Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Unsolicited Perspective

Repurposing existing drugs for the treatment of COVID-19/SARS-CoV-2 infection: A review describing drug mechanisms of action☆

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A B S T R A C T

The outbreak of a novel coronavirus (SARS-CoV-2) has caused a major public health concern across the globe. SARS-CoV-2 is the seventh coronavirus that is known to cause human disease. As of September 2020, SARS-CoV-2 has been reported in 213 countries and more than 31 million cases have been confirmed, with an estimated mortality rate of ~3%. Unfortunately, a drug or vaccine is yet to be discovered to treat COVID-19. Thus, repurposing of existing cancer drugs will be a novel approach in treating COVID-19 patients. These drugs target viral replication cycle, viral entry and translocation to the nucleus. Some can enhance innate antiviral immune response as well. Hence this review focuses on comprehensive list of 22 drugs that work against COVID-19 infection. These drugs include fingolimod, colchicine, N4-hydroxycytidine, remdesivir, methylprednisone, oseltamivir, icatibant, perphanizine, viracept, emetine, homoharringtonine, aloxistatin, ribavirin, valrubicin, famotidine, almitrine, amprenavir, hesperidin, biorobin, cromolyn sodium, and antibodies- tocilzumab and sarilumab. Also, we provide a list of 31 drugs that are predicted to function against SARS-CoV-2 infection. In summary, we provide succinct overview of various therapeutic modalities. Among these 53 drugs, based on various clinical trials and literature, remdesivir, nelfinavir, methylpredinosolone, colchicine, famotidine and emetine may be used for COVID-19.

Significance: It is of utmost important priority to develop novel therapies for COVID-19. Since the effect of SARS-CoV-2 is so severe, slowing the spread of diseases will help the health care system, especially the number of visits to Intensive Care Unit (ICU) of any country. Several clinical trials are in works around the globe. Moreover, NCI developed a recent and robust response to COVID-19 pandemic. One of the NCI's goals is to screen cancer related drugs for identification of new therapies for COVID-19. https://www.cancer.gov/news-events/cancer-currents-blog/2020/covid-19-cancer-nci-response?cid=eb_govdel.

1. Introduction

SARS-CoV-2 is a single-stranded enveloped RNA virus with a symmetrical nucleocapsid. SARS-CoV-2 targets cells via the viral structural spike (S) protein that binds to the angiotensin-converting enzyme 2 (ACE2) receptor to enter the host cell. Host type 2 transmembrane serine protease, (TMPRSS2) facilitates cell entry via the S protein [1]. Mechanistically, host proteases, especially TMPRSS2 cleave virus hemagglutinin to trigger internalization of the virus [2,3]. Once inside the cell, viral polyproteins that encode the replicase-transcriptase complex are synthesized and the RNA-dependent RNA polymerase replicates viral RNA. Consequently, structural proteins are synthesized leading to completion of assembly and release of viral particles [4–6]. So far, promising drugs target different viral enzymes including 3-chymotrypsin-like protease, papain-like protease, and RNA-dependent RNA polymerase. In addition, multiple drugs target viral entry and immune regulation pathways such as suppressing the cytokine storm mediated by the virus [7–9]. COVID-19 pandemic is forcing the scientific community to develop novel therapies immediately, because no vaccine is available yet. Moreover, synthesis and evaluation of new drugs from preclinical to phase III trials is a time-consuming process. Several drugs that are being considered for COVID-19 therapy have already been used in cancer therapies. Similar to cancer cells, virus infected cells enhance the synthesis of nucleic acids, proteins and increase energy metabolism. Thus, drugs that are blocking specific cancer cell pathways may be effective in blocking viral replication as well. Hence, in this review we provide a comprehensive analysis of some cancer drugs and others that can be repurposed for the treatment of COVID-19.

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2. SARS-CoV-2 primary mechanisms of cellular entry and infection

SARS-CoV-2 uses two major pathways to enter the cells. The virus can fuse with the plasma membrane to enter through the plasma membrane. The second route is by fusing with the endosomal membrane. Interestingly, coronavirus fusion depends on proteases in the virus local environment, which signifies the flexibility of coronavirus S proteins to respond to different signal proteins [10,11]. Mechanistically, cellular entry of coronaviruses depends on the binding of the transmembrane spike (S) glycoprotein (forms homotrimers) [12] to a specific cellular receptor and subsequent S protein priming by cellular proteases. In doing so, SARS-CoV-2 recruits ACE2 as a receptor for cellular entry. Studies have shown that binding affinity of S protein and ACE2 is correlated with viral replication rate and disease severity [1,13,14]. Similarly, SARS-CoV-2 entry also depends on TMPRSS2 protease activity and cathepsin B/L activity.

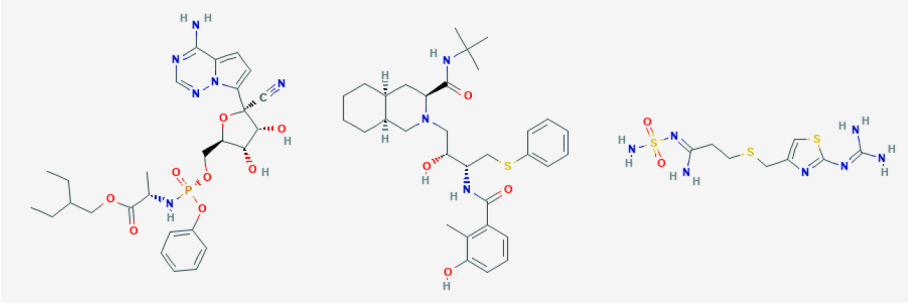
When there are no exogenous or membrane-bound proteases available, coronaviruses can utilize clathrin or non-clathrin-mediated endocytosis for cellular internalization [15]. Surprisingly, for SARS-CoV-2, it is still not clearly understood where exactly fusion of viral and cellular membranes occur. It is possible that fusion occurs at the cell plasma membrane, and this has been proposed as the major cellular entry pathway [10]. Two main scenarios have been proposed for viral endocytosis. Viral RNA can enter the cytosol via the fusion pore as viral coat proteins do not directly enter the cell. Alternatively, the complex of SARS-CoV-2 and cell receptor (ACE2) undergoes endocytosis, and subsequently fusion of the viral membrane with the luminal face of the endosomal membrane promotes translocation of RNA into the cytosol [16–18].

3. Drug candidates being repurposed as potential therapeutics for COVID-19 treatment

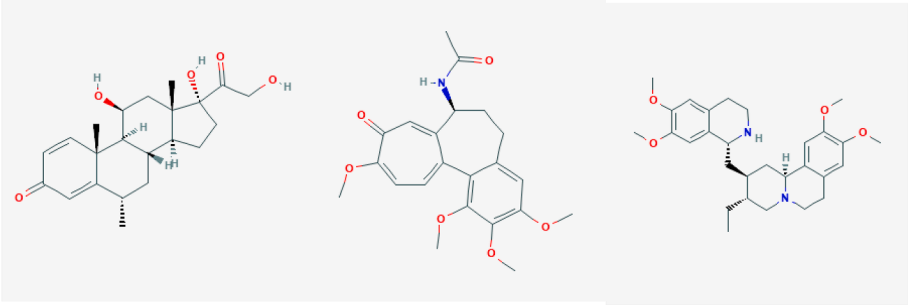
Although there are no approved specific drugs or vaccines that combat coronaviruses, there are several options that can theoretically fight the disease. These options include vaccines, monoclonal antibodies, oligonucleotide-based therapies, peptides, interferon therapies, and small-molecule drugs. Unfortunately, discovery of drugs that can have permanent cure for the disease may take several months to years. Based on crystallography data, some possibilities have been envisaged to control or prevent emerging infections of SARS-CoV-2. Protein structural data indicate that drug binding pockets in viral enzymes are conserved across SARS-CoV-2, SARS and MERS [19]. Thus, several investigators are trying to repurpose the existing drugs for MERS and SARS [20]. Although no effective drug treatments have been identified for COVID-19, several of them are being tested. These include drugs that are meant for cancers, HIV and malaria [20,21]. Since COVID-19 is spreading uncontrollably across the globe, it is essential to discover new drugs, and it can be accomplished by repurposing drugs that are discussed in this article. In this review, first, we will discuss drugs that are currently being investigated for their use in treating patients. In the next section, we will focus on the drugs that are predicted to inhibit COVID-19 based on docking approaches using crystal structure of proteins of SARS-CoV-2. We identified 22 drugs (Figs. 1 and 3) that are actively being pursued for testing/clinical trials. From these, we identified 6 drugs that are higly potent for COVID-19 infection (Fig. 1). Also we show another 31 drugs (Table 1) that are predicted to work against COVID-19 infection. The drugs that are currently considered for therapies against COVID-19 infection are targeted to different steps of viral infection including viral entry, translation, proteolysis, viral RNA replication, viral protein assembly and viral release.

3.1. Drug candidates that attack viral entry (membrane fusion endocytosis)

As shown in Fig. 3, SARS-CoV-2 enter the host cells by fusion and endocytosis. The following drugs potentially attack these steps.



Remdesivir Nelfinavir Famotidine



Methylprednisolone Colchicine Emetine

Fig. 1. List of drugs that are actively being considered for COVID-19 infection. The structures were collected from Kim et al [184].

Table 1
Mechanism of action for the drugs that were identified based on structural data.

Drug name	Mechanism/s	Ref
Ursolic acid	Ursolic acid (UA) is a pentacyclic triterpenoid carboxylic acid that has been reported to possess antioxidant and anti-tumor properties. These properties of UA have been attributed to its ability to suppress NF-κB activation to regulate the expression of inflammatory genes.	[185,186]
Saikosaponin A	Saikosaponin A up-regulates LXRα expression and has shown potent anti-inflammatory activity.	[187–189]
Mulberroside A	Mulberroside A decreases the expressions of TNF-α, IL-1β, and IL-6 and inhibits the activation of NALP3, caspase-1, and NF-κB and the phosphorylation of ERK, JNK, and p38, exhibiting anti-inflammatory and antiapoptotic effects.	[190]
Troxerutin	Troxerutin, also known as vitamin P4, can inhibit the production of reactive oxygen species (ROS) and repress ER stress-mediated NOD activation.	[191–193]
Verbascoside	Verbascoside acts as an ATP-competitive inhibitor of PKC and has antitumor and anti-inflammatory activity.	[194]
Corosolic acid	Corosolic acid is a protein kinase C inhibitor and exhibits anti-angiogenic and anti-lymphangiogenic effects.	[195,196]
cynaroside	Antioxidant and anti-inflammatory activity.	[197,198]
Orientin	Orientin has shown anti-inflammatory, anti-oxidative and anti-tumor activity.	[199]
ε-Viniferin	ε-Viniferin displays a potent inhibitory effect on the CYP activities with potent antioxidant ability.	[200,201]
Myricitrin	Antioxidant activity.	[202,203]
Baicalin	Baicalin reduces the expression of NF-κB. Baicalin treatment inhibits the increased expression of the proinflammatory factors including TLR2/4, MyD88, p-NF-κB, and p- IκB, as well as increase the expression of IκB protein, an NF-κB inhibitor	[204,205]
Corynoline	Corynoline is a reversible and noncompetitive acetylcholinesterase (AChE). Corynoline exhibits anti-inflammatory activity by activating Nrf2.	[206,207]
Protostemonine	Protostemonine is an active alkaloid and has anti-inflammatory effects on asthma and gram-negative bacteria-induced acute lung injury.	[207,208]
Amygdalin	Amygdalin has antitumor activity. Amygdalin inhibits NF-kβ and NLRP3 signaling pathways, and consequently has anti-inflammatory effect by reducing the expression of proinflammatory cytokines such as pro-IL-1β.	[209]
Paeoniflorin	Anti-inflammatory activity.	[210]
Taiwanhomoflavone A	Anti-inflammatory properties have been reported. Also, a SARS-CoV-2 MPro inhibitor with strong binding ability to other targets of SARS-CoV-2, like RdRp and hACE-2.	[203,211]
Lactucopicrin 15-oxalate	Lactucopicrin has reported to be antimalarial compounds. Also, a SARS-CoV-2 MPro inhibitor with strong binding ability to other targets of SARS-CoV-2, like RdRp and hACE-2.	[203,212]
Nympholide A	A SARS-CoV-2 MPro inhibitor with strong binding ability to other targets of SARS-CoV-2, like RdRp and hACE-2.	[203,213]
Saquinavir	Saquinavir has been reported to inhibit invasion and angiogenesis via reducing of MMP expression and activity. Also, saquinavir could increase in MDR1 mediated drug-efflux to exert anti-HIV activity.	[214–216]
Phyllaemblicin B	Antiviral effects of Phyllaemblicin B are due to suppression of virus induced apoptosis. A SARS-CoV-2 MPro inhibitor with strong binding ability to other targets of SARS-CoV-2, like RdRp and hACE-2.	[203,217]
Cassameridin	Moderate antifungal activity.	[203]
Chrysanthemin	Antitumor effects via apoptosis induction, caspase signaling pathway and loss of mitochondrial membrane potential. Also, a SARS-CoV-2 MPro inhibitor with strong binding ability to other targets of SARS-CoV-2, like RdRp and hACE-2.	[203,218]
Scalarane	Anti-inflammatory role.	[219]
Astragaloside A	Antioxidant, anti-apoptotic and antivirus effects.	[220]
Ilexgenin A	Anti-inflammation and anti-angiogenesis effects through inhibition of STAT3 and PI3K pathways and suppressing the inflammatory cytokines including TNF-α and IL-6 levels.	[221]
Rutin	Rutin has shown to have antioxidant, anti-inflammatory, anti-allergic, anti-angiogenic and antiviral properties.	[222–224]
Glycyrrhizin (Glycyrrhizic acid)	Glycyrrhizic acid acting as a direct HMGB1 antagonist, with anti-tumor, anti-diabetic activities.	[225–227]
Dipsacoside B	Anti-inflammatory effects	[228]
Puerarin	Puerarin has been shown to be a 5-HT2C receptor antagonist. Puerarin also inhibits the expression of LPS-induced iNOS, COX-2 and CRP proteins through suppression of p65NF-κB nuclear translocation	[229]
Morusin	Morusin acts as an antitumor, antioxidant, and anti-bacteria drug. Mechanistically, Morusin inhibits NF-κB and STAT3 activity. Morusin could also suppress breast cancer cell growth *in vitro* and *in vivo* through C/EBPβ and PPARγ mediated lipoapoptosis. In colorectal cancer, Morusin significantly inhibits the growth and clonogenicity of human colorectal cancer cells and suppressed the NF-κB activation. In addition, Morusin induced apoptosis in human prostate cancer cells by suppressing STAT3 activity.	[230–232]
Polyphyllin I	Polyphyllin I has been demonstrated to have strong anti-tumor activity in human non-small lung cancer cells. Polyphyllin I is an activator of the JNK signaling pathway and is an inhibitor of PDK1/Akt/mTOR signaling in human gastric carcinoma cells. Polyphyllin I induce autophagy, G2/M phase arrest and apoptosis in human glioma cells.	[233–235]

3.1.1. Aloxistatin (E-64D)

Aloxistatin, is a cysteine protease inhibitor for calpains and cathepsins, and has an important regulatory role in neurodegeneration and cancer therapy. Cathepsin B and L could be considered potential biomarkers for cancer. Catalytic activity of these two proteases lead them to function as cell regulatory enzymes [22]. Moreover, calpain inhibition by aloxistatin has shown promising results in cataracts treatment. Aloxistatin inhibits hepatitis virus replication in a mouse model [23]. Mechanistically, this drug irreversibly forms a thioether bond thus modifying the active site of Cysteine. Nucleophilicity of the Cysteine's active site helps aloxistatin to act selectively toward Cysteine proteases [22]. Aloxistatin inhibits lung cancer metastasis as well [24]. In addition, aloxistatin reduces cellular entry of SARS-CoV-2 by 92.3% since cathepsin L is a necessary factor for SARS-CoV-2 cell entry [25]. Further structural analysis indicated an interaction of membrane permeable aloxistatin with the active site of the SARS-CoV-2 main protease (M^{pro}),

which is important in making nonstructural protein (NSP). Interestingly, it also binds to papain-like proteases with less specificity [26]. In summary, aloxistatin is a potential drug for COVID-19 that could potentially affect SARS-CoV-2 proteases.

3.2. Drug candidates that attack SARS-CoV-2 viral entry (membrane fusion)

3.2.1. Viracept (nelfinavir mesylate)

Viracept is an anti-retroviral drug that selectively inhibits human immunodeficiency virus (HIV) protease. Mechanistically, viracept prevents cleavage of gag-pol viral polyprotein that results in release of immature and noninfectious virions [27]. Previous results with SARS and MERS CoV have shown that Spike (S) glycoprotein is a major determinant of virus infectivity and immunogenicity [28]. Recent studies indicated the potential efficacy of viracept against SARS CoV-2 [29,30]. Viracept inhibits S-n and S-o-mediated cell fusion resulted by SARS-CoV-2 Spike (S) glycoprotein [29,30]. This evidence suggests that viracept blocks SARS-CoV-2 transfer and spread from cell-to-cell and making it more sensitive to neutralizing antibodies. Interestingly, viracept inhibits growth of cancer cells as well [31,32].

3.3. Drug candidates that affect viral RNA replication and translation

Viral RNA is released into the cytoplasm, and translation of genomic RNA yields very large polypeptide, which undergoes proteolysis to generate RNA-dependent RNA polymerase (RDRP). Further, through the action of RNA polymerase, other proteins are made. Coronavirus has four structural proteins, including spike (S), membrane (M), envelope (E) and nucleocapsid (N). M is the most abundant structural protein. RNA replication and translation can be blocked by the drugs below.

3.3.1. β-D-N4-hydroxycytidine (NHC, EIDD-1931)

NHC is an orally bioavailable ribonucleoside analog with a broad-spectrum of antiviral activity against various unrelated RNA viruses. Cytidine analogs of NHC inhibits replication of Ebola virus (EBOV) [33]. Also, NHC blocks replication of hepatitis C virus (HCV) replicon [34]. Similarly, NHC inhibits human coronavirus [35], chikungunya virus [36], respiratory syncytial virus (RSV), hepatitis C virus, norovirus, influenza A (IAV) and B viruses, and Ebola virus [37]. Antiviral activity of NHC has been shown to be against human α-CoV HCoV-NL63, as well as β-CoV SARS-CoV [30,32]. NHC is effective against Venezuelan equine encephalitis virus (VEEV) as well. Most VEEV virions released from NHC-treated cells showed mutated viral genomes, which cannot undergo replication and block the resistance to NHC [38]. In addition, NHC inhibits WT murine hepatitis virus (MHV) and MERS-CoV with minimal cytotoxicity [39]. Therapeutic administration of NHC improved pulmonary function, reduced virus titer and body weight loss in mice. Mechanistically, decreased MERS-CoV is associated with increased transition mutation frequency in viral but not host cell RNA resulting in lethal mutagenesis in CoV [39]. Altogether, these reports indicate that increased introduction of transition mutations in viral genomes after treatment with NHC, as well as a high genetic barrier to resistance, and these both characteristics of NHC might be helpful for COVID-19 treatment.

3.3.2. Remdesivir (GS-5734)

Remdesivir, is a nucleoside prodrug or nucleotide analog with potential efficacy against multiple viruses with sub micromolar range dose of administration [40,41]. Nucleoside analogs (NAs) have been considered the most promising broad-spectrum anti-viral RNA-dependent RNA polymerase (RdRp) inhibitors and they have been effective in the treatment of multiple viral infections. Targeting viral replication within the host cell is one of the best anti-viral therapeutic approaches. These antiviral agents target viral replication enzymes. This could be due to their function as nucleoside analogs during viral replication that result in deadly mutations. Since many viruses depend on RdRp activity, remdesivir has good efficacy against a broad-spectrum of viruses including coronaviruses, SARS, MERS and CoVs [42–44]. In the case of SARS-CoV-2, it is shown that remdesivir inhibits viral replication, highlighting the importance of remdesivir for treatment of CoV infections [45].

Mechanistically, remdesivir functions as an RdRp binding substrate that replaces ATP during polymerization (Fig. 2). Remdesivir (GS-5734) enters cells and metabolized into an adenosine nucleotide analog (GS-441524). Phosphorylation of GS-441524 will make a nucleoside triphosphate (NTP) to utilize as a substrate for RdRp [46]. Originally, it was shown that ATP could be the main substrate for SARS-CoV RdRp [47]. However, NTPs incorporation into viral replication machinery replaces ATP resulting in inefficient elongation, a process known as “chain termination” [42,47]. In addition, NTPs do not show a significant inhibition for both human RNA Pol II and human mitochondrial RNA polymerases [48]. This possible mechanism of action has been detected for Nipah virus (NiV) RdRp as well. Despite potential efficacy of remdesivir, its application for CoV is challenging because of exonuclease activity of CoV nsp14 domain. This proofreading activity can remove the incorporated NTPs from viral RNA [49–51]. Three coronavirus (MERS-CoV, SARS-CoV, and SARS-COV-2) RdRp complexes have specific termination site at position i + 3, which means RNA synthesis is stopped after the addition of three more nucleotides, and this is often referred to as delayed chain-termination. However, higher concentration of natural nucleotide pool can dominate this RdRp-mediated termination. In addition, it is proposed that additional three nucleotides are necessary for providing protection against 3′-5′ exonuclease activity of nsp14 [52]. Studies on remedisivir recognition, incorporation and excision by nsp12 and nsp14 have provided key insights for new NA drug development [53]. Remdesivir is the first FDA approved drug for treatment of hospitalized 2019 coronavirus disease (COVID-19) patients. https://www.fda.gov/media/137564/download.

Several clinical trials are being done worldwide to examine remedesivir function on COVID-19 patients. Gilead Sciences initiated two phase III clinical studies to evaluate efficacy of remdesivir on 1000 COVID-19 patients from all around the world. This study analyzes remdesivir efficacy and safety in two categories, a 5-day and a 10-day remedisivir regimen [54]. It was reported that compassionate use of remdesivir for patients with severe COVID-19 has 68% clinical improvement, however, 13% of patients died. Increased hepatic enzymes, diarrhea, rash, renal impairment, and hypotension were among the common adverse events in 60% of cases. Since this was done in a small cohort, more comprehensive studies must be considered to confirm clinical benefit of remdesivir in patients with severe COVID-19 [55]. A randomized, double-blind, placebo-controlled, multi-center trial from10 hospitals was done on 237 severe COVID-19 patients. The participants were assigned 2:1 ratio to receive either intravenous administration of remdesivir (200 mg of remdesivir on the first day followed by 100 mg per day during a 10-day medication) or the same conditions of placebo. Patients who received remdesivir showed a faster clinical improvement than the other group. Nevertheless, remdesivir treatment was stopped in 12% of cases because of the adverse results which were still less than the results of patients receiving placebo (12% vs 5%) [56]. Despite conventional antiviral drugs that have better efficacy at early stage of infection, remdesivir has been shown to be a potent drug in treatment of late stage COVID-19 patients [57].

3.3.3. Emetine

Emetine is traditionally used as an emetic and expectorant drug [58]. Its mechanism of action is through inhibition of ribosomal protein synthesis [58]. Emetine inhibits aminoacyl-sRNA transfer reaction, preventing its incorporation into polypeptide bonds [58]. A 2018 study reported that emetine inhibits Zika and Ebola virus infections by suppressing viral replication and subsequently decreasing viral entry [59]. Another study also showed that emetine and other alkaloids extracted

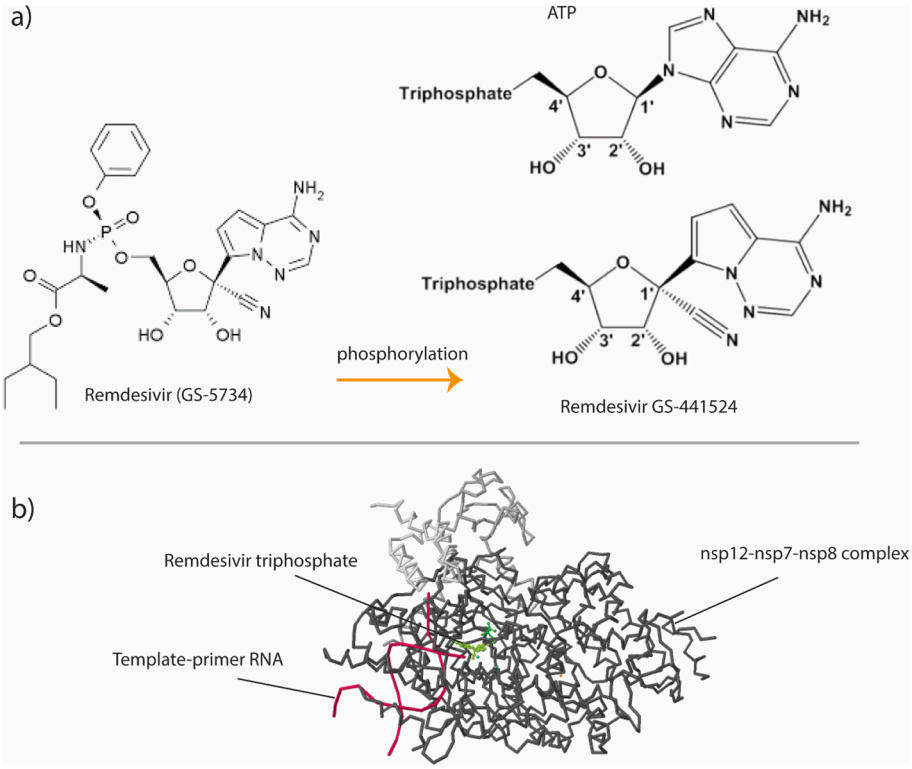


Fig. 2. Remdesivir (GS-5734) modification (phosphorylation) into the adenosine nucleotide analog (GS-441524). Phosphorylation on GS-441524 will make a nucleoside triphosphate (NTP) that can be utilized as a substrate for RNA-dependent RNA polymerase (RdRp) **(a)**. ATP could be the main substrate for NSP12 of SARS-CoV RdRp. NTPs incorporation into the viral replication machinery replaces ATP and finally results in inducing inefficient elongation **(b)**.

from ipecac root are potent inhibitors of HIV reverse transcriptase (RT) [60]. Furthermore, emetine shown to have antiviral activity against human cytomegalovirus and rabies virus [61,62] and has anticancer activity against various solid tumors [63]. Based on these viral inhibitory properties, emetine is now considered one of the drug candidates against COVID-19 infection. Interestingly, emetine inhibits SARS-CoV-2 replication *in-vitro* with EC_{50} of 0.46 μM and also has good synergistic effect with FDA approved remdesivir [64]. Thus, this drug will be a good candidate to repurpose for SARS-CoV-2 infection.

3.3.4. Ribavirin

Ribavirin (l-β-D-ribofuranosyl-l,2,4-triazole-3-carboxamide) is an antiviral agent. Ribavirin works against infection of several viruses including influenza virus, Lassa fever virus, Hantaan virus, and human immunodeficiency virus (HIV). Ribavirin received its FDA approval in 1986 as an aerosol for respiratory syncytial virus infected infants [65]. Also, ribavirin treatment is beneficial for acute leukemia patients [66]. Structurally, ribavirin is a guanosine nucleoside analog and resembles other purines including inosine and adenosine. Furthermore, ribavirin is therapeutically used in humans in combination with interferon-α in hepatitis C virus (HCV) infection. Ribavirin monophosphate interferes with viral RNA replication by inhibiting cellular protein inosine monophosphate dehydrogenase (IMPDH) [67]. IMPDH mediates inosine to GTP conversion and increases the expression of histone genes and E2F transcription factor, and thus controls cell proliferation [68]. Administration of ribavirin reduces intracellular GTP levels that disrupts RNA replication of virus [67,68]. Viral RNA-dependent RNA polymerase can recruit ribavirin-triphosphate as a GTP analog or an ATP analog. However, ribavirin treatment in HCV weakly inhibits polymerase *in vitro*. Another possible antiviral mechanism for ribavirin is that it promotes lethal mutagenesis in viral RNA [67,69]. A plethora of studies also proved that ribavirin can increase host cell immunity by inducing T-helper 1 (Th1) response (increased IFN-γ secretion). This response is through suppression of IL-10 secretion by T-reg cells [70,71]. This drug has also been considered a combinational therapeutic with lopinavir/ritonavir and/or interferon-β1b against SARS-CoV-2 infections [72].

3.4. Drug candidates that only affect viral translation

3.4.1. Valrubicin

Valrubicin is an N-trifluoroacetyl 14-valerate derivative of anthracycline doxorubicin, and known to have anti-tumor activity. However, valrubicin is less effective compared to doxorubicin [73] in human bladder cells. Valrubicin is an anthracycline chemotherapy drug and its mechanism of action is histone loss, thus disruption of DNA repair process in tumor cells [73]. Valrubicin intercalates with dsDNA [74,75]. Valrubicin mediates formation of DNA cleavable complexes and inhibit topoisomerase II activity leading to defects in DNA replication and transcription. Valrubicin has antiangiogenic function by binding to proteasome complex [76]. In addition, valrubicin mediates tumor cell apoptosis through binding to PKC and regulating downstream pathways [77]. Valrubicin can bind to and inhibit SARS-CoV-2 $M^{pro.}$ and proteases [78,79]. Thus, valrubicin is a good candidate drug for COVID-19.

3.4.2. Perphenazine

Perphenazine (PPZ) is an antipsychotic drug classified as a piperazinyl phenothiazine. Phenothiazines, including PPZ, suppress T cell acute lymphoblastic leukemia [80]. Perphenazine directly binds to protein phosphatase 2A, a well-conserved serine/threonine phosphatase, and induces dephosphorylation of ERK1/2 and Akt that in turn trigger apoptosis. So far, there are two clinical trials reported on this drug. First, a phase IV trial, investigated the effectiveness of PPZ (in combination with other antipsychotic drugs) in children and adolescents who have gained weight on their antipsychotic medications [NCT00806234]. Second trial investigated safety and efficacy of PPZ on schizophrenia patients [NCT00802100]. Although PPZ is popularly

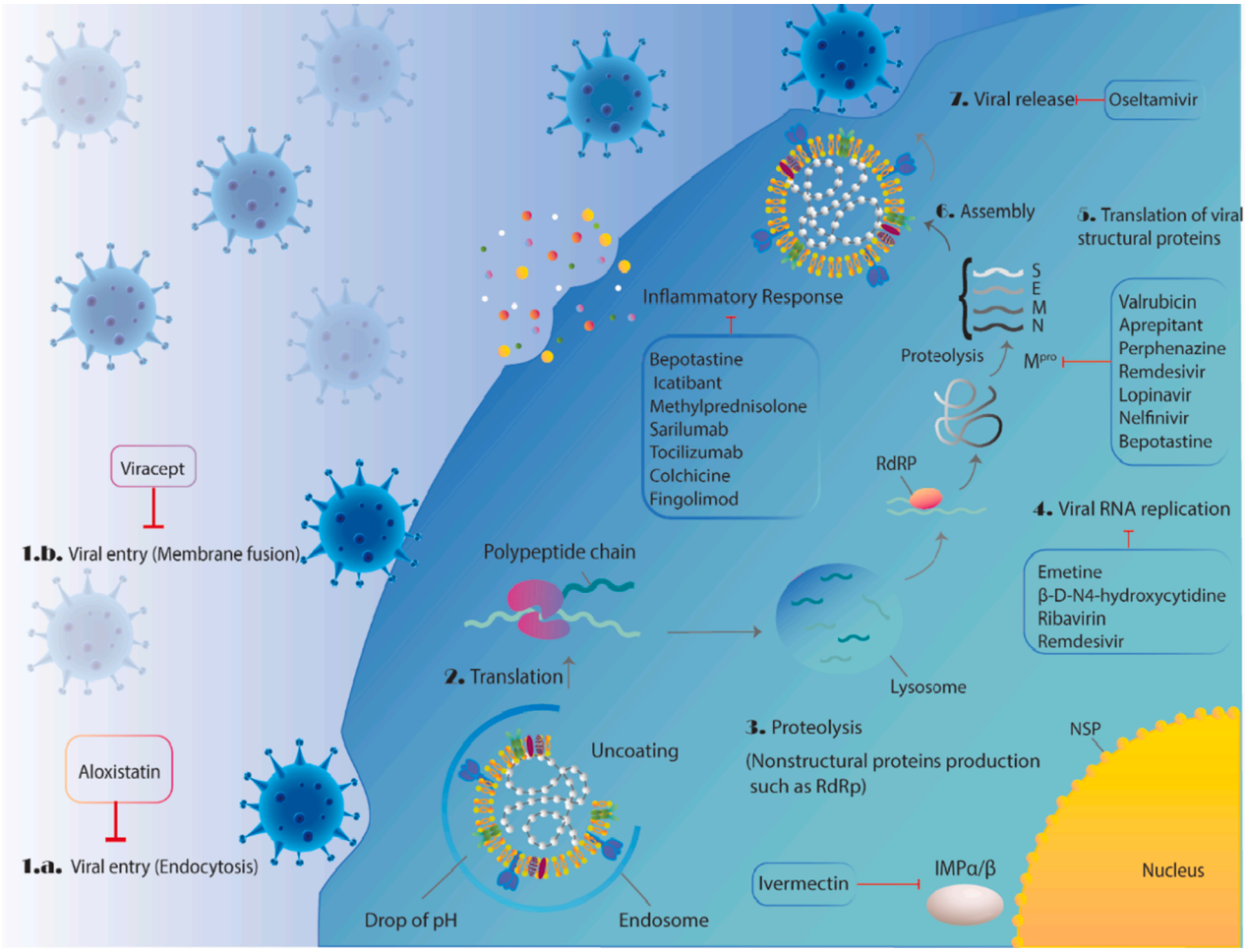


Fig. 3. Schematic overview of the potential therapeutic drugs undergoing clinical trial or have been proposed against SARS-CoV-2 virus with their mechanism of action in different main steps of CoV life cycle in host cells including, viral endocytosis inhibitors, virus–cell membrane fusion inhibitors, the viral RNA-dependent RNA polymerase or replication inhibitors, viral protease inhibitors, and inflammatory response modulators.

known as an antipsychotic drug, currently, it is also being investigated for possible antiviral effect against COVID-19. PPZ is one of the compounds predicted to be able to bind to the amino acid pocket site of 2019-nCoV and interferes its function [81]. Thus, this drug is a good candidate drug for COVID-19 infection.

3.4.3. Homoharringtonine

Homoharringtonine (HHT) is one of the alkaloid compounds extracted from *Cephalotaxus harringtonia* plant [82]. Also another product extracted from *Cephalotaxus fortunei* plant, a related species of *Cephalotaxus harringtonia*, is widely used in Chinese folk medicine for its antiparasitic, anti-inflammatory and antineoplastic effects [83]. HHT and harringtonine are the main alkaloids isolated from *Cephalotaxus harringtonia*. HHT can be distinguished from harringtonine due to the presence of methylene group on its side chain [83]. Though both alkaloids have similar biological and therapeutic potential, HHT has better extraction yield [83,84]. HHT has a positive effect in treatment of chronic myelogenous leukemia (CML), acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) [85,86]. Mechanistically, HHT inhibits translation of proteins through binding and interacting with the A-site in the peptidyl transferase of the ribosome [83,87,88]. HHT inhibits SARS-CoV-2 replication *in vitro* and thus the drug is being investigated for potential therapeutic function for COVID-19 infection [89].

3.5. Drug candidates that affect COVID-19 related inflammatory response

It is known that SARS-CoV-2 infects airway alveolar epithelial, vascular endothelial cells, and macrophages. SARS-CoV-2 infection results in aggressive inflammation and this is due to increased secretion of several interleukins and interferons. The below described drugs inhibit various inflammatory responses.

3.5.1. Fingolimod

Fingolimod (FTY720, Gilenya), is a sphingosine analog and a sphingosine 1-phosphate (S1P) receptor modulator. Fingolimod is the first FDA-approved drug for multiple sclerosis (MM)- a CNS related disease results in oligodendrocyte (OLG) loss. Fingolimod has been shown to be an effective drug for various cancers [90]. Fingolimod is phosphorylated by sphingosine kinase 1 and 2 (SphK1 and SphK2), and binds as an analog of S1P to the G-protein coupled S1P receptor subtypes S1P1, S1P3, S1P4, and S1P5 [91,92]. Fingolimod showed decreased antiviral T-cell response against varicella-zoster virus (VZV) in multiple sclerosis patients [93]. Also, fingolimod is considered a potential therapeutic drug against SARS-CoV-2. Coronaviruses can spread into the CNS and fingolimod is capable of preventing T-cell penetration into the CNS and regulates blood–brain barrier (BBB) permeability. However, some reports show that there is no correlation between SARS-CoV-2 infection and lymphocyte levels in fingolimod treated cases [94,95]. Thus, this drug needs a further evaluation for COVID-19 patients.

3.5.2. Colchicine

Colchicine, a natural product extracted from a plant named genus Colchicum (autumn crocus), has been used for inflammatoy arthritis and gout for centuries [96]. Colchicine disrupts many inflammation related cellular pocesses including inflammosome activation, inflammatory cell chemotaxis, leukotrienes production, cytokine production and phagocytosis. Colchicine inhibits polymerization of tubulin and microtubule assembly. Since these pathways are involved in many inflammatory diseases, colchicine could be a potential therapeutic candidate for further investigation [97]. Colchicine inhibits tumor growth by inducing apoptosis [98]. The NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasome is an intracellular sensor capable of recognizing a plethora of pathogenic microbial motifs. It can trigger an inflammatory type of cell death through caspase-1 activation and its related secretion of pro-inflammatory cytokines, IL-1β and IL-18 [99,100]. In addition, NLRP3 causes cellular stress, which is a part of immune response in autoimmune disorders, neurodegenerative diseases and tumor development. NLRP3 is expressed in immune cells specially antigen presenting cells (APCs) such as macrophages, and is upregulated through TLR-induced NF-κB activation [101]. Recent studies indicate that colchicine is a potential drug for anti-inflammatory response via NLRP3 inflammasome and cytokine storm suppression in COVID-19 patients [102,103].

3.5.3. Tocilizumab

Tocilizumab is a monoclonal antibody that has many therapeutic functions. Interleukin-6 (IL-6) is a pleiotropic cytokine with known multiple functions such as inflammation, and oncogenesis. Binding of IL-6 to IL-6 receptor (IL-6R) induces homodimerization and recruitment of glycoprotein 130 (gp130), which leads to activation of downstream signaling. Emerging evidence suggests that high levels of IL-6 are correlated with poor prognosis in breast cancer patients. IL-6 appears to play a critical role in growth and metastasis of breast cancer cells, renewal of breast cancer stem cells (BCSCs), and drug resistance of BCSCs, making anti-IL-6/IL-6R/gp130 therapies promising options for treatment and prevention of breast cancers [104]. Recent reports showed anticancer effects of tocilizumab in a colon cancer xenograft model and effects of combination therapy of tocilizumab and interferon-alpha against renal cell carcinoma [105]. Tocilizumab also inhibited tumor growth of trastuzumab resistant breast cancer cells [106]. Cytokine storms mediated by overproduction of proinflammatory cytokines have been observed in a large population of critically ill patients infected with COVID-19. [107–109]. The most recent data from China suggested that IL-6 is one of the most important cytokines involved in COVID-19-induced cytokine storms (REF). IL-6 has been shown to regulate immune response, inflammation and oncogenesis. Mechanistically, IL-6 binds to IL-6R (IL-6 receptor) and gp130 to induce homodimerization of gp130. This homodimerization phosphorylates tyrosine residues (Tyr759) in the cytoplasmic domain of gp130. Activated gp130 induces phosphorylation of JAK1, JAK2 and Tyk2 result in activation of STAT1 and STAT3. This JAK- mediated phosphorylation of tyrosine residues in gp130 activates two downstream signaling pathways including JAK/STAT and ERK/MAPK. Consistent with this, soluble form of IL-6R (sIL-6R) also binds to IL-6R and forms a receptor complex with gp130 to further activate these signaling pathways [110]. IL-6 also plays a key role in T helper cell differentiation by regulating balance between IL-17 (T helper 17 cells) and regulatory T-cells (T-reg) [111]. Tocilizumab (TCZ) is an anti-human recombinant monoclonal antibody belongs to the immunoglobulin G1K subclass that binds to both soluble and membrane-bound interleukin 6 receptors (IL-6R) [112]. Tocilizumab has been approved by the FDA for rheumatoid arthritis (RA). In addition, tocilizumab has been shown to be a potential option for other inflammatory diseases, such as Castleman's disease [113]. Since tocilizumab is an antibody for IL-6 receptor and potential alleviator of inflammatory response, this drug has been tried in COVID-19 patients and observed improved clinical outcome [114].

3.5.4. Sarilumab

Sarilumab, a human anti–IL-6R monoclonal antibody that has been used for rheumatoid arthritis and ankylosing spondylitis [113]. Similar to tocilizumab, sarilumab blocks IL-6-induced inflammatory signaling cascade by binding to both IL-6R and sIL-6R [115]. Also, sarilumab inhibits growth of xenograft tumors of DU145 (prostate), Calu3 (lung), and A549 (lung) either as a single agent or in combination with VEGF blocker aflibercept [116]. Sarilumab, like tocilizumab, binds specifically with high affinity to a unique epitope on IL6R (both membrane-bound and soluble IL-6R), and effectively blocks both cis- and transactivation of IL-6 signaling. Regeneron, a pharmaceutical company started a clinical trial of sarilumab on COVID-19 patients and the final data yet to be published.

3.5.5. Methylprednisolone

Methylprednisolone and its derivatives, methylprednisolone acetate succinate, and methylprednisolone sodium, are synthetic glucocorticoids used mainly as anti-inflammatory or immunosuppressive agents. Methylprednisolone has been suggested for palliative therapy for terminal cancer patients and it is five times more potent in its anti-inflammatory activity compared to hydrocortisone (cortisol) [117]. Methylprednisolone's mechanism of action is through its binding to intracellular glucocorticoid receptor. Upon binding, this complex translocates to the nucleus, where it interacts with specific DNA sequences, resulting in suppression of downstream target genes. The methylprednisolone-glucocorticoid receptor complex binds to and blocks promoter sites of proinflammatory genes [118]. This leads to inhibition of synthesis of inflammatory cytokines by blocking the function of transcription factors such as nuclear factor-kappa-B (NF-kB) [119]. Presently, methylprednisolone is being tested in a number of COVID-19 related clinical investigations. A retrospective cohort study of 201 COVID-19 patients (median age-51 years), who developed acute respiratory distress syndrome, indicated that treatment with methylprednisolone decreased mortality [120]. Furthermore, methylprednisolone treatment resulted in good recovery of COVID-19 post-transplant patients with compromised immune systems [121,122].

3.5.6. Icatibant (HOE-140, JE-049)

Icatibant is a highly specific competitive antagonist for the bradykinin type 2 (B2) receptor. It is an analog of bradykinin and is composed of 10 amino acids, five of which are synthetic and resistant to degradation of ACE2. These amino acids are needed to inactivate Des-Arg9-bradykinin (DBK), the potent ligand of bradykinin receptor type 1 (B1) [123]. The problem of pulmonary edema of COVID-19 patients could be due to activation of B1 and B2 receptors in lungs. ACE2 inactivates the ligands of B1 and thus, lung environment is prone for local vascular leakage leading to angioedema [124]. *In vitro* studies have confirmed that icatibant is a highly selective competitive antagonist for the B2 receptor [125]. In addition, icatibant blocks vascular functions of bradykinin *in vivo* [126]. Bradykinin plays a major role in developing pulmonary edema in COVID-19 patients due to inflammation caused by Des-Arg(9)-bradykinin. Thus, it is suggested that icatibant might be helpful in suppressing pulmonary edema and, thereby, will improve the clinical outcomes in COVID-19 patients [127–129].

3.6. Drug candidates that affect viral release

Viral assembly occurs in vesicles and the virus is exocytosed by fusion of virus containing vesicles with the plasma membrane and Ostelmivir blocks this step.

3.6.1. Oseltamivir

Oseltamivir is an ethyl ester oral prodrug against neuraminidase (an enzyme which is expressed on the viral surface) of influenza A and B virus. This drug is approved for treatment and prophylaxis of influenza A and B [130]. Once it enters cells, oseltamivir converts into an active

form (GS4071) [130]. Mechanistically, lipophilic side chain on GS4071 binds to the hydrophobic pocket of the active site of the viral neuraminidase. As a result, it impairs the ability of neuraminidase to cleave sialic acid residues on the surface of the infected host cells and subsequently inhibits release of progeny virions from the infected cells. Inhibition of virions suppresses viral movement within the respiratory tract [130]. The substrate binding domain of influenza neuraminidase is highly conserved due to its critical role in viral replication. However, it is possible that resistant virus may be developed, and the resistance could be due to mutations in the viral neuraminidase or hemagglutinin or both. For example, clinical isolates from treated patients have been shown to be resistant [130–133]. Surprisingly, oseltamivir enhances breast tumor growth [134]. Recently, oseltamivir was administered for COVID-19 in china, either with or without antibiotics and corticosteroids combination [135]. In addition, oseltamivir is also used in a clinical trial with several combinations with chloroquine and favipiravir [136].

4. Other drug candidates that are known to have good therapeutic effect against SARS-CoV-2 infection, but their mechanisms of action are unknown

4.1. Famotidine

It is a competitive antagonist for histamine H2-receptor. Famotidine acts as an inhibitor for gastric secretion. The preventive effect of famotidine on gastric lesions is attributable not only to suppression of acid secretion but to activation of gastric mucosal defensive mechanisms [137,138]. Orally delivered famotidine has shown improved outcomes in COVID-19 patients [139,140].

4.2. Almitrine

This drug is a peripheral chemoreceptor agonist, inhibits selectively Ca2 + -dependent K + channel. *In vivo* data showed that Almitrine could enhance hypoxic pulmonary vasoconstriction and enhanced overall ventilation/perfusion ratio [141]. It has been hypothesized that intravenous almitrine will reduce the need for ventilators patients with COVID-19 related pneumonia https://clinicaltrials.gov/ct2/show/NCT04357457.

4.3. Amprenavir

This drug has been shown to have an HIV protease inhibitory effect and is used against HIV infection. In addition, amprenavir suppressed hepatocarcinoma cell growth *in vivo* through inhibition of angiogenesis [142,143]. Amprenavir forms an inhibitor-enzyme complex with HIV protease preventing the normal maturation process of HIV and formation of mature infectious virions. Amprenavir inhibits both HIV-1 and HIV-2 *in vitro*; however, the FDA approval is only against HIV-1 [144]. Unpublished reports based on bioinformatics analysis indicate that amprenavir may be a good drug for treatment of COVID-19
https://arxiv.org/ftp/arxiv/papers/2003/2003.04524.pdf.

4.4. Cromolyn sodium

Cromolyn sodium functions as a GSK-3β inhibitor. Cromolyn sodium inhibits release of initiators of inflammation, mediated by specific antigens from mast cells. Cromolyn sodium may also inhibit the activity of other cell types that produce inflammation [145–147]. Similar to cancer cells, SARS-CoV-2 activates NFκB pathway and inhibitors of NFκB reduces inflammation associated with viruses. Cromolyn sodium inhibits NFκB in pancreatic cancer patients [148] and inhibits inflammation in several diseases [149]. Thus, cromolyn sodium may be effective in decreasing inflammation and cytokine storm in COVID-19 patients.

4.5. Hesperidin

This drug functions as an anti-inflammatory drug. For instance, hesperidin is shown to reduce inflammation as well as inflammatory pain via reduction of cytokine production, NF-κB activity, and oxidative stress. Anticancer effects of hesperidin are associated with its antioxidant and anti-inflammatory activities. Hesperidin inhibits tumor cell metastasis, angiogenesis, and chemoresistance [150,151]. Unpublished molecular docking studies indicate that hesperidin may bind to multiple regions of SARS-CoV-2 (spike protein, ACE2 and proteases) https://www.drkarafitzgerald.com/2020/04/17/8-potential-natural-anti-avoid-compounds/, and thus hesperidin is a potential drug of COVID-19 therapies. Similar to hesperidin, Biorobin binds to multiple regions of SARS-CoV-2 [152], and hence suggested to be a good drug for COVID-19.

5. Discussion

COVID-19 pandemic is an untimely global healthcare challenge that requires timely social, environmental, and therapeutic interventions to halt or minimize the growing number of casualties. Globally, there are more than 31 million documented cases and approximately 960,000 reported deaths from COVID-19 as of September 2020. While these numbers are steadily increasing, there remain a few established standards of care and therapeutic options available. To date, there is still no available vaccine, although there are several options in various clinical trial stages. To effectively combat the rapid spread of SARS-CoV-2 infection and transmission between people, urgent clinical and therapeutic intervention must be put in place. One can search for a potent and reliable therapy for COVID-19 using the knowledge of drugs that are being used to treat other diseases. Herein, we have described mechanisms of action of leading antiviral, anticancer, and other relevant drugs that are currently being repurposed for the treatment of SARS-CoV-2 infection and COVID-19. In addition, we also briefly described drugs that have potential anti-SARS-CoV-2 effects, but their mechanisms of action are yet to be elucidated. The second category of drugs were identified using docking strategies based on crystal structure of SARS-CoV-2 proteins and potential binding pockets of drugs on these proteins. In this review, we focused on describing drug candidates that are presently being repurposed and how these therapeutic compounds can inhibit SARS-CoV-2 cellular entry, replication, translation of structural proteins and viral release.

Host cell entry is the first step in the life cycle of SARS-CoV-2 [153], and thus, this process constitutes a target for therapeutic inhibition. SARS-CoV-2 cellular entry occurs either through endocytosis or through fusion with host cell receptors [15]. Viral entry is an important determinant of coronavirus infection and COVID-19 pathogenesis. Therefore, drug candidates with the potential to inhibit SARS-CoV-2 entry into cells are in urgent demand. Here, we report that arbidol and viracept are drug candidates that have the potential to inhibit SARS-CoV-2 entry through membrane fusion while aloxistatin, chloroquine and hydroxychloroquine (HCQ) are capable of inhibiting viral entry through endocytosis [154–156]. Research studies have reported puzzling and sometimes controversial findings on the mechanisms by which SARS-CoV-2 uses for entry into cells. It has been shown that entry of SARS-CoV-2 into lung cells occur by fusion at the plasma membrane [15], whereas entry into non-lung cells such as Vero E6 cells occurs through spike mediated fusion of viral membranes with endosome membranes [1]. Additional studies have reported that HCQ does not inhibit SARS-CoV-2 infection of lung cells [157], despite it being a robust inhibitor of SARS-CoV-2 entry into Vero E6 cells which typically occurs via the endosome route [158]. Therefore, this implies that HCQ might have a cell-specific effect. In conclusion, more research studies will have to be conducted on HCQ before its clinical use can be encouraged.

Another molecular mechanism that enhances SARS-CoV-2 infection process is viral replication. The replication of the viral genome within

the infected cells is a critical phase of the SARS-CoV-2 life cycle [159]. Thus, this process of viral replication constitutes another target for the inhibition of COVID-19. Viral replication event is a complex process involving the synthesis of both genomic and multiple sub-genomic RNA species, and the assembly of progeny virions by a pathway that is unique for this enveloped RNA virus [5]. The replication process involves the action of viral and host proteins in order to perform RNA polymerization, proofreading and final capping [160]. One of the widely studied drug candidates that is capable of inhibiting SARS-CoV- 2 replication in host cells is remdesivir [64]. In addition to remdesivir, emetine, ribavirin, and β-D-N4-hydroxycytidine are also among the drug candidates, that are capable of inhibiting SARS-CoV-2 replication inside target cells [161].

It should be noted that screening of most approved drug candidates was performed using workhorse cell line: Vero E6 [1,162,163]. Therefore, caution must be used when interpreting relevance of the data sets derived from studies that tested the efficacy of drugs based on data coming from just one cell line. It is known that different cells often respond differently to drug treatments [164], and thus testing these anti-SARS-CoV-2 drugs on multiple cell lines, especially lung cells, will largely help in identifying a more reliable set of drugs for treating COVID-19 patients. In order for these drugs to advance to the clinical trial stage, cell specificity, dosing, half-life, route of administration and half maximal inhibitory concentration (IC50) are critical components that need to be properly investigated to circumvent undesired patient outcomes [165]. For example, if the IC50 of any of these drugs *in vitro* is greater than what can be achieved with oral dosing, then the drug will never prove useful for COVID-19 patients. Thus, it is essential to look into all these parameters before a drug can be recommendd for clinical use.

Other cellular and molecular processes that constitute potential targets for therapeutic prevention of SARS-CoV-2 infection are nuclear translocation of virus, translation of structural proteins and viral release [166]. One of the symptoms of COVID-19 is the induction of inflammatory responses which triggers the release of cytokines especially IL-6 [167]. Some of the drugs we listed here have capability to reduce inflammatory side-effects of SARS-CoV-2 infection. While we have presented a list of potential antiviral drug candidates, we however think that only a limited number of them will prove clinically relevant for treatment and prevention of SARS-CoV-2 infection. Remdesivir has been shown as a promising drug. Clinical improvement was seen in 68% of the hospitalized patients for severe Covid-19 who were treated with remdesivir [55]. In addition, remdesivir is also effective in shortening the time to recovery and decreasing respiratory tract infection in adult patients hospitalized with Covid-19 [168]. So far, administration of chloroquine and hydroxychloroquine have been controversial as discussed before. The outcomes of recent clinical trials of chloroquine have yielded new information for its usage on COVID-19 patients. Adjunctive therapy for several acute SARS-CoV-2 infected patients showed that higher dosage of chloroquine is lethal and is not recommended especially when combined with azithromycin and oseltamivir. However, lower dosage showed enough safety and efficacy to treat these patients [169–172]. HCQ has been shown to be less toxic compared to CQ, and thus it is a reasonable treatment option [173]. However, several studies showed the controversial usage of HCQ for COVID-19. It was suggested that different factors such as the stage of the disease, treatment duration and combination therapy, must be taken into consideration to obtain an efficient clinical outcome with HCQ [174,175]. Methylprednisonine is another drug of interest. Early administration of prolonged methylprednisolone treatment is correlated with a significantly lower possibility of death (71%) and decreased ventilator dependence in patients with severe COVID-19 pneumonia. Consistent with this, another study indicated that single-dose methylprednisolone has no obvious negative impact on viral removal and production of specific IgG. However, it is effective in stopping the inflammatory cascade [176,177]. Although early, low-dose and short-term administration of methylprednisolone is associated with better clinical outcomes, more randomized controlled trials are needed to confirm these findings [178]. Another potential drug, colchicine is shown a clinical improvement by reducing the length of hospitalization and dependency on supplemental oxygen therapy [179,180]. Famotidine is correlated with lower hazard of mortality [181]. Although famotidine reduced the rates of mortality of the COVID-19 patients, there is no direct evidence of inhibitory effects of famotidine on SARS-CoV-2 replication [182]. Hence, further investigation of its molecular mechanism of action might be important in the context of COVID-19. Emetine is another drug which is effective against SARS-CoV-2 virus in Vero E6 cells. Interestingly, combination therapy of remdesivir and emetine shown to exert synergistic effects against the SARS-CoV-2 virus [64]. Furthermore, nelfinavir, an HIV-1 protease inhibitor, potently inhibits replication of SARS-CoV-2 [183]. Altogether, Remdesivir, Nelfinavir, Methylprednisolone, Colchicine, Famotidine and emetine are potentially considered for use in clinical trial applications or be recommended for further confirmatory studies.

Overall, this review will serve as a very timely and useful compilation of drugs being studied and repurposed for the treatment and prevention of SARS-CoV2 infection. Importantly, the mechanisms of action of these drugs as described herein will serve as a necessary guide for future studies investigating other COVID-19 therapeutic modalities and interventions.

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Authorship contributions

H.Y, L.M, and S.C.O wrote and prepared the manuscript draft. N.A. Worked on couple of sections. Finally, S.A revised the final draft.

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