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Review Article

An Overview of COVID-19 Treatment: Possible Candidates Based on Drug Repurposing and Molecular Docking

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ABSTRACT

The current pandemic of COVID-19 is considered a worldwide threat to public health caused by a novel type of coronaviridae family called SARS-CoV-2. Owing to the urge of finding a treatment for this virulent virus, many aspects of drug development are swept aside. This review aimed to clarify the double-edged sword of drug repurposing in COVID-19 via summarizing the available treatment options and promising candidates for COVID-19 based on drug repurposing preclinical studies and in-silico approach. Different drugs target SARS-CoV-2 main structures under clinical investigation; some showed limited efficacy and severe side effects, while others can be promising solutions. Some drugs suppress the cytokine storm and modulate immune response during viral infection, including anti-interleukin and glucocorticoids. Antiparasitic agents are repurposed for SARS-CoV-2 infection management. Various vaccines and monoclonal antibodies are designed against SARS-CoV-2 and are being evaluated in different preclinical and clinical stages. However, none of them is approved yet. Convalescent Plasma Transfusion is a promising strategy against SARS-CoV-2 infection, where impressive results are reported in clinical trials, requiring more validation. Furthermore, anticoagulant therapy exhibited better disease outcomes in patients admitted to the ICU. Finally, in-silico studies suggested several potential compounds or FDA-approved drugs targeting various viral structure subunits. In conclusion, although many clinical trials were launched to examine potential therapies based on drug repurposing for COVID-19, there is no definitive treatment till now. Moreover, computational approaches identified several compounds and FDA-approved drugs with potential inhibitory effects.

According to the World Health Organization (WHO), the current pandemic of coronavirus disease 2019 (COVID-19) declared on 30th January 2020 is a threat worldwide to public health. COVID-19 was first discovered last December 2019 in Wuhan, China [1]. In a resemblance to SARS-CoV, it causes severe acute respiratory syndrome and other symptoms, including fever, dry cough, fatigue, and muscle aches [2][3]. Both viruses are similar in attacking the lower respiratory system, invading pulmonary epithelial cells, and hijacking the cellular machinery to replicate itself [4]. According to the World Health Organization, this pandemic reached several countries and territories with about 102,399,513 confirmed cases worldwide and 2,217,005 deaths till the 1st of February 2021 [5].

The causative agent of COVID-19 is a novel type of coronaviridae family called severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) [6]. It is an enveloped single-stranded RNA structure with homology to SARS-CoV of about 87-92% [7].

Coronavirus family has a distinct spherical shape, when examined by cryo-electron microscopy as it was elucidated in SARS coronavirus [8]. The family consists of four genera (alpha-beta-gamma-delta). Beta coronavirus has paid our attention because of its adverse pandemic impact accompanied by distinct high mortality and morbidity rates. The most prominent one now is SARS-CoV-2, which like other coronaviruses, possesses a single-stranded and positive-sense RNA [9]. The whole RNA genome contains several genes that encode proteins. The major constituent of the SARS-CoV genome is the replicase gene. It encodes two defined polyproteins (PPs): PP1a and PP1ab, which after further processing, give rise to 16 nonstructural proteins (Nsps) [10]. SARS-CoV-2 consists of 5 structural proteins (i.e., spike (S)- envelope protein (E)- nucleocapsid protein (N)- membrane protein (M) - hemagglutinin esterase (HE)) and 16 (Nsps). Figure 1 presents an overview of the therapeutic drugs used against SARS-CoV-2 various targets during the virus infection, cell entry, invasion, and replication in the human body.

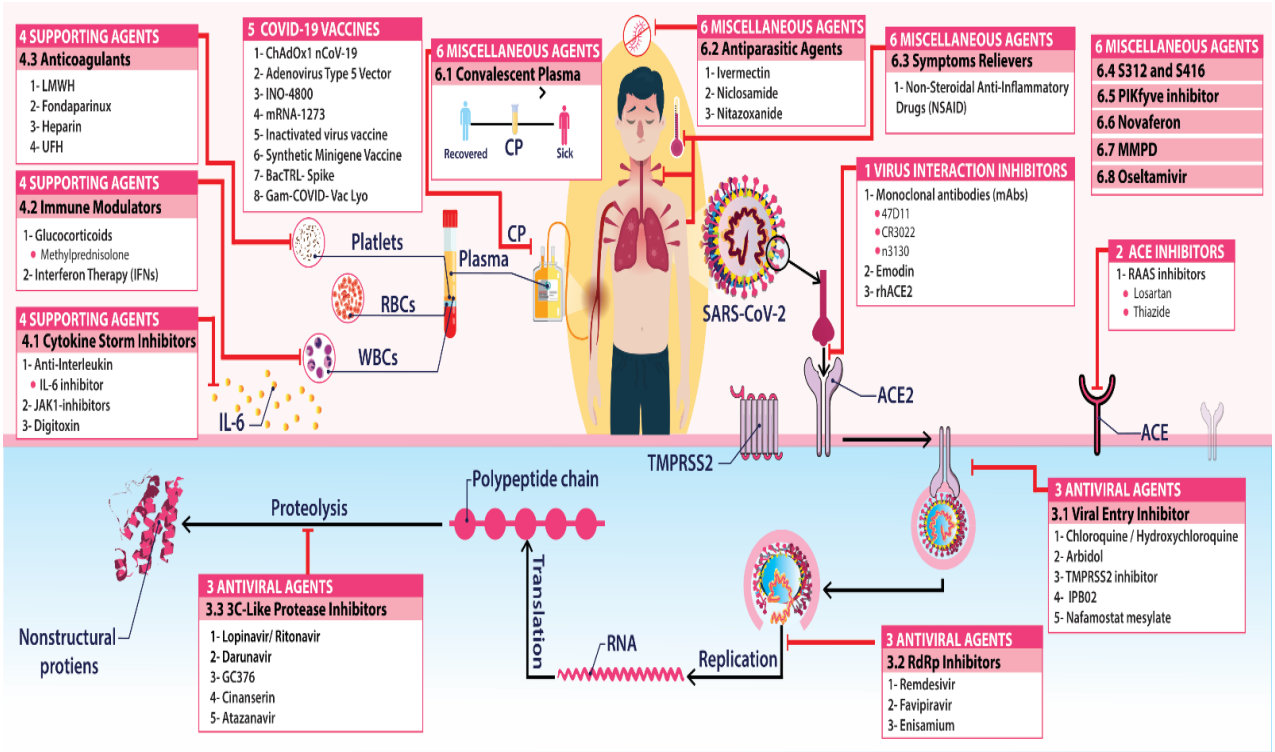

Figure 1. An overview of the therapeutic drugs used against SARS-CoV-2 various targets during the virus infection, cell entry, invasion, and replication in the human body.

Figure 2 illustrates the structure and the function of SARS-CoV-2. As shown in Figure 2, the coronavirus proteins are structural and nonstructural. The main structural proteins are spike glycoprotein (S), an envelope protein (E), nucleocapsid protein (N), and membrane protein (M). Sometimes, coronaviruses may have hemagglutinin esterase (HE), as in SARS-CoV-2, there are also 16 nonstructural proteins. S protein: the structure is S1 and S2 subunits. It is responsible for host cell attachment, invasion, and infection. The RNA-binding domain (RBD) of S1 subunit binds to human angiotensin-converting enzyme 2 (hACE-2), mediating the interaction of the heptad repeat 1 (HR1) and 2 (HR2) domains in S2 subunit, forming a fusion core.[160][161][162] M protein: It has a small N-terminal ectodomain and large C-terminal endodomain [163][164][165]. It maintains the viral shape [166] viral assembly through protein-protein interaction and envelope formation [163] N protein: didomains, N-terminal domain (NTD) or RNA-binding domain (RBD), C-terminal domain (CTD), or dimerization domain (DD) [167]. It binds the replicase-transcriptase complex (RTC) with the viral genome,[168][169] has a role in viral budding and assembly [170]. Interferon suppression and cell apoptosis act as an antigen provoke an immune response [167]. E protein: N-terminal ectodomain and C-terminal endodomain [171]; it shares in virus assembly, budding, and release [172] has an ion channel activity which participates in the process of pathogenesis [173]. HE protein: a dimer that has hemagglutination activity (HA), receptor-binding activity (lectin), and receptor destroying enzyme activity (RDE). Nsp: 16 different types responsible for virus replication and transcription. (PLpro): Forms RTC, antagonizes the innate host immune, and interacts with host proteins to enable its survival [174][175] and cleaves polyproteins [10], Nsp5: Cleaves polyproteins [10]. Nsp12: Forms RTC, the enzyme domain of polymerase present at the C-terminus [176]. Nsp8: Can be used as a primer for (RdRp) [177]. Nsp7-Nsp8 complex: Improves the enzyme activity of Nsp12, binds RdRp to the RNA genome [177]. Helicase (Nsp13): participates in virus central dogma, exploits the energy produced from nucleotide hydrolysis to unwind (dsRNA) [178].

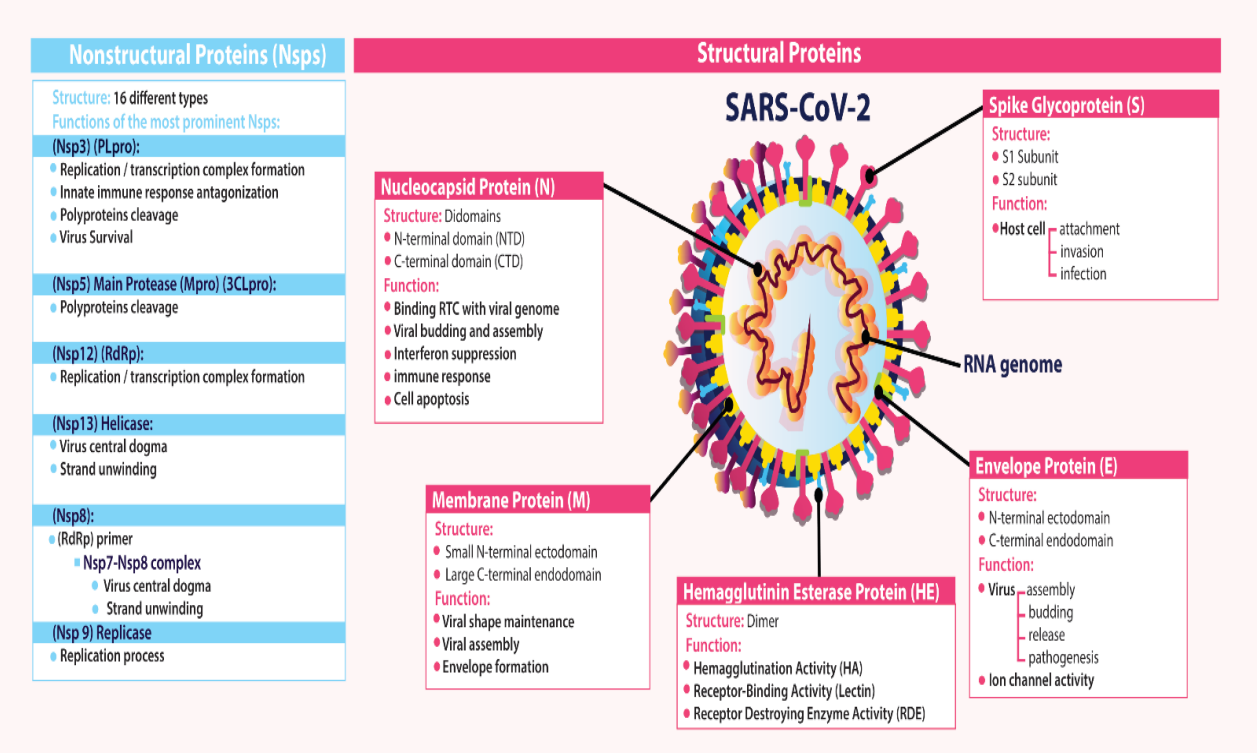

Figure 2. The structure and the function of SARS-CoV-2.

In this review, our main purpose was to illustrate the double-edged sword of drug repurposing in COVID-19. We have insights into the potential therapeutic drugs targeting SARS-CoV-2 and summarized different drugs targeting different virus structural units via reviewing the drug repurposing strategy. Some drugs show limited efficacy and severe adverse undesirable outcome, while others can be promising solutions. We are also focusing on developed vaccines and convalescent plasma administration. Furthermore, we spot the light on computational approaches used via molecular docking techniques, and the candidate drugs targeting the SARS-CoV-2 active pockets of target proteins which are predicted to be effective based on in-silico studies.

Virus Interaction Inhibitors

SARS-CoV-2 infection is mediated by the binding of the viral S protein to Angiotensin-Converting Enzyme2 (ACE2) receptor in human cells, particularly the alveolar epithelial cells, upon that the viral genome is integrated inside the cytoplasm and undergoes replication forming new virions which are released to infect other cells.

Virus interaction inhibitors have the ability to suppress the virus interaction as well as the host cell entry by competing for ACE2 binding or by binding to different viral structures, neutralizing it and consequently impairing the viral attachment to the cell ending by inhibiting its invasion.

Monoclonal Antibodies

Monoclonal antibodies (mAbs) are able to neutralize and inhibit viral infections with high specificity and safety. There are many mAbs developed against SARS-CoV targeting different epitopes along with the S protein, inhibiting viral entry by blocking the interaction between S protein and ACE2 receptors such as m396, 80R, Ab201, 1A9, CR3014, and CR2022, and they showed a potent neutralizing activity in-vitro or in-vivo [11][12]. Most SARS-CoV neutralizing antibodies such as 80R, m396, and S230 failed to bind to SARS-CoV-2; this could be due to lack of conservation at their targeted epitopes [13][14]. Most SARS-CoV neutralizing antibodies such as 80R, m396, and S230 failed to bind to SARS-CoV-2; this could be due to lack of conservation at their targeted epitopes [13][14]. On the other hand, CR3022 was reported to successfully neutralize SARS-CoV-2 by binding to the receptor-binding domain (RBD**)** with a higher binding affinity than that to SARS-CoV, and 1A9 was able to detect the S2 domain of SARS-CoV-2 [14][15][16][17]. Several mAbs under development and investigation for their neutralizing effect against SARS-CoV-2 showed promising results in vitro, including 47D11 mAb, which cross-reacted with the S protein by binding to a conserved epitope in the RBD [18]. n3130 antibody showed a strong neutralizing effect (>90%) at a dose of 10 μg/ml, but don't interfere with ACE2-S protein interaction [19]. Furthermore, 309 is another mAb that neutralizes SARS2-S protein by binding to N343-glycan (N330 in SARS-S) conserved epitope outside the RBD [20]. P2C-1F11 and P2B-2F6 mAbs were derived from the blood of infected patients, capable of blocking RBD-ACE2 interaction. A therapeutic cocktail of P2C-1F11(most potent) and P2C-1F10 (moderate) can be useful to function synergistically as they don't have the same epitope [21].

Emodin

Emodin is a natural compound extract derived from genus *Rheum* and *Polygonum, Rhamnus,* and *Senna,* used as an anthraquinone compound. It showed antimicrobial efficacy after its administration into liposomes. It is used as an antimicrobial, anticarcinogenic, or laxative [22]. Emodin showed promising results as an antiviral agent for SARS-CoV. It could block the viral

attachment to the host cell by impairing the interaction between the viral (S) protein and the target host receptor (ACE2). Consequently, it was capable of impairing the host cell attachment and invasion [23]. *Schwarz et al.* illustrated that Emodin could suppress the SARS-CoV and HCoV-OC43 ion channel formed by 3a protein, and it can inhibit the virus release from HCoV-OC43. This study confirmed the importance of the viral ion channel because of its contribution to viral release. Accordingly, it can be used as a drug target. Emodin might be a useful therapeutic agent in coronavirus infections [24]. Network analysis performed by *Zhou et al.* assumed that emodin could be a potential drug for SARS-CoV-2, particularly when combined with toremifene [25].

Recombinant Human Angiotensin-Converting Enzyme 2 (rhACE2)

Recombinant human angiotensin-converting enzyme 2 was firstly developed by APEIRON Biologics Company. It is a recombinant soluble form of ACE2 with an accepted safety and tolerance profile in human subjects [26]. In phase 2 clinical trial in humans, the infusion of rhACE2 (GSK2586881) twice-daily resulted in decreased AngII, IL-6 while increasing Ang 1-7, Ang 1-5 levels, suggesting that continuous infusion of rhACE2 would result in better outcomes in acute respiratory distress syndrome (ARDS) patients [27][28].

In a recent study, rhACE2 inhibited SARS-CoV-2 infection of Vero-E6 cells and engineered human organoids but in a dose-dependent manner and during the early stage of infection, suggesting that rhACE2 can have a protective effect against ARDS in patients with COVID-19 at the early stages of infection [29]. There is an ongoing trial investigating the role of rhACE2 and Ang 1-7 in patients with COVID-19 (NCT04335136).

ACE Inhibitors

Renin-Angiotensin-Aldosterone System (RAAS) Inhibitors

Angiotensin-converting enzyme inhibitors (ACEi), such as losartan, mediate its function through competitive inhibition with ACE to prevent the conversion of angiotensin I to angiotensin II, and of Ang 1-9 to Ang 1-7 leading to vasodilation, reducing arterial blood pressure, decreasing blood volume, and inhibition of vascular and cardiac hypertrophy. They also prevent the breakdown of bradykinin, enhancing its vasodilatory activity [30]. For angiotensin II receptor blockers (ARBs) such as thiazide, they inhibit the conversion between Ang I to Ang II [31]. There are ongoing debates and theories regarding the administration of ACEi/ARBs during the current pandemic; it's postulated that these drugs can aggravate viral infection by enhancing ACE2 activity [32]. There is limited evidence from the current situation to support or oppose these theories [33][34]. A recent center case series of the 1178 hospitalized patients with COVID-19 infections reported the lack of association of ACEI/ARB treatment with disease progression and hospital stay duration [35]. Also, another cohort study involving 610 (COVID-19) patients showed that ACEI/ARB therapy was not associated with increased disease severity [36]. These results were consistent with many other studies, such as retrospective sampling, over 3017 patients [37]. These results suggest that RAAS inhibitors have no impact on disease severity and mortality and could have a protective effect compared to other anti-hypertensive drugs.

Antiviral Agents

Antiviral agents are the first line of treatment against viral infections. They are capable of mediating their function by inhibition of different viral enzymes or structures responsible for viral entry and replication. They act by arresting the viral replication cycle that is crucial for viral survival.

Therefore, preventing the viral load has to be elevated.

Virus entry inhibitors

Chloroquine (CQ) and Hydroxychloroquine (HCQ)

Both chloroquine (CQ) and hydroxychloroquine (HCQ) are antimalarial drugs with an anti-inflammatory effect that have been widely used to treat rheumatoid arthritis, lupus erythematosus, and multiple sclerosis. Chloroquine and hydroxychloroquine have in-vitro antiviral activity against SARS-CoV infection of Vero E6 cells[38]. The proposed mechanism of chloroquine is that it may inhibit the glycosylation of ACE2 decreasing viral entry to the host cell [39]. Another proposed mechanism is the interference with viral release to the intracellular space [40]. A double-blind, randomized clinical trial showed no benefit from the usage of CQ, HCQ in patients with a high or moderate risk of SARS-CoV-2 infection [41]. Several ongoing clinical trials are investigating the efficacy and safety of these drugs [42]. Yet, both drugs resulted in cardiotoxicity [43]. Till now, there is no reliable evidence supporting the treatment with chloroquine and hydroxychloroquine, despite being included by the Egyptian national guideline for the treatment of COVID-19.

Umifenovir (arbidol)

Umifenovir is an antiviral drug against influenza, inhibiting viral fusion to the host cell [44]. In a recent study, arbidol monotherapy was more efficient than Lopinavir/Ritonavir (LPV/RTV) in reducing viral load and treatment of COVID-19[45]. Favipiravir's recovery rate was higher than that of arbidol in a recent open-labeled clinical trial[46], while controversial findings have been reported by other studies [47].

Transmembrane Protease Serine 2 (TMPRSS2) Inhibitor

TMPRSS2 protease is responsible for S protein priming and facilitating viral fusion and entry to the host cell. Camostat mesylate inhibits TMPRSS2 protease to block viral priming, fusion, and entry [48].

IPB02

It is an HR2 sequence-based lipopeptide inhibitor that inhibits viral fusion to the host cell; it is a promising candidate that can be adjusted against SARS-CoV-2 in clinical studies; further in vitro and in vivo studies are required [49].

Nafamostat Mesylate

Nafamostat Mesylateis, an available drug, is used to treat disseminated intravascular coagulation (DIC) with an acceptable safety profile/It was found that Nafamostat Mesylate is capable of inhibiting SARS-CoV-2 fusion and entry of Calu-3 cells in vitro, suggesting that it can be repurposed for COVID-19 treatment [50].

RNA-dependent RNA-polymerase (RdRp) Inhibitors

Remdesivir (RDV)

Remdesivir is a broad-spectrum adenosine analog that inhibits RdRp [51][52]. It is effective against RNA viruses, including the Nipah virus, Ebola virus, and human coronaviruses, including SARS-CoV, the middle east respiratory syndrome coronavirus (MERS-CoV), and SARS-CoV-2 [53].

Prophylactic and therapeutic RDV decreased SARS-CoV and MERS-CoV, protected from infection, and improved the disease outcome [51][54][55]. In cell cultures of human lung cells and

primary human airway epithelial cells, RDV potently inhibited SARS-CoV-2 infection. While in mouse models, RDV decreased viral load and improved lung function [56]. In January, RDV was used for the first time for the treatment of COVID-19. RDV was administered intravenously on day 7, severe symptoms were relieved after two days, and the patient recovered. It was effective in early and late stages, unlike other antiviral drugs [57][58]. In an ongoing cohort study, RDV resulted in improved disease outcomes in 68% of COVID-19 patients [59], and the preliminary findings of the National Institute of Allergy and Infectious Diseases (NIAID) trial over 1063 patients indicated that Remdesivir at the primary endpoint improved recovery time which was 31% faster than placebo. Also, it was capable of decreasing the mortality rate. [60]. RDV is a promising option for the treatment of COVID-19. Several clinical trials are being conducted to evaluate the efficiency and safety of the drug in patients with SARS-CoV-2 infection.

Favipiravir

Favipiravir, a type of broad-spectrum antiviral drug, is a nucleic purine acid (guanine) analog. Favipiravir is recently approved for the treatment of novel influenza. Since it can selectively inhibit RdRp, it has antiviral activity against RNA viruses, including SARS-CoV-2 [61]. The daily dose of favipiravir is 1600 mg twice daily, 1,600 mg twice from day 2 to day 14 [46][62]. Several clinical trials are evaluating the efficacy of favipiravir against SARS-CoV-2. Open labeled randomized clinical trial reported that favipiravir was more effective in moderate COVID-19 [62]. The recovery rate after a week of treatment with favipiravir was 71.43% in ordinary COVID-19 patients. Furthermore, COVID-19 related symptoms were recovered faster in patients treated with favipiravir than those treated with arbidol [46]. These findings suggest that favipiravir has potent antiviral activity against SARS-CoV-2. Further clinical trials are required to confirm these findings on many subjects to clarify the relationship between the clinical prognosis and viral titer.

Enisamium

Enisamium was capable of inhibiting RNA polymerase of SARS-CoV-2 and influenza viruses in vitro and blocking SARS-CoV-2 replication, suggesting a broad antiviral spectrum in vivo [63].

3C-like Protease (3CLpro) (Mpro) Inhibitors

Lopinavir/ Ritonavir

They are protease inhibitors. Ritonavir is also a cytochrome P450 and glycoprotein inhibitor, prolonging the half-life of lopinavir. Both of them are used in combination for the treatment of human immunodeficiency virus (HIV) infection [64][65]. Treatment with LPV/RTV combined with ribavirin in patients with SARS-CoV decreased ARDS and mortality rates [66]. The prophylactic LPV/RTV combined with interferon-beta during the MERS-CoV infection resulted in a slight decrease of the viral load only, while therapeutic combination resulted in improvement of pulmonary function with no effect on viral load or severity of lung injury [67][68]. LPV/RTV therapy had no clinical improvement compared to standard care procedure [69] or arbidol [45]. Fourteen percent of patients developed several side effects, including nausea, anorexia, diarrhea, abdominal discomfort, and skin eruptions. The only positive outcomes were that patients were discharged from ICU 5 days earlier, and their symptoms improved one day earlier than the control group [69]. The National Health Commission of the People's Republic of China recommended the administration of LPV/RTV combination to treat pneumonia associated with SAS-CoV-2; the daily dose is 400 mg, two times/day [64].

Darunavir/ Cobicistat

It is an antiviral drug against HIV protease enzyme. It was used in clinical trials in China to treat COVID-19, but there is no clinical data available yet. However, in vitro studies revealed that the drug has no antiviral effect against SAR-CoV-2, so it isn't suggested to include the drug in COVID-19 upcoming clinical trials [70].

GC376 and Peptidomimetic Inhibitors

These are SARS-CoV 3CL protease inhibitors. GC376 showed the highest enzymatic activity; however, further in vivo studies are recommended [71][72],

Cinanserin

It is a serotonin receptor antagonist that can inhibit 3CLpro. It is responsible for viral polyprotein cleavage and replication of SARS-CoV and SARS-CoV-2, suggesting that cinanserin could be a promising drug candidate in COVID-19 patients [73][74][75].

Atazanavir

It is an antiretroviral protease inhibitor. In vitro, it showed an inhibitory effect against SARS-CoV-2 in Vero cells, human pulmonary epithelial cell line, and primary monocytes. It also showed an anti-inflammatory effect decreasing IL-6 and TNF-α levels, making it a promising antiviral candidate drug either alone or when combined with ritonavir [76].

Supporting Agents

Infection with COVID-19 can cause severe adverse effects such as cytokine release syndrome, inflammation, and coagulopathy which have been observed to be accompanied symptoms in some patients suffering from COVID-19. Therefore, several medications are not prescribed for viral infection inhibition but rather for managing the resulting adverse severe events associated with increased mortality rates**.**

Cytokine Storm Inhibitors

Anti-interleukin

Patients with COVID-19 usually experience cytokine release syndrome (CRS) which is caused by increased release of cytokines leading to hyper-inflammatory immune response. Histological reports from COVID-19 patients revealed alveolar damage. The right lung showed clear pneumocyte desquamation and hyaline membrane formation, eventually leading to ARDS. Clinically CRS symptoms are ranging from mild, flu-like manifestations to life-threatening situations [77]. CRS pathogenesis is mainly based on releasing inflammatory cytokines such as interferon-Y, IL-10, and IL-6 [78]. Tocilizumab is a recombinant humanized monoclonal anti-IL-6R antibody [79] that revealed impressive clinical results, including fever relief and enhanced respiratory function [80]. Therefore, currently, many trials undergo investigation. Siltuximab, another IL-6 inhibitor, is also being investigated in clinical trials as an option for CRS treatment (NCT04329650).

Janus kinase1 (JAK1)-Inhibitors

In mouse models, JAK1-specific inhibitors were useful in suppressing the cytokine storm and the hyper inflammation accompanying ARDS in COVID-19 patients. JAK1-inhibitors include Xeljanz/Tofacitinib, Olumiant/Baricitinib, Rinvoq/Upadacitinib, and Jakafi/Ruxolitinib. Further

evaluation is required in clinical studies [81].

Digitoxin

Digitoxin as a treatment for heart failure can be useful in suppressing cytokine response [82].

Immune Modulators

Glucocorticoids

Glucocorticoid drugs are usually prescribed to treat immune system disorders to inhibit inflammation and organ damage [83]. Its application for the management of SARS-CoV is inconclusive[84]. It decreased the viral clearance rate and increased the mortality during MERS-CoV infection[85][86]. In ARDS, it was associated with improved clinical outcomes, decreased ICU admission duration and mechanical ventilation, reduced inflammation. The hydrocortisone had not increased survival rates but improved lung function [87][88]. For SARS-CoV-2, an in vitro study reported that Ciclesonide inhibited the viral RNA replication at a dose of (EC90) of 6.3μM with low cytotoxicity [89]. Methylprednisolone was used in combination and immunoglobulin therapy to manage coronavirus fulminant myocarditis patients, preferably in the early stages of infection [90]. WHO does not recommend the use of glucocorticoid therapy for COVID-19 [91][92] because of a lack of clinical evidence about their effectiveness [93]. Other studies suggested using glucocorticoids at doses not exceeding methylprednisolone 1-2 mg/kg/day for severe patients with ARDS [94][95]. There is no evidence supporting the withdrawal of corticosteroid treatment for patients with asthma or chronic obstructive pulmonary disease (COPD), so patients should continue their treatment [96].

Interferon (IFN) Therapy

The immune system usually triggers interferon production after viral infection; IFNα is responsible for strong pro-inflammatory effects against the virus and may cause tissue damage. In contrast, IFNλs have tissue-protective and anti-inflammatory effects against viral load [97]. In VERO E6 cells, IFNα suppressed SARS-CoV-2 infection at doses that can be used in the clinic [98]. IFNα2b sprays decreased infection rates [99]. In vivo studies suggested that IFNα can be useful as prophylaxis against SARS-CoV-2 [98]. Restoration of IFNα may help alleviate disease symptoms in critically ill patients [100]. Recombinant IFN-αs and Recombinant IFN-βs drugs are promising candidates for COVID-19 patients [98].

In human intestinal epithelial cells, IFNλ controlled SARS-CoV-2 replication and spread. It also was capable of decreasing de-novo viral particle production when compared to IFNα [101]. It can be useful to suppress viral replication and prevent the cytokine storm for high-risk patients during early mild symptoms [102], but IFNλ facilitates bacterial superinfection in mice by reducing neutrophils count and activity [103][104], so further studies are highly recommended to determine its interaction with the body and possible side effects. A combination of vapor inhalation of 5 million U of IFNα two times per day and ribavirin at a dose of 500 mg two to three times per day is recommended for COVID-19 patients in China [91]. However, interferon therapy is most suitable in the early stages of infection, while in the late stages, anti-interferon drugs are more preferred.

Anticoagulation Therapy in a Patient with COVID-19

Patients with COVID-19 are at a high risk of developing coagulopathy. Recent case reports showed that patients admitted to the ICU are at higher risk of venous thromboembolism due to

immobilization and other factors [105]. D-dimer was elevated in COVID-19 patients and considered as a predictor for thromboembolism risk. Treatment with anticoagulants decreased mortality rates among patients with COVID-19 meeting Sepsis-Induced Coagulopathy (SIC) criteria or with elevated D-dimer [106]. The International Society on Thrombosis and Haemostasis (ISTH) and American society of hematology suggested that all patients with COVID -19 admitted to the hospital should receive a thrombo-prophylaxis treatment, while Severe cases should receive treatment doses of low molecular weight heparin (LMWH) if not contraindicated. If it's contraindicated, they can receive Fondaparinux [107]. One study suggested switching from oral anticoagulant to parental Heparin or Unfractionated Heparin (UFH) due to common interaction between direct-acting oral anticoagulants (DOAC) and cytochrome 450 (CYP450), antiviral drugs [108].

COVID-19 Vaccines

SARS-CoV-2 is spreading rapidly, affecting everyone with equal susceptibility and different adverse events varying from no symptoms, mild, severe symptoms, and death. There is no treatment available for COVID-19 until now, and there are predictions of a second strong wave of viral transmission during winter. Therefore, it becomes an urgent need to develop an appropriate vaccine to protect and train people's immune systems to fight against SARS-CoV-2, particularly for healthcare workers and the elderly at high risk.

There are significant attempts done by scientists to release a vaccine, and some vaccines are enrolled in different clinical trial stages (Table1). A clinical trial of SARS-CoV that was performed with an inactive virus vaccine and spike protein DNA vaccine encouraged S protein as a target for a vaccine due to the high similarity between S protein of SARS-CoV and SARS-CoV-2. However, DNA and RNA vaccines are usually quicker as they do not need culture media, but they may cause lung disease directly or through an antibody-dependent response associated with T cell response [109]. Many vector-based vaccines containing S protein are being evaluated in laboratory studies. DNA-based vaccine encoded full-length S protein induces neutralizing antibody, S1 receptor binding domain, non-replicative viral vector, virus-like a particle, RNA vaccines are under preclinical investigation (Table 2) [110].

Table 1

SARS-CoV-2 Vaccines in Clinical Trial Different Stages

	Vaccine	Type	Clinical Trial	Stage	Developer
8.1.	**ChAdOx1 nCoV-19**	Non-Replicating Viral Vector	2020-001228-32	Phase 2b/3	University of Oxford
			NCT04324606	Phase 1 /2	
			ISRCTN89951424	Phase 3	
8.2.	**Adenovirus Type 5 Vector**	Non-Replicating Viral Vector	NCT04313127	Phase 1	CanSino Biologics Inc.
			NCT04341389	Phase 2	Beijing Institute of Biotechnology
8.3.	**INO-4800**	DNA Vaccine	NCT04336410	Phase 1/2	Inovio Pharmaceuticals
			NCT04447781		
			NCT04463472		
			NCT04445389		
8.4.	**mRNA-1273**	RNA Vaccine	NCT04283461	Phase 1	Moderna
			NCT04405076	Phase 2	
			NCT04470427	Phase 3	
8.5.	**Inactivated Virus Vaccine**	Inactivated virus	ChiCTR2000031809	Phase 1 /2	Wuhan Institute of Biological Products/ Sinopharm
			ChiCTR200034780	Phase 3	Wuhan Institute of Biological Products/ Sinopharm
			ChiCTR2000032459	Phase 1/2	Beijing Institute of Biological Products/Sinopharm
8.6.	**Synthetic Minigene Vaccine**	Lentiviral based DC and T cell Vaccine	NCT04276896	Phase 1 /2	Shenzhen Geno-Immune Medical Institute
8.7.	**bacTRL- Spike**	DNA Vaccine	NCT04334980	Phase 1	Symvivo
8.8	**Gam-COVID- Vac Lyo**	Adenovirus Vector-Based Vaccine	NCT04437875	Phase 1/2	Gamaleya Research Institute of Epidemiology and Microbiology, Health Ministry of the Russian Federation
			NCT04436471		

Table 2

SARS-CoV-2 Different Vaccine Types

Vaccine technology	General information
Viral Vector-based Vaccines	• Based on replicating, or non- replicating live vectors. • Virus vaccines developed to evolve heterologous viruses' antigen that enters the host cell through a vector. • A wide range of viruses used such as adenovirus
DNA Vaccines	• DNA vaccines are developed by inserting antigen(s) encoding elements into a bacteria-derived plasmid.
RNA Vaccines	• Use two types of RNA (non-replicating mRNA and self-amply fining mRNA). • Exogenous mRNA enters the cytoplasm where protein translation happens
Inactivated Virus Vaccine	• Virions are inactivated by chemical means or radiations
Live Attenuated Virus Vaccines	• Virus genome is mutated using chemical or site-directed mutagenesis
Subunit Vaccine	• Pathogen fragment that used to produce an immune response, usually surface protein

Miscellaneous Agents

Different drugs are primarily used for other purposes rather than viral infections. However, they exhibited promising clinical outcomes for COVID-19 patients so that they can be repurposed for the management of SARS-CoV-2 infection.

Convalescent Plasma (CP) Transfusion

CP transfusion is obtaining plasma from infected individuals with various infectious diseases such as COVID-19, then transfusing it to other infected individuals as postexposure prophylaxis [111]. It is considered a passive antibody treatment. CP-derived antibodies are able to neutralize the virus by inhibiting replication or by binding without interrupting the replication [112]. Previous evidence confirmed that CP treatment could reduce the high mortality risk for critically ill patients[113] because CP antibodies can potentially suppress viremia. During SARS-CoV, viremia generally reaches its zenith during the 1st week of infection [114]. A lethal cytokine storm follows it during the 2nd week due to the patients' immune response [115][116].

Pros and Cons of CP Transfusion

Firstly, the pros of CP transfusion include; the large pool of plasma donors due to the considerable number of COVID-19 recovered individuals, minor significant secondary effects, verified competence in previous viral outbreaks, a conceivable application in critically sick patients, high-titer explicit antibodies binding to SARS-CoV-2 and worked on neutralizing viral particles [117]. Secondly, the cons of CP transfusion include significant expenses, burdensome logistics, passive immunization, and the shortage of knowledge of SARS-CoV-2 basic biology, including virus mutations and variances [117]. Some adverse reactions result from CP treatment associated with the transfusion process, such as fever, transfusion-associated acute lung damage, chills, hemolysis,

anaphylactic reactions, and circulatory overload [105][106]. There is a high risk for transmitting diseases such as syphilis, hepatitis virus (HBV, HCV), and HIV. This risk should not be underestimated or neglected [118].

Clinical Trials on CP Transfusion

Clinical trials on CP showed increasingly progressive results. Also, various controlled randomized and non-randomized clinical trials are under investigation. The interventions for the experimental groups include several options such as conventional treatment and CP transfusion, inactivated plasma anti-SARS-CoV-2 virus, immunoglobulin of cured patients, blood, and derivatives. These interventions are compared to control groups who received different treatment options such as conventional therapy, ordinary plasma, SARS-CoV-2 non-immune Plasma, γ-Globulin, standard supportive care, oxygen, and antibiotics. A wide range of primary and secondary indicators was considered. The primary indicators included the DNA of SARS-CoV-2, SARS-CoV-2 Antibody levels, C-reactive protein, and biological clearance rate. While the secondary indicators had hospitalization time, mortality rate, discharge time, and Viral titers. The number of participants varied from 10 patients [119] to 1500 participants (NCT04344977).

Neutralizing Antibody Titer (NAT) Level and CP Transfusion

NAT plays an important role in determining the CP curative impact on COVID-19 [120]. The CP dosage has high variability. A recent randomized clinical trial was applied on 150 patients at Johns Hopkins University in which 1 unit of 200-250 mL plasma was collected from COVID-19 recovered volunteer patients with NAT>1:64 [121] in the arranged clinical trials. The recommended treatment dosages are one up to two units and one unit for post-exposure prophylaxis [111]. Antibodies' efficacy duration is obscure. However, it is hypothesized to range from one week to a couple of months [122][123].

The dosage started from 200 ml up to 450-550 ml of CP [123], mostly once or twice, depending on the study type. These findings support the significant role of CP against SARS-CoV-2 due to its neutralizing activity. It also led to clinical symptoms improvements, reduced pulmonary lesions on the chest CT examinations, increased neutralizing antibody titers, and SARS-CoV-2 RNA clearance rates for most participants [124].

Antiparasitic Agents

Ivermectin

It is an anthelmintic agent that has in-vitro activity against different types of RNA viruses due to its ability to target importin (IMP alpha/beta1 heterodimer) nuclear transport protein [125][126]. SARS-CoV-2 has IMP alpha/beta1 similar to that of SARS-CoV, suggesting the utility of ivermectin against the virus. It has shown in-vitro antiviral activity in Vero/hSLAM cells infected with SARS-CoV-2 [127]. Till now, there is no published data considering its efficacy or safety in COVID-19 patients. There are two clinical trials still ongoing comparing the efficacy and safety of ivermectin adjuvant use in COVID-19 patients with pneumonia (NCT04343092) (NCT04345419).

Niclosamide

It is an anthelmintic drug that inhibits oxidative phosphorylation as well as stimulates ATP activity in the mitochondria. It can hinder SARS-CoV in Vero E6 cells through the suppression of the cytopathic effect [128]. There is only one clinical trial in phase 2 evaluating the efficacy of

niclosamide against SARS-CoV-2 (NCT04345419).

Nitazoxanide

Antiprotozoal has antiviral activity against different types of viruses [129][130], including coronaviruses [131]. There is only one clinical trial comparing nitazoxanide to other drugs such as ivermectin, niclosamide, and chloroquine (NCT04345419).

Symptoms relievers [Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)]

These drugs function by inhibiting cyclooxygenase1 (COX1) or COX2, leading to inhibition of inflammation, relieving pain, and fever[132]. NSAIDs and other antipyretics drugs used for relieving COVID-19 symptoms in clinical care settings [91]. In a previous animal study, Indomethacin (INDO), a COX inhibitor, had antiviral activity against SARS-CoV [133], suggesting that it could be a beneficial treatment of SARS infection by blocking viral RNA synthesis. Further research is required to examine the role of INDO in the inhibition of SARS-CoV-2. Celebrex, a COX-2 inhibitor, could be capable of suppressing prostaglandin storms observed in COVID-19 patients and can also be used as an adjuvant drug, but a further recommendation in clinical trials is required [134]. There are many concerns regarding the use of NSAIDs during the SARS-CoV-2 pandemic [135][136], but no evidence in the literature supports that the use of NSAIDs may worsen COVID-19 symptoms or may result in adverse side effects [137][138]. Further research is needed to confirm the role of NSAIDs in COVID-19 disease progression.

S312 and S416

They are broad-spectrum antiviral drugs with low toxicity and high efficiency. They function by inhibiting dihydroorotate dehydrogenase (DHODH), responsible for de-novo pyrimidine synthesis in RNA viruses [139].

PI-3P-5-kinase (PIKfyve) Inhibitor

It can block SARS-CoV-2 infection and inhibit viral genome release from endosomes in vitro; previously, it was found to have an acceptable safety profile [140].

Novaferon

It is an available drug in China for the treatment of chronic hepatitis B. It inhibited viral infection in vitro in Vero E6 cells and in vivo in SARS-CoV-2. It improved clinical outcomes and three-day reduction of viral clearance time in patients treated with Novaferon or Novaferon plus PV/RTV [141].

Inosine-5′ Monophosphate Dehydrogenase (IMPDH) inhibitor Merimepodib (MMPD)

It inhibited SARS-CoV-2 in vitro. It can be tested with other antiviral or immunomodulatory drugs in COVID-19 patients [142].

Oseltamivir

It is an FDA-approved drug for the treatment of influenza type A and B for adults and children [143]. It inhibits viral neuraminidase enzymes expressed on the viral surface, thus preventing virions from the infected cells to the surroundings in the respiratory tract[144]. Oseltamivir was prescribed for COVID-19 patients in china, but there is no evidence concerning its effectiveness [94][145]. Several clinical trials are evaluating its efficiency in combination with other drugs

(NCT0433299) (NCT04261270) (NCT04338698).

Azithromycin

It is a macrolide antibiotic with in-vitro antiviral activity against Zika, H1N1, and influenza A viruses. Non-randomized clinical trials in Marseilles and France suggested its combination with antimalarial hydroxychloroquine for decreasing viral load [146]. Additional data is needed before drawing any conclusions. While there are no conclusive results, caution must be taken, and patient monitoring must be done regularly for toxicities.

In Silico Studies

Bioinformatic analysis is a beneficial tool used in drug development, essentially. On the other hand, drug development is time-consuming, as it takes years to develop a drug from scratch. Therefore, scientists try to make either drug repurposing or in silico study to develop a cure for COVID-19. Computational methods such as homology modeling and molecular docking are exploited to predict the SARS-CoV-2 protein structure and perform molecular docking. This part will have insights into the potential compounds used by computational approaches against the virus targets.

Papain-like Protease (PLpro)

Canrong Wu et al. performed target-based drug screening against 21 targets in SARS-CoV-2 by docking several compounds, including their natural product database and ZINC drug database. Lead compounds against specific targets were predicted according to the target based on the results [147]. The compounds targeting PLpro and might have high binding affinity against it were (ribavirin, valganciclovir, thymidine, chloramphenicol, cefamandole, tigecycline, chlorphenesin carbamate, and levodropropizine) [147]. While from their natural product database, platycodinD, baicalin, sugetriol-3,9-diacetate, phaitanthrin D, and 2,2-di (3-indolyl)-3-indolone and catechin compounds, which displayed a high binding affinity to PLpro [147]. A study virtually screened around 54 antiviral drugs approved by the FDA and 3300 investigational drugs against SARS-CoV-2 proteins [148], Elbasvir, and HCV, and is considered a component of ZepatierTM could exhibit a high affinity to RdRp, helicase, PLpro, and S protein. Since the drug has a well-defined interaction and low toxicity at the therapeutic dose, it could be used as an antiviral agent against SARS-CoV-2 [148]. Virtual screening of around sixteen FDA-approved drugs indicated that (Biltricide, Ethoheptazine, Chloroquine, Tetrahydrozoline, Naphazoline, Cinacalcet, Pethidine, Levamisole, Procainamide, Terbinafine, Labetalol, Ticlopidine, Amitriptyline, Chlorothiazide) possess a high affinity to PLpro [149]. One study found that anti-SARS PLpro (Mycophenolic acid, GRL-0617, and GRL-0667) and anti-HCV NS3 (Boceprevir, Telaprevir, and Grazoprevir) could interfere with the active site of SARS-CoV-2 PLpro [150].

3C-like Protease or (3CLpro) or (Mpro)

Canrong Wu et al. elucidated that the compounds targeting 3CLpro and exhibiting the highest affinity were lymecycline, demeclocycline, doxycycline, oxytetracycline, nicardipine, telmisartan, and conivaptan. Several compounds are showing high affinity regarding the natural product library, including kouitchenside I and deacetylcentapicrin [147]. On the other hand, Nukoolkarn et al. identified lopinavir and ritonavir, HIV-1 protease inhibitors, as SARS-CoV main protease inhibitors [151]. Since Mpro proteins are 96% identical between SARS-CoV and SARS-CoV-2 and the binding site of Mpro with these two drugs are conserved, virtual screening can be done to

find drugs that can do the same action as the previous mentioned two drugs. Therefore, *Xin Liu* searched for commercial drugs that can inhibit SARS-CoV-2 targeting Mpro with referencing to lopinavir and ritonavir and their binding site. The result showed ten candidate clinical medicines (i.e., icatibant, aprepitant, colistin, valrubicin, bepotastine, epoprostenol, Epirubicin, vapreotide, caspofungin, and perphenazine) may function as inhibitors [152]. Jin et al. developed a novel technique to find promising compounds against SARS-CoV-2 Mpro and have clinical potential simultaneously [153]. Based on their determination of the crystal 3D structure of SARS-CoV-2 Mpro in complex with the inhibitor compound N3 and considering it as a model, the authors screened over 10,000 compounds against the target. The result showed that six compounds with IC50 (0.67 to 21.4) μM suppressed it, and Ebselen showed antiviral activity in a cell-based assay [153]. While cinanserin, a well-defined serotonin antagonist proved to inhibit Mpro of SARS-CoV, exhibited a high binding affinity to the binding site of Mpro with IC50 value [125]. μM. [153] Hypericin, Cyanidin 3- glucoside, Baicalin, Glabridin, α-ketoamide-11r, which are antiviral drugs, were docked against Mpro and showed high binding affinity in SARS-CoV-2 by inhibition of the catalytic residues Cys145 and/ or His41 in Mpro active site [154]. On the other hand, homology modeling of Mpro and docking results showed that Zanamivir, Saquinavir, Indinavir, and Remdesivir displayed the best, and they were nominated to be potential inhibitors [155].

RNA-dependent RNA Polymerase (RdRp)

Canrong Wu et al. showed that itraconazole, novobiocin, cortisone, idarubicin, silybin, and the natural products (betulonal, gnidicin and gniditrin, 2β,30β -dihydroxy-3,4-seco-friedelolactone-27-lactone, 14-deoxy-11,12-didehydroandrographolide, 1,7-dihydroxy-3- methoxyxanthone, theaflavin 3,3'-di-O-gallate) displayed high binding affinity to RdRp [147]. Drug repurposing of Elbasvir is performed using in-silico studies, where the result showed that RdRp could bind effectively to RdRp, reflecting its antiviral activity by inhibiting the replication process [148]. Homology modeling was done to predict the structure of RdRp of SARS-CoV-2 with the help of the SARS-Hcov model. Molecular docking against the RdRp indicated that Remidisvir, Sofosbuvir, IDX-184, and Ribavirin showed the best binding affinity [156].

Helicase

Molecular docking results by Canrong Wu et al. demonstrated that lymecycline, cefsulodine, rolitetracycline, itraconazole, saquinavir, dabigatran, and canrenoic acid were anticipated to be potential inhibitors to the helicase target. The natural products with high binding capacity were several flavonoids, xanthones, phyllaemblicin B, and phyllaemblinol [147]. Another study illustrated that Elbasvir could not only be used as anti-HCV but also as anti- SARS-CoV-2 drug therapy. The virtual screening showed that Elbasvir had a great affinity to helicase protein, thus impairing the viral replication process [148].

Spike Protein

Canrong Wu et al. reported compounds having a high binding affinity against (S) protein (i.e., rescinnamine, iloprost, prazosin, posaconazole, itraconazole, sulfasalazine, azlocillin, penicillin, cefsulodin, and dabigatran etexilate). However, the natural compounds (i.e., flavonoids, licoflavonol, cosmosiin, neohesperidin, mangostin, kouitchenside D, excoecariatoxin, and piceatannol) are not expected to bind with ACE2- spike protein complex, only hesperidin did [147]. Elbasvir is an FDA-approved compound used in treating chronic HCV infection. It showed stable

binding to the viral S protein that binds to the ACE2 receptor in the host cell. Therefore, it can be used either alone or in combination to block the virus pathogenesis and host entry [148]. Screening for several compounds from ZINC database illustrated compounds with the best binding affinity against spike protein of SARS-CoV-2 after performing homology modeling (i.e., Cangrelor, Dpnh, Flavin Adenine Dinucleotide Adeflavin, Iomeprol, Coenzyme A, Tiludronate) [155]. Saikosaponin U and Saikosaponin V showed the best binding affinity to the target [157].

ACE2 Target

The host ACE2 is considered the receptor for the coronavirus Spike RBD. The Canrong Wu et al. screening results illustrated that troglitazone, losartan, ergotamine, cefmenoxime, silybin were anticipated to have a binding affinity to ACE2 [147]. In addition, some natural ingredients such as neohesperidin, phyllaemblicin G7, xanthones, and hesperidin exhibited such binding affinity to ACE2 [147].

Nsp1, Nsp3c, and ORF7a

The virtual screening of Nsp1, Nsp3c, and ORF7aperformed by *Canrong Wu et al.* showed that piperacillin, cefpiramide, streptomycin, lymecycline, tetracycline, and the natural product (i.e., platycodin D, wogonoside, vitexin, rographolide derivatives, and xanthones) have binding affinity against them [147].

Nsp15

Twenty-three Saikosaponins were screened against (Nsp15) SARS-CoV-2. Saikosaponin U and V were able to bind to Nsp15. Therefore, they are considered potential target inhibitors by interfering with the viral replication process and penetration of the virus [157].

TMPRSS2 Target

It has a role in the cleavage of the Spike protein to trigger the SARS-CoV infection. Potential TMPRSS2 inhibitors such as pivampicillin, hetacillin, cefoperazone, clindamycin, phyllaemblicin G7, neoandrographolide, and kouitchenside were predicted by virtual screening [147].

Envelope Protein

A computational approach was used to target the ion channel of (E) protein in SARS-CoV-2 using several phytochemicals. It has been revealed that Vibsanol B, Macaflavanone E, and Belachinal were capable of decreasing the random motion in the E protein [158]. Accordingly, they could inhibit the role of the ion channel and E protein. Therefore, the previously mentioned phytochemicals might be suitable antiviral therapies utilized against SARS-CoV-2 because they pass the ADMET property in addition to ‘Lipinski’s Rule of 5s’[158].

Nucleocapsid Protein

Around 56,079 compounds were virtually screened against the SARS-CoV-2 N protein, particularly the N- terminal domain (NTD). The NTD can attach to the viral RNA to form the ribonucleoprotein (RNP) complex[159]. The results showed that two promising hits exhibited a binding affinity to it; thereby, they might be possible inhibitors for RNA binding to NTD. The two hits, namely ZINC000003118440 (theophylline derivative)and ZINC000000146942 (pyrimidine derivative) showed antiviral activity against other viruses, and this study illustrated for the first time that they could act against SARS-CoV-2 N protein with a binding affinity [159].

Conclusion

SARS-CoV-2 is spreading rapidly worldwide, leading to over 100 million infected patients and more than 2.2 million of them died. There is no specific antiviral drug or vaccine for SARS-CoV-2 until now. In addition to drug repurposing, Remdesivir is the most promising among antiviral drugs until now, while oseltamivir, umifenovir, darunavir, and favipiravir have limited advantages. Treatment with different IFNs and anti-IL-6 is proposed to balance the immune response, while glucocorticoid therapy is not recommended. There are no conclusive results for using Ivermectin, Nitazoxanide, and Niclosamide. Additionally, no effect of chloroquine was found against the virus and, its use resulted in cardiotoxicity. Among SARS-CoV monoclonal antibodies, CR3022 showed positive outcomes in favor of neutralizing SARS-CoV-2. Additionally, other promising mAbs such as 47D11 and n3130 are in progress. Various vaccines are being developed, and some of them are entering clinical evaluation while the remaining are still in preclinical stages. Patients with chronic diseases who are treated with RAAS inhibitors or glucocorticoids should not stop taking their medication as there is not enough evidence in the literature supporting their withdrawal. Convalescent plasma transfusion showed promising results and is evaluated in several clinical trials in different countries. CP could be involved in relieving disease symptoms, reducing pulmonary lesions, and increasing virus-neutralization in COVID-19 patients. Anticoagulant therapy has improved disease outcomes, decreased thromboembolism, especially in those with high risk and admitted to the ICU, resulting in reduced mortality rates. Computational and in-silico approaches have identified several molecules and FDA-approved drugs with potential inhibitory effects against various viral structure subunits, but their safety and efficiency require further evaluation to be verified against COVID-19 in clinical trials as many of them are still in the preclinical stages.

The limitation of our study is the lack of strength of some of the publications cited here, as they are not peer-reviewed yet. Therefore, the interpretation of our summary should be considered with caution.

Abbreviations

PPs: Polyproteins, **Nsps:** Nonstructural Proteins, **S:** Spike Glycoprotein, **E:** Envelope Protein, **N:** Nucleocapsid Protein, **M:** Membrane Protein, **HE**: Hemagglutinin Esterase, **ACE2:** Angiotensin-Converting Enzyme, **mAbs:** Monoclonal antibodies, **RBD:** receptor-binding domain, **rhACE2:** Recombinant Human Angiotensin-Converting Enzyme 2, **ARDS:** Acute Respiratory Distress Syndrome, **ACEi:** Angiotensin-Converting Enzyme Inhibitors, **RAAS:** Renin-Angiotensin-Aldosterone System, **ARBs:** Angiotensin II Receptor Blockers, **CQ:** Chloroquine **HCQ:** Hydroxychloroquine, **LPV/RTV:** Lopinavir/ Ritonavir, **TMPRSS2:** Transmembrane Protease Serine 2, **DIC:** Disseminated Intravascular Coagulation, **RdRp:** RNA-Dependent RNA-Polymerase, **RDV:** Remdesivir, **MERS-CoV:** Middle East Respiratory Syndrome Coronavirus, **NIAID:** National Institute of Allergy and Infectious Diseases, **3CLpro/ Mpro:** 3C-like Protease, **HIV:** Human Immunodeficiency Virus, **CRS :**Cytokine Release Syndrome, **JAK1:** Janus Kinase1, **COPD :** Chronic Obstructive Pulmonary Disease, **IFN:** Interferon, **SIC**: Sepsis-Induced Coagulopathy**, ISTH:** The International Society on Thrombosis and Haemostasis, **LMWH:** Low Molecular Weight Heparin, **UFH:** Unfractionated Heparin, **DOAC:** Direct-acting Oral Anticoagulants, **CP:** Convalescent Plasma, **NAT** :Neutralizing Antibody Titer, **IMP:** Importin,

NSAID: Non-steroidal Anti-inflammatory, **COX1:** Cyclooxygenase1, **INDO:** Indomethacin, **DHODH:** Dihydroorotate Dehydrogenase**, PIKfyve:** PI-3P-5-kinase**, IMPDH:** Inosine-5' Monophosphate Dehydrogenase, **MMPD:** Merimepodib, **PLpro:** Papain-like protease, **NTD:** N-Terminal Domain, **RNP:** Ribonucleoprotein

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Conflict of Interest

The authors declare that there are no conflicts of interest.

Author Contribution

The first four authors contributed equally to this work.

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