites, resulting in death (Sullivan 2002). Furthermore,

these medications have anti-inflammatory effects and may be used in rheumatic diseases (Katzung and Trevor 2007). Although the mechanism of these drugs in rheumatic diseases is unclear, there are some proposed trials that illustrated the mechanism as decreasing leukocyte chemotaxis, suppressing the response of T lymphocyte to mitogens, stabilizing lysosomal enzymes, inhibiting DNA and RNA synthesis, and/or trapping free radicals (Katzung and Trevor 2007).

Currently, hydroxychloroquine and chloroquine have received exceptional attention due to positive results with some cases of COVID-19-related pneumonia in patients (Gao et al. 2020; Colson et al. 2020; Yao et al. 2020). Chinese clinical trials recommend administration of 500 mg of chloroquine twice daily in patients with mild, moderate, and severe forms of COVID-19 pneumonia (Colson et al. 2020; Gao et al. 2020). These medications increase the pH through the alkalinizing process in the endosome compartments that cells use to ingest the outside materials, which some viruses may pick up during infection (Kupferschmidt and Cohen 2020).

Molecular modeling shows that chloroquine or hydroxychloroquine tightly binds to sialic acid's gangliosides in a way that prevents the viral S protein from binding to gangliosides (Fantini et al. 2020).

Moreover, some non-randomized clinical trials indicated that the use of hydroxychloroquine in patients with COVID-19 reduces the viral load in nasal swabs, and shows significant effects when with the antibiotic azithromycin (Tobaiqy et al. 2020). Although both chloroquine and hydroxychloroquine have been reported for treatment, hydroxychloroquine was found to be more potent than chloroquine due to its EC50 was 0.72 Mm. In contrast, the EC50 of chloroquine was 5.47 µM. Therefore, hydroxychloroquine has a more tolerable safety profile which makes the drug of choice (Yao et al. 2020).

However, chloroquine and hydroxychloroquine have serious adverse effects, such as abdominal pain, nausea, vomiting, dyspepsia, rashes, and nightmares (Katzung and Trevor 2007). Therefore, for prolonged treatment, it is not recommended to use chloroquine at a dose greater than 250 mg/day and hydroxychloroquine at a dose greater than 6.4 mg/kg/day, as it may lead to ocular toxicity (Katzung and Trevor 2007; Browning 2014). For current clinical trials of treating patients with COVID-19, the recommended doses of hydroxychloroquine are higher than those found in previous treatment for malaria (Duan et al. 2020b). Despite the promising activity of these two medications against COVID-19, there is a potential risk of arrhythmia at higher cumulative doses that require special caution during treatment (Colson et al. 2020). Thus, it is suggested that their utilization in suspected, as well as confirmed cases of COVID-19, be restricted to hospitalized patients (Tobaiqy et al. 2020).

9. Neutralizing antibodies

There is still a shortage of vaccines and targeted therapeutics to treat SARS-CoV2, thus there are multiple clinical trials now underway in many countries that are considering new COVID-19 vaccines. Consequently, developing neutralizing antibodies may be an important and challenging task (Duan et al. 2020a). Monoclonal therapeutic antibodies to SARS were developed against vulnerable sites on viral surface proteins, including lipid attachment signals, spike protein, and RBDs of S, S2, N, and M proteins (Xu et al. 2020b). Over 90% of the potent neutralizing antibodies are directed against RBD within the S1 unit (193-amino acid, residues N318–V510), which disrupts the receptor interactions (Zhou and Zhao 2020; Wong et al. 2004; ter Meulen et al. 2006). In 2006, Ter Meulen demonstrated that human SARS-CoV monoclonal antibodies CR3014 and CR3022 recognize different epitopes and non-competitively bind to the RBD of SARS-CoV S protein, and their combination neutralizes the virus in a synergistic fashion (ter Meulen et al. 2006). Because the genomic sequence of SARS-CoV2 is closely related to the SARS-CoV sequence and the RBDs in S proteins share a high sequence identity, researchers hope to generate cross-reactive and neutralizing antibodies against SARS-CoV2 infection, based on previously discovered SARS-CoV neutralizing antibodies (Jiang et al. 2020; Tian et al. 2020). Tian et al. (2020) found that CR3022 can strongly bind to SARS-CoV2 RBD and its epitope does not interfere with the ACE2 binding site. Therefore, CR3022 cross-neutralizes SARS-CoV2 using a mechanism independent of receptor binding inhibition (Tian et al. 2020). Thus, CR3022 may have the potential to be developed as a therapeutic candidate, alone or in combination with other neutralizing antibodies to prevent and treat COVID-19 infection.

10. Convalescent plasma therapy

The simplest and most direct approach to combating SARS-CoV2 outbreaks is to use passive antibodies transferred from convalescent patient sera (Kruse 2020). This passive immunization for the prevention and treatment of human infectious diseases can be traced back to the twentieth century when specific antibodies were sought from the serum of stimulated animals, especially rabbits and horses (Marano et al. 2016). This idea has highlighted the potential use of human convalescent plasma therapy in which immunity can be transferred from recovered patients to infected ones using blood plasma. Convalescent blood products contain antiviral antibodies (IgG, IgA, IgM, IgE, and IgD), especially IgG and IgM (Roback and Guarner 2020; Zhang et al. 2020a). Convalescent whole blood or plasma can effectively treat patients with viral infections such as Ebola and influenza A (H5N1) viruses, because

these are the only therapeutic strategies available in some cases, due to the unavailability of vaccines, drugs, or other specific treatments (Zhou et al. 2007; van Griensven et al. 2016; WHO 2014; Marano et al. 2016).

In 2006, Liu et al. conducted a study of 56 convalescent SARS patients and reported that IgG and neutralizing antibody titers against SARS-CoV highly peaked at the four-month mark and showed a marked decrease two years after the onset of SARS. There have been always doubts concerning the finding that neutralizing antibodies, even after two years, were reassuring in terms of protection provided against reinfection (Liu et al. 2006). In 2020, Hoffmann et al. showed that sera obtained from convalescent SARS patients were found to inhibit SARS-S- and cross-neutralized-SARS-2-S-driven entries with lower efficiency than SARS-S. The results revealed important commonalities between SARS-CoV2 and SARS-CoV infections and identified a potential target for antiviral intervention (Hoffmann et al. 2020b).

A study in Wuhan, China conducted by Duan et al. (2020a) reported that convalescent plasma therapy shows potential efficacy, and no severe adverse effects were observed treating patients with severe SARS-CoV2. A single dose (200 mL) of convalescent plasma from recently recovered donors is well tolerated and may significantly increase or maintain the level of neutralizing antibodies at a high concentration, which tends to improve clinical outcomes and laboratory parameters (i.e., increased oxyhemoglobin saturation and lymphocyte counts and decreased C-reactive protein), within three days after transfusion, can rapidly reduce viremia in seven days. Convalescent plasma transfusion is able to neutralize the pathogen and finally eliminates it from the circulatory system, nonetheless this has not been tested clinically (Roback and Guarner 2020; Shen et al. 2020). Therefore, some issues examining larger, well-controlled trials are required to determine the advisability of convalescent plasma therapy as well as the optimal dose and treatment time.

11. Worldwide completed clinical trials

Combined drug therapy for COVID-19 aims to reduce the viral load inside the human body and modulate the immune system. Whereas, the goal of drug reformulation is to target the tested therapeutics of the infected main organ (the lungs). The reformulation was implemented by providing different inhaled reformulations for potential previous tested therapeutics such as HCQ in an effort to avoid troubling side effects. Table 2 showed the complete trials of drug combination and reformulation as registered on clinicaltrials.gov.

Conclusion

SARS-CoV2 is a global public health crises due to the high infection rates that resemble the 1918 influenza pandemic. Despite the different drugs mechanisms used to treat COVID-19 (Fig. 1) that works on the domain of virus-binding, viral RNA, and the proteins, as well as factors that facilitate virus invasion. Nevertheless, all clinical trials that have been launched to find a treatment for this virus failed to determine an effective therapy. To develop a specific treatment or vaccine against this virus, the structure and function of all viral proteins must be well interpreted, as this virus attack has various cell receptors and mechanisms during cell invasion. Moreover, understanding the structure and function of protein S is a hypothesized target for developing SARS-CoV2 antibodies, and could open possibilities for therapeutic intervention and vaccine development. In addition, elevating antibody responses against protein S during infection or vaccination, may provide a certain level of protection against SARS-CoV2 infection.

The first step in replicating the coronavirus involved attaching the virus to the ACE-2 receptors on the surface of respiratory cells via the S protein. This binding leads to conformational changes in the S protein and facilitates the viral envelope fusion with the cell membrane through the endosomal pathway (pH acidification), and need additional triggers such as proteolytic activation by TMPRSS211 and furin (proteases). On entring to the host cells, the viral genome is released as a positive single-stranded RNA that can directly produce the viral proteins and new genomes. The virus synthesizes an RNA polymerase that only recognize and produce viral RNAs (negative strand). This negative strand is used to the positive transcribe small subgenomic RNAs by discontinuous transcription and translated into relevant viral proteins. Furthermore, the negative strand used to replicate the new positive strand RNA. Subsequently, viral proteins and RNA genomes are subsequently assembled into virions that are released from the cell via exocytosis. ACE2, angiotensin-converting enzyme 2; ACEIs, angiotensin-converting enzyme inhibitors; TMPRSS2, type 2 transmembrane serine protease; Low MWH, low molecular weight heparin; tPA, tissue-type plasminogen activator.

Table 2 Completed clinical trials of the combination treatment and reformulations used for managing COVID-19

Clinical condition	Intervention	Phase	Identifier
Combinations			
Anti-viral + Anti-malarial			
Moderate	Lopinavir/ritonavir + HCQ	NA	NCT04376814
	Favipiravir + HCQ		
Moderate	Oseltamivir + HCQ + AZT	3	NCT04530422
Anti-viral combination			
Moderate	Sofosbuvir + Ledipasvir	3	NCT04530422
Mild- critical	Sofosbuvir + Ledipasvir	4	NCT04498936
Hospitalized + Pneumonia	Danoprevir + Ritonavir	4	NCT04345276
	Danoprevir + Ritonavir ± Interferon nebulization	4	NCT04291729
Anti-viral + immune- modulator			
Mild—severe	Remdesivir + Baricitinib	3	NCT04401579
Hospitalized	Lopinavir/Ritonavir + Baricitinib	2/3	NCT04358614
Moderate—critical	Remdesivir + Tocilizumab	NA	NCT04492501
Hospitalized	Lopinavir/ritonavir + Ribavirin + IFN β-1b	2	NCT04276688
Anti-malarial + Antibiotic + Anthelmintic			
Hospitalized + Pneumonia	HCQ + IVM + AZT	1	NCT04343092
Anti-malarial + Antibiotic			
Severe ± Pneumonia	HCQ + AZT	3	NCT04321278
Hospitalized + Pneumonia	HCQ + AZT	3	NCT04358081
Hospitalized + Not Critical Pneumonia	HCQ + IVM	3	NCT04391127
Mild—severe	HCQ + AZT	2/3	NCT04349410
	HCQ + DOXY		
	HCQ + Clindamycin		
	HCQ + Clindamycin + Primaquine		
Outpatient	HCQ + AZT + Zn sulfate	4	NCT04370782
	HCQ + DOXY + Zn sulfate		
Anti-malarial + immune- modulator			
Hospitalized	HCQ + interferon β-1b	2	NCT04350281
Reformulation			
Healthy Volunteers	Liposomal suspension of HCQ for inhalation	1	NCT04697654*
Healthy Adult	Aerolized HCQ	1	NCT04461353
Healthy Volunteers	Cyclops Dry Powder HCQ Inhalation	1	NCT04497519

AZT Azithromycin, *DOXY* Doxycycline, *HCQ* Hydroxychloroquine, *IVM* Ivermectin, *Zn* Zinc, *IFN* Interferon

*Study status is active not recruiting by the date of January 2021. The table includes the discussed drugs in the current review as registered on clinicaltrials.gov

Compliance with Ethical Standards

References

Amarelle L, Lecuona E, Sznajder JI (2017) Anti-influenza treatment: drugs currently used and under development. Arch Bronconeumol 53:19–26

Amici C, di Caro A, Ciucci A, Chiappa L, Castilletti C, Martella V, Decaro N, Buonavoglia C, Capobianchi MR, Santoro MG (2006) Indomethacin has a potent antiviral activity against SARS coronavirus. Antivir Ther 11:1021–1030

Andreone P, Fiorino S, Cursaro C, Gramenzi A, Margotti M, di Giammarino L, Biselli M, Miniero R, Gasbarrini G, Bernardi M (2001) Vitamin E as treatment for chronic hepatitis B: results of a randomized controlled pilot trial. Antiviral Res 49:75–81

Balzarini J, Keyaerts E, Vijgen L, Egberink H, de Clercq E, van Ranst M, Printsevskaya SS, Olsufyeva EN, Solovieva SE, Preobrazhenskaya MN (2006) Inhibition of feline (FIPV) and human (SARS) coronavirus by semisynthetic derivatives of glycopeptide antibiotics. Antiviral Res 72:20–33

Balzarini J, Pannecouque C, de Clercq E, Pavlov AY, Printsevskaya SS, Miroshnikova OV, Reznikova MI, Preobrazhenskaya MN (2003) Antiretroviral activity of semisynthetic derivatives of glycopeptide antibiotics. J Med Chem 46:2755–2764

Baron SA, Devaux C, Colson P, Raoult D, Rolain J-M (2020) Teicoplanin: an alternative drug for the treatment of COVID-19? Int J Antimicrob Agents 55:105944–105944

Browning DJ (2014) Pharmacology of chloroquine and hydroxychloroquine. *Hydroxychloroq Chloroq Retinopathy* 35–63

Chandwani A, Shuter J (2008) Lopinavir/ritonavir in the treatment of HIV-1 infection: a review. Ther Clin Risk Manag 4:1023–1033

Chen C, Zhang Y, Huang J, Yin P, Cheng Z, Wu J, Chen S, Zhang Y, Chen B, Lu M, Luo Y, Ju , L, Zhang J, Wang X (2020a) Favipiravir versus arbidol for COVID-19: a randomized clinical trial. *medRxiv,* 2020.03.17.20037432

Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, Xia J, Yu T, Zhang X, Zhang L (2020) Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 395:507–513

Choy KT, Wong AY, Kaewpreedee P, Sia SF, Chen D, Hui KPY, Chu DKW, Chan MCW, Cheung PP, Huang X, Peiris M, Yen HL (2020) Remdesivir, lopinavir, emetine, and homoharringtonine inhibit SARS-CoV-2 replication in vitro. Antiviral Res 178:104786

Colson P, Raoult D (2016) Fighting viruses with antibiotics: an overlooked path. Int J Antimicrob Agents 48:349–352

Colson P, Rolain JM, Lagier JC, Brouqui P, Raoult D (2020) Chloroquine and hydroxychloroquine as available weapons to fight COVID-19. Int J Antimicrob Agents 55:105932

Dabo S, Meurs EF (2012) dsRNA-dependent protein kinase PKR and its role in stress, signaling and HCV infection. Viruses 4:2598–2635

Derbyshire E, Delange J (2020) COVID-19: is there a role for immunonutrition, particularly in the over 65s? *BMJ Nutrition*. Prevent Health 3:000071

Duan K, Liu B, Li C, Zhang H, Yu T, Qu J, Zhou M, Chen L, Meng S, Hu Y, Peng C, Yuan M, Huang J, Wang Z, Yu J, Gao X, Wang D, Yu X, Li L, Zhang J, Wu X, Li B, Xu Y, Chen W, Peng Y, Hu Y, Lin L, Liu X, Huang S, Zhou Z, Zhang L, Wang Y, Zhang Z, Deng K, Xia Z, Gong Q, Zhang W, Zheng X, Liu Y, Yang H, Zhou D, Yu D, Hou J, Shi Z, Chen S, Chen Z, Zhang X, Yang X (2020) Effectiveness of convalescent plasma therapy in severe COVID-19 patients. Proc Natl Acad Sci USA 117:9490

Duan YJ, Liu Q, Zhao SQ, Huang F, Ren L, Liu L, Zhou YW (2020) The trial of chloroquine in the treatment of corona virus disease 2019 (COVID-19) and its research progress in forensic toxicology. Fa Yi Xue Za Zhi 36:157

Fang M, Chen JH, Xu XL, Yang PH, Hildebrand HF (2006) Antibacterial activities of inorganic agents on six bacteria associated with oral infections by two susceptibility tests. Int J Antimicrob Agents 27:513–517

Fantini J, di Scala C, Chahinian H, Yahi N (2020) Structural and molecular modelling studies reveal a new mechanism of action of chloroquine and hydroxychloroquine against SARS-CoV-2 infection. Int J Antimicrob Agents 55:105960–105960

Farouk F (2019) Comparing surface modifications of zinc oxide nanoparticles for modulating their antiviral activity against herpes simplex virus type-1

Fehr AR, Perlman S (2015) Coronaviruses: an overview of their replication and pathogenesis. Methods Mol Biol 1282:1–23

Furuta Y, Komeno T, Nakamura T (2017) Favipiravir (T-705), a broad spectrum inhibitor of viral RNA polymerase. Proc Jpn Acad Ser B 93:449–463

Gao J, Tian Z, Yang X (2020) Breakthrough: chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. Biosci Trends 14:72–73

García MA, Gil J, Ventoso I, Guerra S, Domingo E, Rivas C, Esteban M (2006) Impact of protein kinase PKR in cell biology: from antiviral to antiproliferative action. Microbiol Mol Biol Rev 70:1032–1060

Ghaffari H, Tavakoli A, Moradi A, Tabarraei A, Bokharaei-Salim F, Zahmatkeshan M, Farahmand M, Javanmard D, Kiani SJ, Esghaei M, Pirhajati-Mahabadi V, Monavari SH, Ataei-Pirkooh A (2019) Inhibition of H1N1 influenza virus infection by zinc oxide nanoparticles: another emerging application of nanomedicine. J Biomed Sci 26:70

Gozzetti A, Capochiani E, Bocchia M (2020) The Janus kinase 1/2 inhibitor ruxolitinib in COVID-19. Leukemia 34:2815–2816

Gramberg T, Hofmann H, Möller P, Lalor PF, Marzi A, Geier M, Krumbiegel M, Winkler T, Kirchhoff F, Adams DH, Becker S, Münch J, Pöhlmann S (2005) LSECtin interacts with filovirus glycoproteins and the spike protein of SARS coronavirus. Virology 340:224–236

Grant WB, Lahore H, McDonnell SL, Baggerly CA, French CB, Aliano JL, Bhattoa HP (2020) Evidence that vitamin D supplementation could reduce risk of influenza and COVID-19 infections and deaths. Nutrients 12:988

Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, Liu L, Shan H, Lei C, Hui D (2019) China Medical Treatment Expert Group for Covid-19. *Clin Charact Coronavirus Dis.*

Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, Du B, Li LJ, Zeng G, Yuen KY, Chen RC, Tang CL, Wang T, Chen PY, Xiang J, Li SY, Wang JL, Liang ZJ, Peng YX, Wei L, Liu Y, Hu YH, Peng P, Wang JM, Liu JY, Chen Z, Li G, Zheng ZJ, Qiu SQ, Luo J, Ye CJ, Zhu SY, Zhong NS (2020) Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. https://doi.org/10.1056/NEJMoa2001316

Guo J, Huang Z, Lin L, Lv J (2020) Coronavirus disease 2019 (COVID-19) and cardiovascular disease: a viewpoint on the potential influence of Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers on onset and severity of severe acute respiratory syndrome coronavirus 2 infection. J Am Heart Assoc 9:e016219

Hardaway RM, Harke H, Tyroch AH, Williams CH (2001) Treatment of severe acute respiratory distress syndrome: a final report on a phase I study. Am Surg 67:377

Hemilä H, Louhiala P (2007) Vitamin C may affect lung infections. J R Soc Med 100:495–498

Hoffmann M, Kleine-Weber H, Kruger N, Muller M, Drosten C, Pohlmann S (2020a) The novel coronavirus 2019 (2019-nCoV) uses the SARS-coronavirus receptor ACE2 and the cellular protease TMPRSS2 for entry into target cells. *bioRxiv,* 2020.01.31.929042

Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu NH, Nitsche A, Müller MA, Drosten C, Pöhlmann S (2020) SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 181:271-280.e8

Huang Z, Liu Y, Qi G, Brand D, Zheng SG (2018) Role of vitamin A in the immune system. J Clin Med 7:258

Imai Y, Kuba K, Penninger JM (2006) The renin-angiotensin system in acute respiratory distress syndrome. Drug Discov Today Dis Mech 3:225–229

Jean S-S, Lee P-I, Hsueh P-R (2020) Treatment options for COVID-19: the reality and challenges. J Microbiol Immunol Infect 53:436

Jiang S, Hillyer C, Du L (2020) Neutralizing antibodies against SARS-CoV-2 and other human coronaviruses. Trends Immunol 41:355

Kai H, Kai M (2020) Interactions of coronaviruses with ACE2, angiotensin II, and RAS inhibitors-lessons from available evidence and insights into COVID-19. Hypertension Res 43:648

Kandeel M, Al-Nazawi M (2020) Virtual screening and repurposing of FDA approved drugs against COVID-19 main protease. Life Sci 251:117627

Katzung BG, Trevor A (2007) Chapter 36. Nonsteroidal anti-inflammatory drugs, disease-modifying antirheumatic drugs, nonopioid analgesics, & drugs used in gout. Basic Clin Pharmacol 9:1

Kitchens CS (2009) Thrombocytopenia and thrombosis in disseminated intravascular coagulation (DIC). ASH Educ Program Book 2009:240–246

Kruse R (2020) Therapeutic strategies in an outbreak scenario to treat the novel coronavirus originating in Wuhan, China [version 2; peer review: 2 approved]. F1000Research 9:72

Kupferschmidt K, Cohen J (2020) Race to find COVID-19 treatments accelerates. Science 367:1412–1413

Lam KW, Chow KW, Vo J, Hou W, Li H, Richman PS, Mallipattu SK, Skopicki HA, Singer AJ, Duong TQ (2020) Continued In-hospital angiotensin-converting enzyme inhibitor and angiotensin II receptor blocker use in hypertensive COVID-19 patients is associated with positive clinical outcome. J Infect Dis 222:1256–1264

Lazarczyk M, Favre M (2008) Role of Zn2+ ions in host-virus interactions. J Virol 82:11486–11494

Lippi G, Plebani M, Henry BM (2020) Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: a meta-analysis. Clin Chim Acta 506:145

Liu W, Fontanet A, Zhang P-H, Zhan L, Xin Z-T, Baril L, Tang F, Lv H, Cao W-C (2006) Two-year prospective study of the humoral immune response of patients with severe acute respiratory syndrome. J Infect Dis 193:792–795

Liu W, Tang L, Zhang G, Wei H, Cui Y, Guo L, Gou Z, Chen X, Jiang D, Zhu Y, Kang G, He F (2004) Characterization of a novel C-type lectin-like gene, LSECtin: demonstration of carbohydrate binding and expression in sinusoidal endothelial cells of liver and lymph node. J Biol Chem 279:18748–18758

Magro C, Mulvey JJ, Berlin D, Nuovo G, Salvatore S, Harp J, Baxter-Stoltzfus A, Laurence J (2020) Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: a report of five cases. Transl Res 220:1–13

Maleki A, Jebeli MA, Kalantar E, Daraei H, Davari B, Safari M (2015) Inactivation of *Pseudomonas aeruginosa* by zinc oxide nanoparticles in aqueous solution. Antimicrob Resist Infect Control 4:I6–I6

Marano G, Vaglio S, Pupella S, Facco G, Catalano L, Liumbruno GM, Grazzini G (2016) Convalescent plasma: new evidence for an old therapeutic tool? Blood Transfus 14:152–157

Mattiuzzi C, Lippi G (2020) Which lessons shall we learn from the 2019 novel coronavirus outbreak? Ann Transl Med 8:48

McCartney D, Byrne D (2020) Optimisation of vitamin D status for enhanced immuno-protection against covid-19. Ir Med J 113:58–58

USNLO MEDICINE (2020) The impact of camostat mesilate on COVID-19 infection (CamoCO-19)

Meydani SN, Leka LS, Fine BC, Dallal GE, Keusch GT, Singh MF, Hamer DH (2004) Vitamin E and respiratory tract infections in elderly nursing home residents: a randomized controlled trial. JAMA 292:828–836

Mishra YK, Adelung R, Röhl C, Shukla D, Spors F, Tiwari V (2011) Virostatic potential of micro-nano filopodia-like ZnO structures against herpes simplex virus-1. Antiviral Res 92:305–312

Moore HB, Barrett CD, Moore EE, McIntyre RC, Moore PK, Talmor DS, Moore FA, Yaffe MB (2020) Is there a role for tissue plasminogen activator (tPA) as a novel treatment for refractory COVID-19 associated acute respiratory distress syndrome (ARDS)? J Trauma Acute Care Surg 88:1–2

Moriguchi S, Muraga M (2000) Vitamin E and immunity. Vitam Horm 59:305–336

Munir MA, Kuganda H, Basry A (2020) The efficacy and safety of antivirus drugs for COVID-19: a systematic review. Syst Rev Pharm 11:162–166

Neunert C, Terrell DR, Arnold DM, Buchanan G, Cines DB, Cooper N, Cuker A, Despotovic JM, George JN, Grace RF, Kuhne T, Kuter DJ, Lim W, McCrae KR, Pruitt B, Shimanek H, Vesely SK (2019) American Society of Hematology 2019 guidelines for immune thrombocytopenia. Blood Adv 3:3829–3866

Nonnecke BJ, McGill JL, Ridpath JF, Sacco RE, Lippolis JD, Reinhardt TA (2014) Acute phase response elicited by experimental bovine diarrhea virus (BVDV) infection is associated with decreased vitamin D and E status of vitamin-replete preruminant calves. J Dairy Sci 97:5566–5579

Overlack A (1996) ACE inhibitor-induced cough and bronchospasm. Incidence, mechanisms and management. Drug Saf 15:72–78

Quiles JL, Rivas-García L, Varela-López A, Llopis J, Battino M, Sánchez-González C (2020) Do nutrients and other bioactive molecules from foods have anything to say in the treatment against COVID-19? Environ Res 191:110053–110053

Richardson P, Griffin I, Tucker C, Smith D, Oechsle O, Phelan A, Stebbing J (2020) Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. Lancet 395:e30–e31

Roback JD, Guarner J (2020) Convalescent plasma to treat COVID-19: possibilities and challenges. JAMA 323:1561

Roomi M, Khan Y (2020) Potential compounds for the inhibition of TMPRSS2. ChemRxiv

Rosa SGV, Santos WC (2020) Clinical trials on drug repositioning for COVID-19 treatment. Rev Panamer Salud Pub 44:e40–e40

Rossen JW, Bouma J, Raatgeep RH, Büller HA, Einerhand AW (2004) Inhibition of cyclooxygenase activity reduces rotavirus infection at a postbinding step. J Virol 78:9721–9730

Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB (2020) Pharmacologic treatments for coronavirus disease 2019 (COVID-19): a review. JAMA 323:1834

Seltzer S (2020) Linking ACE2 and angiotensin II to pulmonary immunovascular dysregulation in SARS-CoV-2 infection. Int J Infect Dis 101:42–45

Shen C, Wang Z, Zhao F, Yang Y, Li J, Yuan J, Wang F, Li D, Yang M, Xing L, Wei J, Xiao H, Yang Y, Qu J, Qing L, Chen L, Xu Z, Peng L, Li Y, Zheng H, Chen F, Huang K, Jiang Y, Liu D, Zhang

Z, Liu Y, Liu L (2020) Treatment of 5 critically ill patients with COVID-19 with convalescent plasma. JAMA 323:1582

Sheppard M, Laskou F, Stapleton PP, Hadavi S, Dasgupta B (2017) Tocilizumab (Actemra). Hum Vacc Immunother 13:1972–1988

Simmons G, Zmora P, Gierer S, Heurich A, Pohlmann S (2013) Proteolytic activation of the SARS-coronavirus spike protein: cutting enzymes at the cutting edge of antiviral research. Antiviral Res 100:605–614

Skalny AV, Rink L, Ajsuvakova OP, Aschner M, Gritsenko VA, Alekseenko SI, Svistunov AA, Petrakis D, Spandidos DA, Aaseth J (2020) Zinc and respiratory tract infections: perspectives for COVID-19. Int J Mol Med 46:17–26

Stebbing J, Phelan A, Griffin I, Tucker C, Oechsle O, Smith D, Richardson P (2020) COVID-19: combining antiviral and anti-inflammatory treatments. Lancet Infect Dis 20:400–402

Sullivan DJ (2002) Theories on malarial pigment formation and quinoline action. Int J Parasitol 32:1645–1653

Tang N, Bai H, Chen X, Gong J, Li D, Sun Z (2020) Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost 18:1094

Tang N, Li D, Wang X, Sun Z (2020) Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost 18:844

te Velthuis AJ, van den Worm SH, Sims AC, Baric RS, Snijder EJ, van Hemert MJ (2010) Zn(2+) inhibits coronavirus and arterivirus RNA polymerase activity in vitro and zinc ionophores block the replication of these viruses in cell culture. PLoS Pathog 6:e1001176

ter Meulen J, van den Brink EN, Poon LLM, Marissen WE, Leung CSW, Cox F, Cheung CY, Bakker AQ, Bogaards JA, van Deventer E, Preiser W, Doerr HW, Chow VT, de Kruif J, Peiris JSM, Goudsmit J (2006) Human monoclonal antibody combination against SARS coronavirus: synergy and coverage of escape mutants. PLoS Med 3:e237

Thachil J, Tang N, Gando S, Falanga A, Cattaneo M, Levi M, Clark C, Iba T (2020) ISTH interim guidance on recognition and management of coagulopathy in COVID-19. J Thromb Haemost 10:1823

Tian X, Li C, Huang A, Xia S, Lu S, Shi Z, Lu L, Jiang S, Yang Z, Wu Y, Ying T (2020) Potent binding of 2019 novel coronavirus spike protein by a SARS coronavirus-specific human monoclonal antibody. Emerg Microb Infect 9:382–385

Tobaiqy M, Qashqary M, Al-Dahery S, Mujallad A, Hershan AA, Kamal MA, Helmi N (2020) Therapeutic management of COVID-19 patients: a systematic review. Infect Prevent Pract. https://doi.org/10.1016/j.infpip.2020.100061

Tufan A, Avanoglu Guler A, Matucci-Cerinic M (2020) COVID-19, immune system response, hyperinflammation and repurposing anti-rheumatic drugs. Turk J Med Sci 50:620

Ueda M, Uchimura K, Narita Y, Miyasato Y, Mizumoto T, Morinaga J, Hayata M, Kakizoe Y, Adachi M, Miyoshi T, Shiraishi N, Kadowaki D, Sakai Y, Mukoyama M, Kitamura K (2015) The serine protease inhibitor camostat mesilate attenuates the progression of chronic kidney disease through its antioxidant effects. Nephron 129:223–232

Vainchenker W, Leroy E, Gilles L, Marty C, Plo I, Constantinescu SN (2018) JAK inhibitors for the treatment of myeloproliferative neoplasms and other disorders. F1000Research 7:82–82

van Griensven J, Edwards T, de Lamballerie X, Semple MG, Gallian P, Baize S, Horby PW, Raoul H, Magassouba NF, Antierens A, Lomas C, Faye O, Sall AA, Fransen K, Buyze J, Ravinetto R, Tiberghien P, Claeys Y, de Crop M, Lynen L, Bah EI, Smith PG, Delamou A, de Weggheleire A, Haba N (2016) Evaluation of convalescent plasma for ebola virus disease in Guinea. N Engl J Med 374:33–42

Vane JR, Botting RM (1998) Mechanism of action of nonsteroidal anti-inflammatory drugs. Am J Med 104:2S-8S

Vankadari N, Wilce JA (2020) Emerging COVID-19 coronavirus: glycan shield and structure prediction of spike glycoprotein and its interaction with human CD26. Emerg Microb Infect 9:601–604

Wang D, Chai X-Q, Magnussen CG, Zosky GR, Shu S-H, Wei X, Hu S-S (2019) Renin-angiotensin-system, a potential pharmacological candidate, in acute respiratory distress syndrome during mechanical ventilation. Pulm Pharmacol Ther 58:101833–101833

Wang X, Xu W, Hu G, Xia S, Sun Z, Liu Z, Xie Y, Zhang R, Jiang S, Lu L (2020) SARS-CoV-2 infects T lymphocytes through its spike protein-mediated membrane fusion. Cell Mol Immunol. https://doi.org/10.1038/s41423-020-0424-9

Wenzhong L, Hualan L (2020) COVID-19: attacks the 1-beta chain of hemoglobin and captures the porphyrin to inhibit human heme metabolism. ChemRxiv. https://doi.org/10.26434/chemrxiv

WHO (2014) Use of convalescent whole blood or plasma collected from patients recovered from Ebola virus disease for transfusion, as an empirical treatment during outbreaks: interim guidance for national health authorities and blood transfusion services. World Health Organization, Geneva

Wilson L, McKinlay C, Gage P, Ewart G (2004) SARS coronavirus E protein forms cation-selective ion channels. Virology 330:322–331

Wong SK, Li W, Moore MJ, Choe H, Farzan M (2004) A 193-amino acid fragment of the SARS coronavirus S protein efficiently binds angiotensin-converting enzyme 2. J Biol Chem 279:3197–3201

Xiong Y, Liu Y, Cao L, Wang D, Guo M, Jiang A, Guo D, Hu W, Yang J, Tang Z, Wu H, Lin Y, Zhang M, Zhang Q, Shi M, Liu Y, Zhou Y, Lan K, Chen Y (2020) Transcriptomic characteristics of bronchoalveolar lavage fluid and peripheral blood mononuclear cells in COVID-19 patients. Emerg Microbes Infect 9:761–770

Xu T, Gao X, Wu Z, Selinger DW, Zhou Z (2020a) Indomethacin has a potent antiviral activity against SARS CoV-2 in vitro and canine coronavirus in vivo. bioRxiv, 2020.04.01.017624

Xu X, Han M, Li T, Sun W, Wang D, Fu B, Zhou Y, Zheng X, Yang Y, Li X, Zhang X, Pan A, Wei H (2020) Effective treatment of severe COVID-19 patients with tocilizumab. Proc Natl Acad Sci USA 117:10970

Yang H, Zhang Q, Chen Y, He Y, Yang F, Lu Z (2018) Microwave-ultrasonic synergistically assisted synthesis of ZnO coated cotton fabrics with an enhanced antibacterial activity and stability. ACS Appl Bio Mater 1:340–346

Yao X, Ye F, Zhang M, Cui C, Huang B, Niu P, Liu X, Zhao L, Dong E, Song C, Zhan S, Lu R, Li H, Tan W, Liu D (2020) In Vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Clin Infect Dis. 71:732

Zhang C, Wu Z, Li JW, Zhao H, Wang GQ (2020) sThe cytokine release syndrome (CRS) of severe COVID-19 and Interleukin-6 receptor (IL-6R) antagonist Tocilizumab may be the key to reduce the mortality. Int J Antimicrob Agents 55:105954

Zhang H, Penninger JM, Li Y, Zhong N, Slutsky AS (2020) Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target. Intensive Care Med 46:586–590

Zheng J, Zhou R, Chen F, Tang G, Wu K, Li F, Liu H, Lu J, Zhou J, Yang Z, Yuan Y, Lei C, Wu X (2020) Incidence, clinical course and risk factor for recurrent PCR positivity in discharged COVID-19 patients in Guangzhou, China: a prospective cohort study. PLoS Negl Trop Dis 14:e0008648

Zhou B, Zhong N, Guan Y (2007) Treatment with Convalescent Plasma for Influenza A (H5N1) Infection. N Engl J Med 357:1450–1451

Zhou G, Zhao Q (2020) Perspectives on therapeutic neutralizing antibodies against the Novel Coronavirus SARS-CoV-2. Int J Biol Sci 16:1718–1723

Zhou N, Pan T, Zhang J, Li Q, Zhang X, Bai C, Huang F, Peng T, Zhang J, Liu C, Tao L, Zhang H (2016) Glycopeptide antibiotics potently inhibit cathepsin L in the late endosome/lysosome and block the entry of ebola virus, Middle East Respiratory Syndrome Coronavirus (MERS-CoV), and Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV). J Biol Chem 291:9218–9232

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