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Identification of potential antivirals against SARS-CoV-2 using virtual screening method

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A B S T R A C T

SARS-CoV-2 has triggered a major epidemic among people around the world, and it is the newest in the sequence to become prevalent among other infectious diseases. The drug repurposing concept has been utilized effectively for numerous viral infections. Considering the situation and the urgency, the idea of drug repurposing for coronavirus infection (COVID-19) is also being studied. The molecular docking method was used for the screening of 29 antiviral drugs against primary protease proteins (MPP) of SARS-CoV-2, spike ecto-domain, spike receptor binding domain, Nsp9 RNA binding protein, and HR2 domain. Among these drugs, in terms of least binding energy, Indinavir, Sorivudine, Cidofovir, and Darunavir showed minimum docking scores with all the key proteins. For ADMET (Absorption, Distribution, Metabolism, Excretion and Toxicity) analysis, the ADMET properties of the top 4 drug candidates were retrieved through literature study. This analysis revealed that these drug candidates are well metabolized, distributed, and bioavailable, but have some undesirable effects. Furthermore, some approved structural analogues, such as Telbivudine, Tenofovir, Amprenavir, Fosamprenavir, etc., were predicted as similar drugs which may also be used for treating viral infections. We highly recommend these drug candidates as potential fighters against the deadly SARS-CoV-2 virus, and suggest in vivo trials for experimental validation of our findings.

1. Introduction

The Health Authority of China notified the World Health Organization (WHO) about severe pneumonia cases in Wuhan City of Hubei Province in central China on December 31, 2019 [1,2]. Later, this emerging infectious disease was named novel coronavirus disease 2019 (COVID-19), and the causative agent was determined to be severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [3]. A well-known scientist in the field of SARS, Dr. Zhengli Shi, suggested the bats as the origin of SARS-CoV-2 [4], and other researchers in China also narrated that Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS) like coronaviruses are likely to originate from bats in China [5,6]. This SARS-CoV-2 is an envelope and positive-sense single-stranded RNA (+ssRNA) virus [7]. It belongs to the genus Beta-coronavirus, and shares about 79% and 50% genetic similarity with SARS-CoV and MERS-CoV, respectively [8]. The virus has become more perilous because of human-to-human transmission via respiratory droplets, especially when people are closely contacted (within 1–2 m) [9–11]. The disease may be symptomatic, paucisymptomatic, and asymptomatic [12]. Commonly appeared respiratory symptoms of this disease include fever, dry cough, dyspnea, chest pain, fatigue, and myalgia. Besides, headache, dizziness, abdominal pain, diarrhea, nausea and vomiting are the less common symptoms of the disease [13,14]. After the emergence, the disease has spread so fast and extensively around the world that WHO announced it as a pandemic on March 11, 2020.

The pandemic stymied the strong health sectors of the leading countries, namely China, the UK, the United States, Russia, Germany, Canada, Italy, Spain, France, and others. As of 2 July 2020, a total of 10,694,288 people were infected with COVID-19, and 516,210 deaths were calculated worldwide [15]. Researchers from different countries are making every attempt to develop new vaccines and anti-illness medications. Many research and pharmaceutical companies are trying to develop new medicines and vaccines using their sophisticated and...
advanced laboratories [16,17]. However, it takes around a year before the drugs and/or vaccines to be available for patients because of the time-consuming process. In that case, repurposing of existing drugs can play a momentous role in reducing symptoms or treating the disease. In many studies, some drugs, such as antimalarial drugs (e.g. chloroquine, hydroxychloroquine) or anti-HIV drugs (e.g. lopinavir, ritonavir, saquinavir), showed positive results against COVID-19 [18–20].

Drug repurposing, alternatively known as repositioning, is considered as an important approach for speedy identification of the therapeutics drugs with proven safety profiles to fight novel infectious diseases [21–23]. This repurposing strategy was effective in identifying potential drugs that combat diseases such as hepatitis C virus infection, Zika virus infection, and Ebola disease [24,25,26,27]. Moreover, in-silico based screening has become a felicitous method for mitigating the drawbacks of antiviral drug discovery. This computational methods of drug screening, including molecular docking, save both money and time [28,29,30,31,32]. On the other hand, currently licensed medicines of certain diseases, which are safe for human use, need to be proved as effective drugs against the target diseases [22,23]. Therefore, in silico repurposing can be a great way to identify suitable drugs which target essential proteins of SARS-CoV-2, such as proteins required for viral replication or proteins that bind to the human receptors (ACE2: angiotensin-converting enzyme 2). Our present research focused on virtual screening of a variety of antiviral drugs approved by the Food and Drug Administration (FDA). These drugs were screened against the promising targets, namely SARS-CoV-2 main protease (Mpro, PDB ID:6W63), which is very necessary for viral replication, and spike receptor binding domain (PDB ID:6MOJ), which is needed to bind to human receptor ACE2. Other drug targets include Nsp9 (Nonstructural protein-9) RNA binding protein, Spike Ectodomain and HR2 domain, which are involved in viral replication, receptor binding and fusion, and viral fusion with cell membrane, respectively. The studied FDA approved antiviral drugs such as Sorivudine, Tipranavir, Zalcitabine, Zidovudine, Indinavir, Nelfinavir, Nevirapine, etc. show efficacy against human immunodeficiency virus (HIV). Other screened drugs like Tri-fluridine, Valganciclovir, Vidarabine, Pritelivil, etc. are used for the treatment of human herpes virus disease. Along with these drugs, we also tested drugs that are workable against Influenza A virus, Influenza B virus, Hepatitis B virus, Hepatitis C virus, Respiratory Syncytial Virus (RSV), and other RNA/DNA viruses in order to detect their effectiveness against SARS-CoV-2.

2. Materials and methods

2.1. Retrieval of SARS-CoV-2 proteins/protein-domains and antiviral drugs

The 3D structures of SARS-CoV-2 main protease (PDB ID: 6W63), Nsp9 RNA binding protein (PDB ID: 6W4B), Spike receptor binding domain (PDB ID: 6MOJ), spike ecto-domain (PDB ID: 6YVB), and HR2 Domain (PDB ID: 6LVN) were retrieved from the RCSB Protein Data Bank [34]. A total of 29 antiviral drugs previously used against various viruses (e.g., HIV, Hsv, etc.) were collected in SDS (3D) format from the PubChem database [35] (Supplementary file 1). These drugs were also crosschecked in Drugbank database [36] (Supplementary file 2). Then, OpenBabel v2.3 program was used to transform the retrieved SDS structures in PDB format for further analysis [37].

2.2. Molecular docking of antiviral drugs against SARS-CoV-2 proteins/protein-domains and dynamics simulation

Molecular docking is an efficient method that ranks docked compounds by the binding affinity of ligand-receptor complexes [38–40]. PatchDock server was used to measure the binding affinity of 29 antiviral drugs with different SARS-CoV-2 proteins/protein domains (drug targets/macromolecules) [41,42]. The docking was performed with the help of shape based complementary principal of docking algorithm (provided by the patchdock server). The Crystal PDB structure of protein molecules were prepared for docking by removing all water molecules and hetatoms [41–44]. The spike glycanics were excluded from this model because spike protein N-glycosylation occurs regularly at each site which made them more diverse and heterogeneous [45]. To refine the docked complexes, FireDock refinement tool [46] was employed. An experimental study claimed alpha-ketoamide (CID 6482451) as a primary protease inhibitor for SARS-CoV-2 [47]. Thus, it was docked against all five macromolecules being used as a positive control in this study. Finally, Discovery Studio v3.1 and PyMOL v2.0 were utilized to visualize the ligand receptor complexes [48,49]. Next, stabilization of the structure was determined through deformability analysis and calculation of Eigen value of the complexes. The deformability and Eigen value were predicted through IMOD server [50]. Molecular dynamics of the complexes were studied in water explicit model for 4ns using LARMD server, and from which RMSD and RMSF values were determined [51].

2.3. Analyzing drug profiles of active antiviral drugs

A typical drug candidate should have proper properties of absorption, distribution, metabolism, excretion, and toxicity (ADMET) along with sufficient efficacy against the therapeutic targets [52]. As the studied drugs are approved, the ADMET properties of these drugs were retrieved from the literature study, and then were analyzed.

2.4. Prediction of drug targets and available structural analogs

Screening of the top drugs was performed to find similar potential drugs that could be used for SARS-CoV-2 therapy. To predict the probable macromolecular targets of the top drugs, Swiss Target Prediction tool was utilized [53]. Furthermore, the Swiss-Similarity web tool was used to evaluate the potential drug molecules that fight against SARS-CoV-2 by screening homology of the predicted top drugs [54]. The server uses several strategies, such as FP2 fingerprints, spectrophores, electroshape, and align-IT to predict approved drugs from DrugBank, which are commercially available, via virtual screening of numerous repositories of small molecules [54].

3. Results

3.1. Molecular docking of antiviral drugs against SARS-CoV-2 proteins/protein-domains and dynamics simulation

The retrieved structures of five SARS-CoV-2 proteins/protein-domains (macromolecules) and antiviral drugs (ligands) were optimized and executed for molecular docking to compute the binding affinity between the selected macromolecules and ligands. Based on binding energy, the antiviral drugs were ranked, and the drugs showing minimum binding energy were selected as top scorers (Supplementary File 3). In this way, four top scorers, Indinavir, Sorivudine, Cidofovir, and Darunavir, were chosen for further analysis (Table 1, Fig. 1). Sorivudine, Darunavir, and Cidofovir showed the highest binding affinity with spike receptor binding domain (−52.99 kcal/mol), Nsp9 RNA binding protein (−52.74 kcal/mol), respectively, while Indinavir showed the best binding affinity with both HR2 Domain (−37.42 kcal/mol) and main protease (−69.23 kcal/mol) (Table 1 and Figs. 2 and 3). Besides, Sorivudine also experienced excellent binding interactions with spike ecto-domain (−52.28 kcal/mol) and main protease (−59.62 kcal/mol), while Darunavir showed considerable interactions with spike receptor binding domain (−46.88 kcal/mol), Nsp9 RNA binding protein (−47.62 kcal/mol), and main protease (−55.06 kcal/mol). The observations of our analyzed complexes showed that each of them has a low propensity for flexibility, and...
3.2. ADMET analysis of selected top drugs

All the top drug candidates except cidofovir show good bioavailability. Darunavir and Indinavir are extensively metabolized by CYP3A4 enzymes, while Cidofovir is converted via cellular enzymes, and Sorivudine metabolism is found higher in animals. These drugs show binding capacity with plasma proteins. In healthy people, approximately 79.5% and 13.9% of the administered dose of radiolabeled darunavir was obtained in the feces and the urine, respectively, whereas the proportion of eliminated unchanged indinavir in the urine was found approximately 11%, and >47% in the feces. Cidofovir and Sorivudine are excreted greatly by the kidneys, and are eliminated as almost unchanged in the urine. These drugs have some toxic effects. Limited cytotoxicity and drug-induced hepatitis (e.g. acute hepatitis, cytolytic hepatitis) have been reported with darunavir. No cytotoxicity was detected for indinavir, but it can cause transient and usually asymptomatic elevations in serum aminotransferase levels. Moreover, it can cause mild elevations in indirect bilirubin concentration that creates a risk of acute renal failure. Cidofovir creates a risk of nephrotoxicity, and it has carcinogenic potential based on animal studies, while there is absence of hepatotoxicity. Lastly, Sorivudine shows a lethal effect when co-administered with 5-fluorouracil anti-cancer drugs (Table 2).

3.3. Prediction of effective drug targets and structural drug analogs from DrugBank

Prediction of effective drug targets against the top drugs revealed some other similar drugs that may be potential against SARS CoV2. Maximum targets belong to protease, transferase and enzyme class.
Other target class includes electrochemical transporter, cytochrome p450, family A G protein-coupled receptor, phosphodiesterase, oxido-reductase, transferase DNA polymerase alpha subunit transferase, etc. (Table 3, Fig. 5). One of the most significant concepts in chemoinformatics, particularly for drug design, is chemical similarity [73]. This concept has been successful and widely applied for the identification of novel inhibitors of various targets of biological importance [74–79]. To predict structural similar bioactive small compounds from DrugBank that act against SARS-CoV-2, a ligand-based screening strategy was employed (Table 4). Quinapril (DB00881) and Sirolimus (DB00877), two approved drugs along with an experimental drug, L-756,423 (DB02009), were found as analogous to Indinavir with a score of 0.048, 0.014, and 0.906, respectively. Sorivudine predicted two similar approved drugs, Telbivudine (DB01265) and Idoxuridine (DB00249), while Cidofovir predicted Tenofovir (DB00300) and Riboflavin (DB00140) as similar approved drugs. Besides, Darunavir also

![Chemical structures of Indinavir (A), Sorivudine (B), Cidofovir (C) and Darunavir (D).](image1)

![Molecular interaction of Sorivudine with spike receptor-binding domain (A), Indinavir with main protease(B), Indinavir with HR2 Domain (C), Cidofovir with Nsp9 RNA binding protein (D) and (E) Darunavir with spike ectodomain.](image2)
predicted two similar approved drugs, Amprenavir (DB00701) and Fosamprenavir (DB01319). These similarity findings indicate the efficacy of these related drugs against SARS-CoV-2, and suggest further experimental studies.

4. Discussion

SARS-CoV-2 belongs to a group of viruses that can contaminate humans as well as vertebrate animals. There has no recorded or approved potent drug or vaccine for treating the patient infected with SARS-CoV-2. However, there are a few candidates within the investigational stages, but many of them raised controversial issues [4,80]. In this study, attempts were taken to screen and suggest some FDA approved antiviral drugs as inhibitory agents of SARS-CoV-2 using molecular docking strategy. The study suggested that Indinavir, Sorivudine, Cidofovir, and Darunavir along with their top derivatives may be effective against SARS-CoV-2. The drug repurposing is one of the exciting applications of computational pharmacology for finding new uses of existing drugs. Computer-based analysis can speed up the identification of drug targets, and facilitate the screening and refinement of drug candidates. It also simplifies the detection of side effects, and sees the patterns of drug resistance. Antiviral drugs such as Ledipasvir, Elbasvir, Nelfinavir, Danoprevir, Darunavir, lopinavir, and ritonavir were previously used as the inhibiting agents for HCV and HIV [81]. Lopinavir, Ritonavir, and Nelfinavir have been reported as potential drug candidates in earlier studies, which used repurposing strategies targeting Main protease protein (Mpro) of SARS-CoV-2 [82]. Besides, a recent study focused on alpha-ketoamide as a Mpro inhibitor to determine its efficacy against SARS-CoV-2 [47]. Main protease proteins (Mpro) or RNAdependent RNA polymerase of SARS-CoV-2 were used as possible drug targets in almost all previous experiments. In this study, we assessed the potency of 29 FDA approved commercially available antiviral drugs against SARS-CoV-2 main protease (6W63), spike ecto-domain (6VYB), spike receptor binding domain (6MUJ), Nsp9 (Non-structural protein-9) RNA binding protein (6W4B), and HR2 domain (6LVN) using molecular docking approach [83]. SARS-CoV-2 Mpro is a desirable pharmacological target for designing covid-19 drugs because the cleavage of Mpro polyprotein facilitates the formation of helicase and RNA-dependent RNA polymerase (RdRp), which are the prerequisites for the initiation of viral replication [84,85]. Besides, human proteases have no cleavage specificity that resembles coronavirus proteases, which is why the inhibitors of these proteins are considered safe [47]. ORF1a encodes Nsp9 RNA binding protein that is involved in the synthesis of viral RNA. Nsp9 has evolved, possibly, from a protease, and it is a dimeric protein. This Nsp9 communicates with nsp8 that may be crucial for its function. Viral replication complexes are also connected with membranes, and in this case, Nsp9 aids. In the replication Complex, Nsp9 may have the RNA binding activity as a putative component. In this way, it makes a difference in viral replication by binding with single stranded RNA. SARS-Cov-2, moreover, has a surface structural spike glycoprotein (S) which plays a crucial role in association with the cell receptor, and subsequent viral passage into the cell. The S protein is composed of two subunits, the S1 (receptor-binding) and the S2 (membrane fusion) domain [40]. Interaction between the HR1 and HR2 domains in the membrane fusion subunit is enabled via the attachment of the receptor-binding subunit to the receptor, and forms a six-helix bundle. This conformational shift results in a close apposition of the fusion peptide that leads to virus-cell membrane fusion [86]. Hence, spike protein binds to human ACE2 and CLEC4M/DCSIGNR receptors, and the internalization of the virus into the host cell endosomes results in the conformational changes in the S glycoprotein [87]. Therefore, all these macromolecules are the potential targets for repurposing study.

Based on global energy, four drugs among our studied 29 drugs showed comparatively well binding affinity against our targeted macromolecules. Indinavir had highest binding affinity with SARS-CoV-2 main protease (−69.23 kcal/mol) and HR2 domain (−37.42 kcal/mol). The remaining three drug candidates, i.e. Sorivudine, Cidofovir and Darunavir, had the highest binding affinity with Spike receptor binding domain (−52.99 kcal/mol), Nsp9 RNA binding protein (−52.74 kcal/mol) and Spike ecto-domain (−68.01 kcal/mol), respectively. The ligands showed the highest binding interaction in 38–68 regions of Nsp9

Fig. 3. Ligand binding site of Sorivudine with spike receptor-binding domain (A), Indinavir with main protease (B), Indinavir with HR2 Domain (C), Cidofovir with Nsp9 RNA binding protein (D) and (E) Darunavir with spike ectodomain.
RNA binding protein (6W4B) where Gly38, Gly39, Phe41, Val42, Phe57, Pro58, Ile66, and Thr68 were most dominant. Again, the residues from 94 to 99 and from 563 to 566 regions were identified as top surface hotspots for spike receptor binding domain (6M0J) where the position Lys94, Leu95, Tyr196, Asp206, Lys562, Pro565, and Trp566 were most dominant (Table 1). The top candidates were well fitted into the active pocket of MPP, in which several hydrophobic amino acid residues, including Met49, Gly143, Cys145, and Met165, compose a relatively hydrophobic environment that may help to stabilize it’s conformation [7]. In the present study, we revealed the molecular interactions of top drug candidates with SARS-CoV-2 key proteins (Figs. 2 and 3; Table 1). The binding sites for each ligand occupied at the catalytic domain of SARS-CoV-2 main protease protein [88]. Among the common binding residues, His41 and Cys44, Met49, Gly143, Asn142, Cys145, and Met165 in maximum cases. Indinavir, an alpha-amino acid amide protease inhibitor, is used in the treatment of Human immunodeficiency virus (HIV) infection. Indinavir inhibits enzyme activity by binding to the active site of the protease. This inhibition facilitates the formation of immature non-infectious viral particles by preventing cleavage of the viral polyproteins [91]. Sorivudine is an antimetabolite and synthetic analogue of thymidine Kinase activity of thymidine induces sorivudine phosphorylation in the body, and is absorbed into the viral DNA instead of the correct nucleoside [92]. Thus, the viral DNA cannot be replicated, and the virus cannot grow because sorivudine is a competitive inhibitor of DNA polymerase. Cidofovir, a nucleotide analogue, is active against chronic hepatitis B and herpes cytomegalovirus (CMV) retinitis infection. It works selectively by inhibiting viral DNA polymerase. As a result, Cidofovir reduces the synthesis of viral DNA. Darunavir is a non-peptide protease inhibitor, with a distinct chemical structure that enhances the binding affinity of the drug [93]. This antiviral drug prevents HIV replication by binding to the enzyme that leads to the cessation of the catalytic activity, and dimerization of HIV-1 protease. Specifically, it inhibits the cleavage of HIV encoded Gag-Pol proteins in virus infected cells, by blocking the formation of mature virus particles that are required to spread the infection [94]. The molecular dynamics study showed that the complexes were resistant to deform with higher eigen value, and were fluctuated almost regularly in RMSD and RMSF plots (Fig. 4). ADMET data is crucial in drug development projects whether it is determined by in vitro, in vivo, or computational approaches because

Fig. 4. Molecular Dynamics: Deformability analysis: A-i) Sorivudine with spike receptor-binding domain, B-i) Indinavir with main protease, C-i) Indinavir with HR2 Domain, D-i) Cidofovir with Nsp9 RNA binding protein and (E) Darunavir with spike ectodomain; Eigen value: A-ii) Sorivudine with spike receptor-binding domain, B-ii) Indinavir with main protease, C-ii) Indinavir with HR2 Domain, D-ii) Cidofovir with Nsp9 RNA binding protein and E-ii) Darunavir with spike ectodomain; RMSD plot: A-iii) Sorivudine with spike receptor-binding domain, B-iii) Indinavir with main protease, C-iii) Indinavir with HR2 Domain, D-iii) Cidofovir with Nsp9 RNA binding protein and E-iii) Darunavir with spike ectodomain; RMSF plot: A-iv) Sorivudine with spike receptor-binding domain, B-iv) Indinavir with main protease, C-iv) Indinavir with HR2 Domain, D-iv) Cidofovir with Nsp9 RNA binding protein and E-iv) Darunavir with spike ectodomain.
many drug development projects previously failed during clinical trials due to poor ADMET data [95]. The ADMET analysis of these drugs showed that these are well metabolized, distributed, and bioavailable, but have some undesirable effects. Most of the target class for the top drug candidates fall into the enzyme categories such as electrochemical transporter, protease, transferase, Family A G protein-coupled receptor, etc., (Table 3).

Ligand based drug similarity analysis identified three structural
analogs of Indinavir where two (Quinapril, Sirolimus) are approved, and another one (L-756,423) is in the experimental stage. Quinapril, an ACE (angiotensin converting enzyme) inhibitor, is used for treating heart failure and hypertension [96]. As we know that, SARS-CoV-2 enters the host cell by interacting with ACE-2 receptor, thus this analog could be a drug of choice to treat Covid-19. Besides, drug similarity analysis revealed two (Telbivudine & Idoxuridine) approved analogs for Sorivudine, and both of them act by incorporating into viral DNA in place of thymidine resulting in the termination of replication process. Telbivudine and Idoxuridine are used to treat hepatitis B virus (HBV) and Herpes simplex virus, respectively [97,98]. Amprenavir and Fosamprenavir are two approved analogs of Darunavir, and both of them are protease inhibitors. These analogs prevent the processing of viral Gag and Gag-Pol polyprotein, and produce noninfectious and immature viral particles that are harmless to host cell [99,100]. The findings suggest that all these compounds may be used against SARS-CoV-2 as potential drug candidates.

5. Conclusion

The results indicate that it may be possible for Indinavir, Sorivudine, Cidofovir, and Darunavir to fight SARS-CoV-2 infection. Furthermore, several biologically active structural analogs from DrugBank, i.e. Telbivudine, Tenofovir, Fosamprenavir, Tenofovir, etc., may also be successful against the viral pathogen. We strongly recommend these drug candidates as potential warriors because of promising results, and refer to in vivo trials for experimental confirmation of our findings.

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Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.imu.2021.100531.
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