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ORIGINAL ARTICLE

Screening of potential inhibitors of COVID-19 with repurposing approach via molecular docking

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Abstract

SARS-CoV-2 (COVID-19) is the causative organism for a pandemic disease with a high rate of infectivity and mortality. In this study, we aimed to assess the affinity between several available small molecule and proteins, including Abl kinase inhibitors, Janus kinase inhibitor, dipeptidyl peptidase 4 inhibitors, RNA-dependent RNA polymerase inhibitors, and Papain-like protease inhibitors, using binding simulation, to test whether they may be effective in inhibiting COVID-19 infection through several mechanisms. The efficiency of inhibitors was evaluated based on docking scores using AutoDock Vina software. Strong ligand–protein interactions were predicted among some of these drugs, that included: Imatinib, Remdesivir, and Telaprevir, and this may render these compounds promising candidates. Some candidate drugs might be efficient in disease control as potential inhibitors or lead compounds against the SARS-CoV-2. It is also worth highlighting the powerful immunomodulatory role of other drugs, such as Abivertinib that inhibits pro-inflammatory cytokine production associated with cytokine release syndrome (CRS) and the progression of COVID-19 infection. The potential role of other Abl kinase inhibitors, including Imatinib in reducing SARS-CoV and MERS-CoV viral titers, immune regulatory function and the development of acute respiratory distress syndrome (ARDS), indicate that this drug may be useful for COVID-19, as the SARS-CoV-2 genome is similar to SARS-CoV.

Keywords COVID-19 · Abl kinase inhibitors · Janus kinase inhibitor · Dipeptidyl peptidase 4 inhibitors · RNA-dependent RNA polymerase inhibitors · Papain-like protease inhibitors

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Abbreviations

ARDS	Acute respiratory distress syndrome
SARS-CoV	Severe acute respiratory syndrome coronavirus
MERS-CoV	Middle East respiratory syndrome coronavirus
ACE	Angiotensin-converting enzyme
PDB	Protein Data Bank
PDBQT	Protein Data Bank, Partial Charge (Q), and Atom Type (T)
MVD	Molecular docking software
CML	Chronic myelogenous leukemia
ALL	Acute lymphocytic leukemia
TKI	Tyrosine kinase inhibitor
EGFR	Epidermal growth factor receptor
BTK	Bruton's tyrosine kinase
CRS	Cytokine release syndrome
JAK inhibitor	Janus kinase inhibitor
ACE2	Angiotensin-converting enzyme 2
AT2R	Angiotensin II receptor
DPP4i	Dipeptidyl peptidase 4 inhibitors
RdRP	RNA-dependent RNA polymerase
RDV	Remdesivir

1 Introduction

Coronaviruses are enveloped RNA viruses that include those causing severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) (Divya et al. 2020). SARS-CoV-2 is a newly emergent coronavirus that causes a respiratory illness and that has resulted in a global pandemic, having been first identified in Wuhan, China, in December 2019 (Sisk et al. 2018; WHO 2020). COVID-19 has two categories of proteins; structural proteins that include: Spike (S) that characterize all coronaviruses, Nucleocapsid (N), Matrix (M), and Envelope (E); and non-structural proteins, that include: proteases (nsp3 and nsp5) and RdRp (nsp12) (Divya et al. 2020; Ibrahim et al. 2020). An essential step for replication of the enveloped viruses such as coronaviruses is their entry into the host cells by fusing with cell membranes (Prompetchara et al. 2020). The virus attaches and enters the host cells in the respiratory tract using the spike protein (Ibrahim et al. 2020). It has also been shown that SARS-CoV-2 can infect T cells through a receptor-dependent, S protein-mediated membrane fusion (Wang et al. 2020a). COVID-19 infection may be associated with lymphopenia and occasionally the release of very high levels of inflammatory cytokines that has been described as a "cytokine storm." The latter has a major role in the development of inflammation-induced lung injury, that can lead to acute respiratory distress syndrome (ARDS), respiratory failure, and death (Prompetc.hara et al. 2020; Chen et al. 2020). Symptoms of COVID-19 include: dry cough, fever, breathing difficulties, headache, pneumonia (Zhou et al. 2020), new loss of taste or smell, nausea or vomiting and diarrhea (DeBiasi et al. 2020). An increased total neutrophil count and decreased total lymphocytes are related to disease severity and risk of mortality (Sun et al. 2020). There is currently no specific medication for COVID-19, so neutralizing monoclonal antibody-based therapeutics and small-molecules are being evaluated to treat COVID-19 (Choudhary et al. 2020). There are three key drug-targeting strategies for SARS-CoV-2:

1. Blocking the entry of the virus into the host cells.
2. Host's undirected inflammatory response reduction.
3. Block replication within the host (Jakovac 2020; Quartuccio et al. 2020).

Moreover, there are many factors that might contribute to viral infection through different mechanisms of action directly or indirectly, including Abl kinase, Janus kinase, dipeptidyl peptidase 4, RNA-dependent RNA polymerase, viral main protease and Papain-like protease, which will be discussed further. Repurposing FDA-approved drugs create opportunities to develop new treatments for COVID-19, especially for patients who are suffering from severe disease; for example, there is the possibility that some drugs such as Imatinib can be repurposed (Shaw et al. 2019). Other drugs are being evaluated in clinical trials, such as Abelson (Abl) kinase inhibitors (Imatinib), anti-malarials, RNA-dependent RNA polymerase (RdRP) inhibitors, and Papain-like protease inhibitors. The ClinicalTrials.gov Web site describes the candidate drugs currently being tested for COVID-19 prevention and/or treatment (Table 1). In silico evaluation of the possible viral inhibitory effectiveness of small molecules can be assessed by ligand-binding simulations. Therefore, the aim of this study was to evaluate the efficiency of candidate drugs and binding affinity with structural component of SARS-CoV-2, particularly in the contest of small-molecule inhibitors; Abl kinase inhibitors (Imatinib), Janus kinase inhibitor, dipeptidyl peptidase 4 inhibitors, RdRP inhibitors, and Papain-like protease inhibitors using in silico simulations by AutoDock Vina software.

2 Methods

2.1 Protein preparation

For molecular docking, SARS-CoV-2 spike protein (PDB: 6XR8), SARS-CoV spike protein (PDB: 5X58), SARS-CoV-2 main protease (PDB:6LU7), RNA-dependent RNA polymerases (RdRps) (PDB: 6M71), and papain-like protease (PLpro) (PDB: 6W9C) were chosen to be the target proteins which

Table 1 Clinical trials related to the coronavirus disease 2019-nCoV and candidate drugs

ClinicalTrials.gov identifier	Drug class	Drug name	Estimated enrollment	Aim	Primary purpose
NCT04357613	Abl kinase inhibitor	Imatinib	99 participants	Test the value of Imatinib as an early treatment of COVID–19	Treatment
NCT04330300	ACE inhibitor, angiotensin receptor blocker	Benazepril, Captopril, Enalapril, Fosinopril, Lisinopril, Perindopril, Quinapril, Ramipril, Trandolapril	2414 participants	Coronavirus angiotensin–converting enzyme inhibitors, angiotensin receptor blockers investigation	Prevention
NCT04280705	RdRps inhibitor	Remdesivir	1062 participants	Evaluate the efficacy and safety of Remdesivir (Phase 3)	Treatment
NCT04276688	RdRps inhibitor, 3CLpro inhibitor	Ribavirin, Lopinavir, Ritonavir	127 participants	Investigate a combination of Lopinavir, Ritonavir, Ribavirin and interferon beta–1b	Treatment
NCT04310228	RdRps inhibitor, interleukin–6 (IL–6) blockers	Favipiravir, Tocilizumab	150 participants	Evaluate the efficacy and safety of Favipiravir combined with Tocilizumab	Treatment
NCT04307693	3CL protease inhibitor	Lopinavir, Ritonavir	65 participants	Investigate Lopinavir, Ritonavir in patients with mild coronavirus disease	Treatment
NCT04440007	EGFR tyrosine kinase inhibitor and BTK inhibitor	Abivertinib	80 participants	A phase 2 randomized study of the efficacy and safety of Abivertinib maleate in hospitalized patients with COVID–19	Treatment
NCT04321993	Janus kinase inhibitor	Baricitinib	800 participants	Treatment of moderate–to–severe coronavirus disease in hospitalized patients	Treatment
NCT04365517	Dipeptidyl peptidase 4 inhibitor	Sitagliptin	170 participants	The effect of Sitagliptin treatment in COVID–19–positive diabetic patients	Treatment
NCT04377620	Janus–associated kinase (JAK) inhibitor	Ruxolitinib	500 participants	Assess the efficacy and safety of Ruxolitinib in participants with COVID–19–associated ARDS	Treatment
NCT03891420	Viral RNA polymerase inhibitor	Galidesivir	132 participants	Evaluate the safety, pharmacokinetics, and antiviral effects of Galidesivir	Treatment

were obtained from the RCSB (http://www.rscb.org) Protein Data Bank in PDB format. Due to the high number of reported structures, in the present study, we used the structures, which had been previously studied in similar bioinformatics studies.

2.2 Ligand preparation

Based on literature reviews, we tested 3D structures of the drugs, including: Imatinib (Abl kinase inhibitor), Ruxolitinib and Baricitinib (JAK inhibitors), Sitagliptin (dipeptidyl peptidase 4 inhibitors), Remdesivir, Ivermectin, Galidesivir, Ribavirin, Favipiravir (RdRps inhibitors), Telaprevir, Boceprevir, Grazoprevir (protease inhibitors) using Drug bank (https://www.drugbank.ca/) in Structure-data file (PDB) format. They also were converted into (PDBQT) by AutoDock Tools software. The PDBQT format is similar to PDB. However, it includes partial charges that are required for docking.

2.3 Docking analysis

To simulate protein and ligand-binding affinity, molecular docking softwares (MVD) including AutoDock Tools

(version 1.5.6) (http://autodock.scripps.edu) and AutoDock Vina (http://autodock.scripps.edu) were used (Trott and Olson 2010; Tools 2016). After that, the downloaded proteins were inserted to the work place to be prepared. First, the water molecules were deleted, and then, polar Hydrogen and Kollman charges were added by the software tools. Then, Autogrid determined the native ligand position on the binding site by arranging the grid coordinates (*X*, *Y*, and *Z*). After the preparations, the bioactive conformations were simulated by AutoDock Vina. The exhaustiveness parameter that controls the extent of the search was chosen as 8, and 9 models were generated for each ligand. According to the received results, lower energy scores demonstrate the best protein–ligand interactions. Models with binding energy lower than 6 kcal/mol can be considered. Therefore, the lowest binding energy value of 10 kcal/mol as a threshold to define a physical drug–target interaction was used. Different poses of the ligands affect the estimation of the docking score, so the most active forms were used to obtain an accurate estimation. RMSD values of three or more indicate that no docking has occurred. Only one docking position with the root-mean-square deviations of atomic positions (RMSD = 0) is highly valid and reported. The interactions of amino acids and ligands were also examined using Discovery Studio 4.5.

2.4 Clinical trials

Clinical trials data were downloaded from clinicaltrials.gov on 4 April 2020. Small molecule drugs used to prevent or treat COVID-19 were selected in interventional category (Table 1).

3 Results and discussion

In the present study, based on the importance of inhibition in reducing or stopping the activity of COVID-19, ligand with the ability to inhibit the virus in the drug database has been used. For this purpose, and considering the importance of identifying ligand–receptor interactions, the effectiveness of each of these ligands on the related proteins has been evaluated during the molecular docking simulation process.

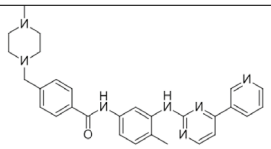
3.1 Abl kinase inhibitors

Abl kinases are non-receptor tyrosine kinases that are involved in various cellular processes, especially as mediators of viral infection and/or may be involved in T-cell signaling (Khatri et al. 2016). Imatinib is an Abl kinase inhibitor used to treat Philadelphia chromosome-positive chronic myelogenous leukemia (CML) and acute lymphocytic leukemia (ALL). This small-molecule inhibitor works by inhibiting *Bcr-Abl* tyrosine kinase (Kerkelä et al. 2006). It has been shown, from previous studies, that an Abelson (Abl) kinase inhibitor, Imatinib, reduces SARS-CoV and MERS-CoV viral titers. In the same study, they also investigated the bronchitis virus (IBV) to study the function of Abl kinase activity during coronavirus infection and found that Imatinib and two different Abl kinase inhibitors, GNF2 and GNF5, reduced IBV titers by blocking virus infection (Sisk et al. 2018). Previously, Imatinib was shown to block the entry of SARS-CoV or MERS-CoV S protein (Sisk et al. 2018). SARS-CoV-2 is highly homologous to SARS-CoV, so studying the effects of Abl kinase inhibitors on IBV, SARS-CoV and MERS-CoV may be useful in identifying the host cell pathways required for COVID-19 infection. It may also provide insights into potential strategies for the treatment of COVID-19 especially using Imatinib. Virus–cell and cell–cell fusion induced by the coronavirus S protein has a very similar mechanism. Abl kinase activity plays a role in cytoskeletal rearrangement, regulating endothelial barrier, and junctional dynamics, and hence Abl kinase inhibitors might also be capable of interacting by interfering with the actin dynamics needed for virus–cell and cell–cell fusion in SARA-CoV-2. Furthermore, studies have indicated that Abl kinase regulates inflammatory signaling, NFκB signaling, and oxidant-induced epithelial cells injury caused by infection and ARDS which can be followed by COVID-19 (Sisk et al. 2018; Rizzo et al. 2015). In epithelial cell injury, H_2O_2 release leads to C-Abl activation and nuclear translocation. C-Abl inhibition by Imatinib increases the expression of antioxidant proteins such as catalase and glutathione peroxidase, which have been reduced due to oxidative stress. Therefore, treatment with Imatinib during ARDS may prevent the death of lung cells (Rizzo et al. 2015). Coleman et al. investigated the Abl kinase inhibitors, including Imatinib, in SARS-CoV and MERS-CoV in vitro. In the early stages of infection, after internalization and endosomal trafficking, the anti-CoV activity of Imatinib is affected by inhibiting virion fusion in the endosomal membrane. Imatinib inhibits a step-in virion replication before the genomic production of RNA. They also investigated the role of Abl_2 in the replication of SARS-CoV and MERS-CoV. To knock down the Abl_2 protein levels, siRNA was used. They demonstrated that Abl_2 expression is essential for a productive viral replication and can be blocked by Imatinib (Coleman et al. 2016). Imatinib and its methane sulfonate derivative can be used in treating viral liver diseases, in particular viral hepatitis by inhibiting replication, transmission, or both, of hepatitis viruses or of other RNA viruses including respiratory syncytial virus, herpes virus, influenza virus, poxvirus, para influenza virus, rhinovirus, yellow fever virus, West Nile virus, and encephalitis virus to maintain or decrease RNA viral load. Although it is not meant to be limited to any particular mechanism of action or bound by definition, it is suspected that Imatinib's

antiviral properties may be partly due to its ability to inhibit viral replication and transmission. Cellular signal transduction pathways are known to play an important role in viral infection, and cellular phosphorylation events during viral infection so they are required to effectively replicate and proliferate the virus. Several cellular signaling pathways, related to viral replication, have been investigated. Tyrosine kinase inhibitors can be used, for example, epidermal receptor growth factor (EGFR) inhibitors such as monoclonal antibodies and small-molecule inhibitors. EGFR inhibitors including monoclonal antibodies, such as IMC-C225 (Cetuximab), Trastuzumab (Herceptin), and others (ABX-EGF, EMD 72000), and tyrosine kinase inhibitors, such as OSI-774 (Erlotinib, Tarceva), ZD1839 (Gefitinib, Iressa), and others (GW2016, CI-1033), can be used in combination therapy with Imatinib. Monoclonal antibodies can block extracellular ligand binding, but at the intracellular portion of the receptor, the small-molecule inhibitors may exert their effects to prevent tyrosine kinase phosphorylation and the activation of signal transduction pathways (Riviere et al. 2012). Consequently, combination therapy may be useful in COVID-19 treatment, similar to other RNA viruses. According to the Hubei Anti-Cancer Association Chronic Myeloid Leukemia Standardized Management Collaboration Group research on 299 CML patients who responded optimally to anti-CML therapy using Imatinib and other tyrosine kinase inhibitors, 0.3% of patients were infected by SARS-CoV-2 and among those who failed to respond to CML treatment, 2% of patients were diagnosed with COVID-19. Therefore, patients who failed to receive an appropriate response to anti-CML therapy medications were more likely to get infected by SARS-CoV-2. Although more detailed clinical data and studies on the prevalence of COVID-19 in patients with CML is required, this idea may be consistent with several possibilities (Wang et al. 2020). For instance, it has been shown that the total number of natural killer (NK) cells and Regulatory T cells was decreased markedly in patients with CML as well as COVID-19 infection (Zheng et al. 2020; Qin et al. 2020) while tyrosine kinase inhibitors are able to regulate the immune system by increasing the number of natural killer cells (NK) and Regulatory T cells (Wang et al. 2020). To assess the potential effectiveness of Imatinib on COVID-19, using molecular docking, we investigated the affinity and efficiency of Imatinib and possible intermediary proteins: Spike protein and RNA-dependent RNA polymerases (RdRps). According to the NCBI database and using the Basic Local Alignment Search Tool (BLAST), we found that SARS-CoV-2 spike protein (PDB: 6XR8) and SARS-CoV spike protein (PDB: 5X58) Query Cover is 76.16% with a GMQE of 0.80, which indicates that it is reasonable to consider these proteins similar. The docking results are shown in Table 2; low energy indicates the optimum protein–ligand complexes. Accordingly, docking scores for SARS-CoV-2 and SARS-CoV were − 9.6 and − 10 kcal/mol, respectively, which are low enough to show the appropriate protein–ligand complexes. Docking interactions of Imatinib based on docking studies are shown in Fig. 1. Furthermore, the type of interaction with the number of active site amino acids is also considered effective. In terms of interactions, the presence of hydrogen bond interactions can be very important as they have critical contributions to the binding structures and binding free energies, although the van der Waals and Pi-interactions contributed to the stabilization of the binding structures. If these interactions take place in the active position of proteins, it will be much better and more desirable. The interaction types and amino acids involved in the inhibition of proteins are shown in Table 6.

Binding interactions of Imatinib and SARS-CoV-2 spike protein shows that Imatinib interacts by forming hydrogen bonds with residue SER B: 50 and SER B: 967. A Pi–sigma interaction is also visible between the drug and amino acid THR B: 302 and Pi–Alkyl interactions with LEU C: 754

Table 2 The docking score of Imatinib to SARS-CoV-2 and SARS-CoV spike protein, SARS-CoV-2 RNA-dependent RNA polymerases (RdRps) (RMSD: 0.00)

Drug name	Drug bank ID	2D structure	Drug use	Binding affinity (total energy): SARS-CoV-2 spike protein	Binding affinity (total energy): SARS-CoV spike protein	Binding affinity (total energy)[1]: SARS-CoV-2 RNA-dependent RNA polymerases (RdRps)
Imatinib	DB00619		Anti-cancer	-9.6	-10	-8.1

[1]Kcal/mol

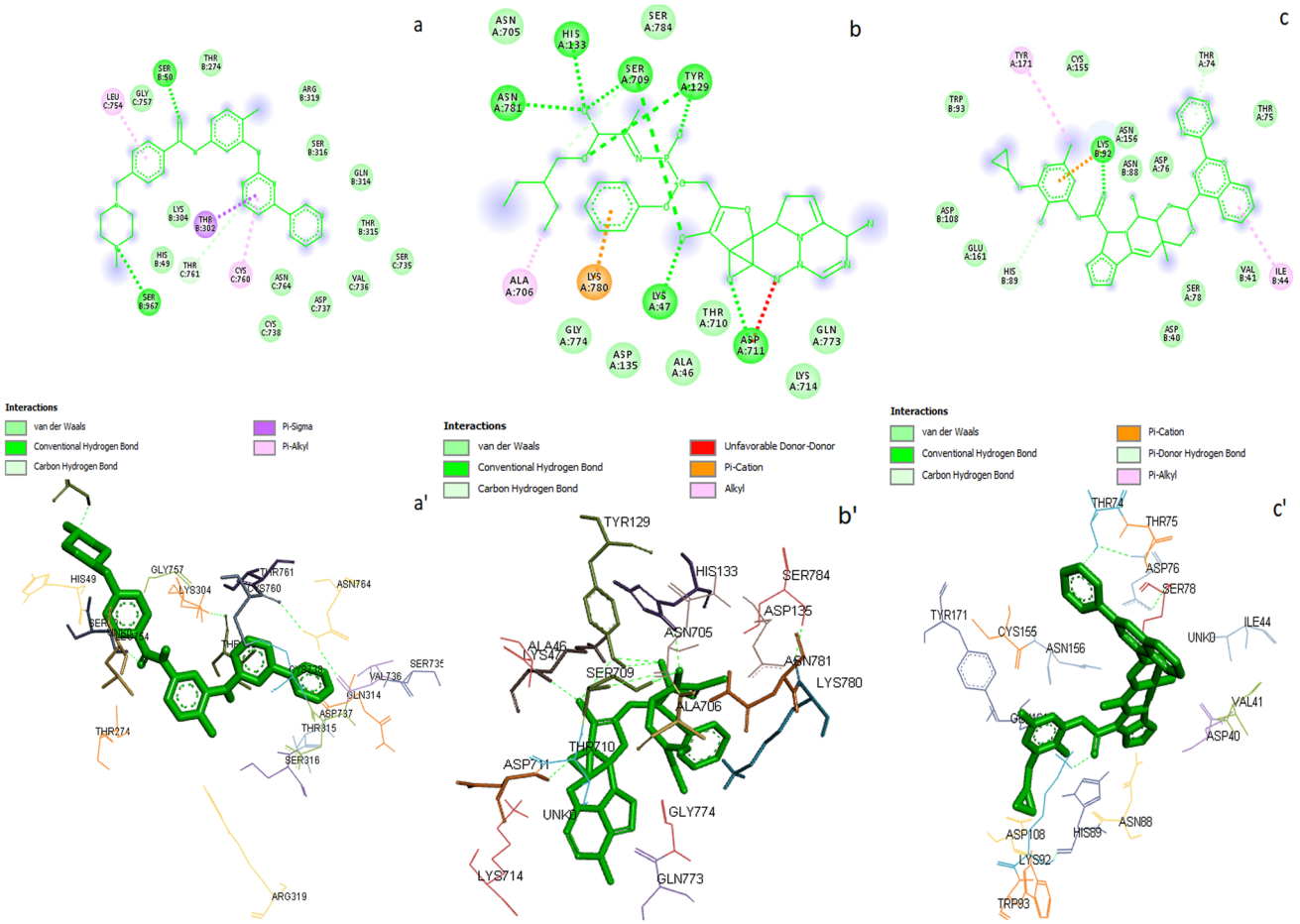


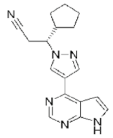
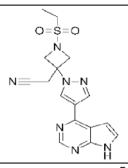
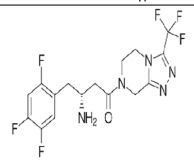
Fig. 1 Visualization of docked poses of top three drug candidates with their protein target. **a** Binding interactions of Imatinib with active site residues of SARS-CoV-2 spike protein. **a′** 3D view of Imatinib with surrounding amino acids of 6XR8. **b** Binding interactions of Remdesivir with active site residues of RdRP. **b′** 3D view of Remdesivir with surrounding amino acids of 6M71. **c** Binding interactions of Telaprevir with active site residues of PLpro. **c′** 3D view of Telaprevir with surrounding amino acids of 6W9C

and CYS C: 760. The large number of Pi–sigma interactions which involves charge transfer and helps in intercalating the drug in the binding site of the receptor. Pi–Alkyl bond also improves the hydrophobic interactions of the ligand in the binding pocket of the receptor. With regards to the van der Waals interactions, it should be mentioned that there are 13 amino acids contributing to the ligand binding, including: LYS B: 304, HIS B: 49, ASN C: 764, CYS C: 738, ASP C: 737, VAL C: 736, SER C: 735, THR B: 315, GLN B: 314, SER B: 316, ARG B: 319, THR B: 274, and GLY C: 757. Imatinib inhibits SARS-CoV-2 with an IC50 of 130 nM. But, although imatinib binds to the receptor-binding domain (RBD) of SARS-CoV-2 spike protein, it does not inhibit the spike RBD:ACE2 interaction, suggesting a Bcr-Abl kinase-mediated fusion inhibition mechanism is responsible for the inhibitory action (Mulgaonkar et al. 2020). Abivertinib is another small-molecule tyrosine kinase inhibitor (TKI) that is used in lung cancer treatment, targeting both mutant forms of the epidermal growth factor receptor (EGFR) and Bruton's tyrosine kinase (BTK). Abivertinib binds to the BTK receptor which results in receptor phosphorylation prevention. It also plays a powerful immunomodulatory role in vitro by inhibiting pro-inflammatory cytokine production that are associated with cytokine release syndrome (CRS) or cytokine storm and progression of COVID-19 infection such as IL-1beta, IL-6 and TNF-alpha in patients with acute respiratory distress syndrome (ARDS). It is worth noting that FDA clears Abivertinib for Phase 2 safety and efficacy study in hospitalized patients with moderate-to-severe COVID-19 (http://www.aceatherapeutics.com). This strongly indicates that the Abl kinase signaling pathway is a promising area to study for the development of antiviral therapies.

3.2 Janus kinase inhibitor (JAK inhibitor)

Janus kinase inhibitors are being used in the treatment of cancer and inflammatory diseases by inhibiting the activity of the Janus kinase family of enzymes (JAK1, JAK2,

Table 3 The docking score of candidate inhibitors to SARS-CoV-2 main protease and SARS-CoV-2 spike protein (RMSD: 0.00)

Drug name	Drug bank ID	2D structure	Protein target	Drug use	Binding affinity (total energy)[1]
Ruxolitinib	DB08877		SARS-CoV-2 main protease	treatment of intermediate or high-risk myelofibrosis	-6.2
baricitinib	DB11817		SARS-CoV-2 main protease	treatment of rheumatoid arthritis (RA)	-6.1
Sitagliptin	DB01261		SARS-CoV-2 spike protein	Treatment of diabetes mellitus type 2	-6.0

[1]Kcal/mol

JAK3, and TYK2), by interfering with the JAK–STAT signaling pathway (Pesu et al. 2008). Ruxolitinib is one of those inhibitors with an anti-inflammatory effect related to the inhibition of the release of cytokines. This drug is used for the treatment of myelofibrosis and polycythemia vera (PCV) (Mesa et al. 2012). Ruxolitinib has been approved in COVID-19 patients with respiratory failure with no invasive assisted ventilation required (Lorenzo et al. 2020). Improvement in chest computed tomography and faster recovery from lymphopenia were seen in patients as well (Cao et al. 2020). Another JAK inhibitor is Baricitinib used for rheumatoid arthritis. A randomized phase 2 trial for this drug has been licensed to the usual treatment of pneumonia in COVID-19 patients (Lorenzo et al. 2020). Transcription by interferon-activated JAK–STAT signaling pathway (mainly mediated by JAK1 and JAK2) contributes to the upregulation of several interferon-controlled genes which destroy viruses in infected cells rapidly. Many viruses have formed strategies to combat interferon effects by blocking their signaling pathways, and viral-encoded factors that antagonize the JAK–STAT pathway are important virulence determinants. Therefore, the blocking of the JAK–STAT signal by Baricitinib results in interferon-mediated antiviral response inhibition that has an impact on SARS-CoV-2 infection progression (Favalli et al. 2020). According to another cohort study, Baricitinib in combination with Remdesivir and Hydroxychloroquine showed clinical improvement in patients (Titanji et al. 2020). Moreover, docking results between SARS-CoV-2 main protease and our two JAK inhibitors (Ruxolitinib and Baricitinib) were − 6.2 and − 6.1 kcal/mol, respectively (Table 3).

3.3 Dipeptidyl peptidase 4 inhibitors (DPP4i)

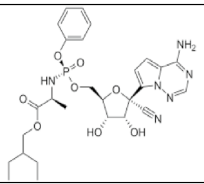
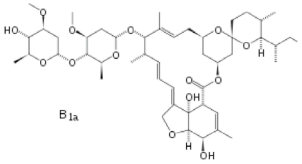
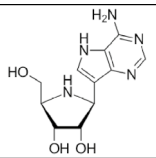
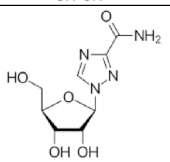
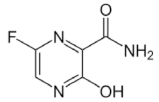
Besides the main viral entrance port, angiotensin-converting enzyme 2 (ACE2), dipeptidyl peptidase 4 (DPP4) can be investigated as well. DPP4 is a type II transmembrane glycoprotein with its major role in glucose and insulin metabolism which is expressed in many tissues, such as the immune cells. In addition, it plays a significant role in immune regulation by activating T cells, modulating NF-jB pathway, and the expression of CD86. Dipeptidyl peptidase 4 inhibitors mainly sitagliptin can be used to treat diabetes mellitus type 2. Moreover, it was identified as a functional receptor for the MERS-CoV spike protein and although SARS-CoV-2 spike protein does not necessarily need DPP4. In spite of Sitagliptin and SARS-CoV-2 spike protein docking result with the score of − 6.0 kcal/mol and the possibility that it does not alter ACE2, the potential anti-inflammatory involvement of DPP4 inhibitors raises concerns about DPP4 modulation that might decrease the cytokine-mediated acute respiratory complications of COVID-19 infection (Lorenzo et al. 2020; Pal and Bhadada 2020) (Table 3).

3.4 RNA-dependent RNA polymerase inhibitors

RNA-dependent RNA polymerase (RdRP) is an enzyme that catalyzes the replication of RNA from an RNA template which is encoded in the genomes of all RNA viruses

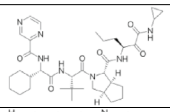
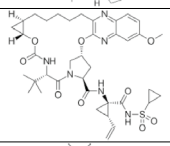
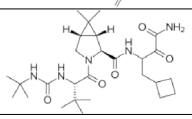
(Koonin et al. 1989) including SARS-CoV-2. There are some drugs that are considered to be nucleotide analog inhibitors of RdRps. Remdesivir (RDV) is one of those investigational drugs that have a wide variety of antiviral activities against RNA viruses including coronaviruses (Gordon et al. 2020). Remdesivir suppresses viral replication and it was initially tested in clinical trials to prevent the 2014 Ebola outbreak. Later investigations indicated Remdesivir's ability to inhibit replication of coronavirus, including SARS-CoV-2 as well (Eastman et al. 2020). In another cohort study, medical progress was observed in 68% of patients taken to the hospital with severe COVID-19 treated with Remdesivir (Grein et al. 2020). Ivermectin is another medication that we investigated via molecular docking. It is used to treat many types of parasite infestations, but recently, the antiviral effects against several SARS-CoV-2 have been identified. Ivermectin may inhibit the replication of SARS-CoV-2 in monkey with an IC50 of 2.2–2.8 µM, which makes it a possible candidate for drug repurposing research. In addition, it is an in vitro inhibitor of SARS-CoV-2 replication via Importin α/β1 function (Caly et al. 2020; Yavuz and Ünal 2020). According to our docking result, it showed high affinity value of − 8.8 kcal/mol with RdRP. In Japan, Favipiravir, an antiviral drug that targets the influenza viral RNA-dependent RNA polymerase, has been used against SARS-CoV-2 (Chen et al. 2020). Ribavirin and Galidesivir (Ibrahim et al. 2020) are other recommended drugs that we studied using AutoDock Vina. Accordingly, Remdesivir (Fig. 1) has the best binding capability with the score of − 9.0 kcal/mol. From our docking studies, with the better binding energy compounds, the identified active residues were Lys47, Ser784, Ser709, Tyr129, His133, and Thr141. The major interaction between Remdesivir and RdRP is characterized by hydrogen bonding between the oxygen with TYR A: 129. A Pi–Cation interaction of aromatic ring and LYS A: 780 and an Alkyl interaction with ALA A: 706 have been observed. The docked result of the shown in Fig. 1 indicates the drug has eight hydrogen bond interactions with six amino acids shown in Table 6. Other important interactions such as alkyl, Pi–Cation interactions were also reported Table 6. Remdesivir high affinity has also been correlated with the existence of van der Waals forces formed on the amide substituents backbone with the respective amino acids GLY A: 774, ASP A:135, ALA A: 46, THR A: 710, LYS A: 714, GLN A: 773, ASN

Table 4 The docking score of candidate inhibitors to SARS-CoV-2 RNA-dependent RNA polymerases (RdRps) (RMSD: 0.00)

Drug name	Drug bank ID	2D structure	Drug use	Binding affinity (total energy)[1]
Remdesivir	DB14761		Antiviral	-9.0
Ivermectin	DB00602		anti-parasite	-8.8
Galidesivir	DB11676		Antiviral	-6.9
Ribavirin	DB00811		Antiviral	-6.3
Favipiravir	DB12466		Antiviral	-5.4

[1]Kcal/mol

Table 5 The docking score of candidate HCV protease inhibitors to SARS-CoV-2 Papain-like protease (PLpro) (RMSD: 0.00)

Drug name	Drug bank ID	2D structure	Drug use	Binding affinity (total energy)[1]
Telaprevir	DB05521		Anti-Hepatitis C	-9.9
Grazoprevir	DB11575		Anti-Hepatitis C	-8.7
Boceprevir	DB08873		Anti-Hepatitis C	-7.8

[1]Kcal/mol

Table 6 Interaction types and amino acids involved in the inhibition of PDB: 6XR8, PDB: 6M71 and PDB: 6W9C with the top three drug candidates

Ligand	Protein	Conventional hydrogen bond	Carbon hydrogen bond	Pi–sigma and amide interaction	Alkyl interaction	Pi–cation interaction
Imatinib	PDB: 6XR8	SER B:50 SER B: 967	THR C: 761	THR B: 302	CYS C: 760 LEU C: 754	–
Remdesivir	PDB: 6M71	ASN A: 781 HIS A: 133 SER A: 709 TYR A: 129 LYS A: 47 ASP A: 711	SER A: 709	–	ALA A: 706	LYS A: 780
Telaprevir	PDB: 6W9C	LYS B: 92	HIS B: 89 THR A: 74	–	ILE B: 44 TYR A: 171	LYS B: 92

A: 705, and SER A: 784, which established a strong cohesive environment, thus, stabilizing the formed complex. It exhibits effective in vitro activity against SARS-CoV-2 with an EC_{50} at 48 h of 0.77 µM in Vero E6 cells (Wang et al. 2020a). On the other hand, Favipiravir had the least affinity to RdRps despite the recorded efficiency based on clinical trials (Table 4).

3.5 Papain-like protease inhibitors

Papain-like protease (PLpro) is characterized in different coronaviruses, including SARS and MERS (Elfiky and Ibrahim 2020). The genome of SARS-CoV-2 encodes for different proteins including PLpro (Durdagi et al. 2020). The SARS-CoV PLpro and SARS-CoV-2 PLpro protein sequences are similar, so protease inhibitors that have shown efficacy against SARS-CoV might be similarly effective against SARS-CoV-2. Papain-like protease (PLpro) has a crucial role in the viral life cycle (Arya et al. 2020; Talluri 2020). Targeting PLpro with antiviral drugs may result in viral replication blockage and the deregulation of signaling cascades in infected cells inhibition (Claudio and Juan 2020). Consequently, anti-HCV drugs (Telaprevir, Grazoprevir, and Boceprevir) that bind to the SARS-CoV-2 PLpro active site (contained residues Asp164, Val165, Arg166, Glu167, Met 208, Ala246, Pro247, Pro248, Tyr 264, Gly266, Asn267, Tyr 268, Gln269, Cys217, Gly271, Tyr273, Thr301 and Asp302), may, therefore, oppose viral replication (Elfiky and Ibrahim 2020; Arya et al. 2020). Similarly, our study showed that Telaprevir (Fig. 1), Grazoprevir, and Boceprevir (HCV protease inhibitor) may be effective in binding to SARS-CoV-2 papain-like protease (PLpro) active sites to prevent viral replication (Table 5) (Elfiky and Ibrahim 2020). Regarding the lowest binding energy, the best ligand was found to be Telaprevir with a score of -9.9 kcal/mol. The results of docking analysis (Table 6) showed that Telaprevir forms hydrogen bonds with the 6W9C amino

acids LYS B:92, HIS B:89 and THR A:74. In addition, there can be seen that the ligand interacts with LYS B: 92 via Pi–Cation and TYR A: 171 and ILE B: 44 via Pi–Alkyl interactions.

4 Conclusions

Our results show that the treatment of COVID-19 may potentially be addressed by repurposing existing, approved pharmaceutical drugs. In this virtual drug repurposing study based on docking analysis, using an established database for protein and ligand structures, we obtained the predicted binding scores of several drugs. This will be important in evaluating the findings of continuing clinical trials testing small molecule drugs for efficacy against SARS-CoV-2 and the drugs different mechanisms of action. Imatinib plays roles in cytoskeletal rearrangement, inflammatory signaling, NK and Regulatory T-cell modulation, and oxidant-induced epithelial cell injury followed by infection and ARDS which has been diagnosed among COVID-19 patients. Another TKI, Abivertinib, has an immunomodulatory function in patients with ARDS. In addition, Remdesivir, and Telaprevir have the most efficiency with their docked proteins in silico as well.

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Availability of data and material The data supporting the findings of this study are available within the article.

Declarations

Ethics approval and consent to participate Not applicable.

Consent for publication Not applicable.

Conflict of interest The authors declare that they have no competing interests.

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