Potential therapeutic and pharmacological strategies for SARS-CoV2

Doaa A. Ghareeb1,2 · Samar R. Saleh1,2 · Mohammed S. Nofal2 · Mohamed M. Y. Kaddah2 · Salma. F. Hassan2 · Inas K. Seif1 · Sally A. El-Zahaby3 · Shaimaa M. Khedr2 · Marwa Y. Kenawy4 · Aliaa A. Masoud1 · Salma A. Soudi2 · Ahmed A. Sobhy1,2,5 · Jaillan G. Sery2 · Miral G. Abd El-Wahab2 · Alshimaa A. Abd Elmoneam1 · Abdulaziz Mohsen Al-mahallawi6,7 · Maha A. El-Demmellawy2,8

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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
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, 3CLpro), and papain-like protease (PLpro). 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 (LSECtin), 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 3CLpro and PLpro (Fehr and Perlman 2015). PLpro 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 3CLpro | 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 | 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 | 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* | | Reduce the mortality rate for patients with ARDS | Hardaway et al. (2001) |
| *Plasminogen activators* | Efficient clot lysis ability | Increase the arterial pO2 | Moore et al. (2020) |
| **Angiotensin-converting enzyme inhibitors (ACEIs)** | | |
| *ACEIs and ARBs* | Hypotensive drugs | Reduce lung, renal, and cardiac damage resulted from RAS hyperactivation | Gao 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 Munaga, (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 Alkalization 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 ant carcino- genic 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 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 (Amarell 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 3CLpro, which is essential for viral RNA treatment. Recently, lopinavir has proven to have anti-SARS-CoV2 activity in vitro (Choy et al. 2020).

Treatening 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 produg 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). Xue 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 (AAKI) 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 pO₂, which also helps to reduce arterial pCO₂. 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 properties (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 which 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 μM. 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-CoV-2 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 (Robby 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 TMPRSS2 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

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Compliance with Ethical Standards

Conflict of interest All authors (D.A. Ghareeb, S.R. Saleh, M.S. Nofal, M.M.Y. Kaddah, S.F. Hassan, I.K. Seif, S.A. El-Zahaby, S.M. Khedr, M.Y. Kenawy, A.A. Masoud, S.A. Soudi, A.A. Sobhy, J.G. Sery, M.G. Abd El-Wahab, A.A. Abd Elmoneam, A.M. Al-mahallawi, and M.A. El-Demellawy) declare that they have no conflict of interest.
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