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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A search for medications to treat COVID-19 via *in silico* molecular docking models of the SARS-CoV-2 spike glycoprotein and 3CL protease

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ABSTRACT

Background: The COVID-19 has now been declared a global pandemic by the World Health Organization. There is an emergent need to search for possible medications.
Method: Utilization of the available sequence information, homology modeling, and *in slico* docking a number of available medications might prove to be effective in inhibiting the SARS-CoV-2 two main drug targets, the spike glycoprotein, and the 3CL protease.
Results: Several compounds were determined from the *in silico* docking models that might prove to be effective inhibitors for SARS-CoV-2. Several antiviral medications: Zanamivir, Indinavir, Saquinavir, and Remdesivir show potential as and $3CL^{PRO}$ main proteinase inhibitors and as a treatment for COVID-19.
Conclusion: Zanamivir, Indinavir, Saquinavir, and Remdesivir are among the exciting hits on the $3CL^{PRO}$ main proteinase. It is also exciting to uncover that Flavin Adenine Dinucleotide (FAD) Adeflavin, B2 deficiency medicine, and Coenzyme A, a coenzyme, may also be potentially used for the treatment of SARS-CoV-2 infections. The use of these off-label medications may be beneficial in the treatment of the COVID-19.

1. Introduction

The World Health Organization has now declared a global emergency and pandemic for the coronavirus disease (COVID-19) that has been actively spreading around the globe. COVID-19 which is caused by the virus SARS-CoV-2; can cause symptoms such as fever, cough, pneumonia, nausea, and fatigue. As of now SARS-CoV-2 has reached 24 countries around the globe, with more than 190,000 cases confirmed as of March 18, 2020[1].

The epidemiological background of the virus was thought to stem from a seafood market in Wuhan, China [2]. However, the true epicenter of the initial transfer to humans is still unknown. Currently, there are > 100 complete genome sequences known in the NCBI GenBank, from over 10 countries. The variation between these sequences is less than 1%.

This virus is closely related to the SARS-CoV and this allows utilization of the known protein structures to quickly build a model for drug discovery on this new SARS-CoV-2 [3]. While traditional methods of drug discovery could take years, the approach taken here to search for possible medications for the SARS-CoV-2 is *in silico* docking models from the most variable proteins in the SARS-CoV-2, the spike glycoprotein, and the SARS-CoV-2 3CL main protease.

The CoV spike protein binds to a host cell membrane through a receptor-mediated interaction which allows entrance to the host cell. It has been computationally determined that the SARS-CoV-2 has similar mechanism to that of the SARS virus and the receptor to which it has the highest affinity is ACE2 (angiotensin-converting enzyme 2) [4]. While there are structural similarities between the SARS-CoV-2 spike protein and the SARS spike protein, the conservation is only 73% with most of the variability being in the host cell interaction region of the protein. Currently, there is no crystal structure available for the SARS-CoV-2 spike protein, so we employed homology modeling of the SARS-CoV-2 utilizing the SARS spike protein (PDB: 2GHV) as a template.

The second *in silico* docking model is the $3CL^{PRO}$ main protease, which is responsible for controlling several major functions of the virus and has a highly conserved catalytic domain from the SARS virus [5]. Some of its functions include the replication processes of the virus which makes it an ideal target for drug development [6]. The SARS-CoV-2 main protease was determined by Ref. [7] (PDB: 6LU7).

Both these proteins, spike and protease, are essential to the transmission and virulence of the virus. By inhibiting anyone of these two proteins or both for a higher active therapy, the severity of the infection will be reduced. Our efforts have been placed in competitively inhibiting the binding of its natural substrates. A library of known bioactive compounds has been run against several sites on the spike protein and the catalytic site of the SARS-CoV-2 main protease.

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By utilizing an approved compound database, quick trials of these compounds, with minimal effort of approval by food and drug agencies, could be carried out. We have chosen to run the Zinc15 database which is classified by Zinc15 [8] as "Approved drugs in major jurisdictions, including the FDA, i.e DrugBank approved". This database covers all major bioactive pharmaceutical compounds utilized around the globe, and currently has 3447 entries.

2. Methods

2.1. Molecular docking

Molecular docking calculations were completed using Schrodinger® docking suits (Schrödinger Maestro, New York, NY, USA. Version 11.9.011, MMshare Version 4.5.011, Release 2019–1, Platform Windows-x64) using a virtual screening workflow. This workflow utilized three docking precisions, HTVS, SP, and XP, which yielded the top 10% of hits for each binding site. Both proteins were prepared by restrained minimization using force field OPLS3e. The grid sites were created using Glide® receptor grid generator with docking length of 20 Å. Grids centers were determined from active resides on target protein. Ligands were prepared using force field OPLS3e and possible states were generated from pH 7.0 ± 2.0. Docking scores are reported in kcal/mol, the more negative the number, the better binding.

2.2. Homology modeling of spike protein

The surface glycoprotein [Wuhan seafood market pneumonia virus] (Sequence ID: YP_009724390.1) structure was modeled using ModBase [9] which utilized Modeller [10] for the structural modeling. The sequence (NCBI Accession: YP_009724390) was uploaded to the ModBase interface and was run with the template being SARS spike protein receptor binding domain (PDB: 2GHV, Chain E). The sequence identity was found to be 73% (Fig. 1A). The calculation was completed and imported into Schrödinger Maestro®. The structure was then minimized using the force field OPLS3e, the overlay of the pre and post minimized structure can be seen in Fig. S2.

3. Results

3.1. Spike glycoprotein

Sequencing has revealed that the SARS-CoV-2 is similar to that of the SARS-CoV virus which allows for genomic and proteomic homology comparison. Using the homology modeling we have been able to develop a model of the Spike glycoprotein (Fig. 1). This model has allowed us to perform docking calculations utilizing a database of known bioactive and approved compounds.

The MODELLER and ModBase programs were able to use a homologue SARS spike protein (PDB: 2GHV) and the original SARS-CoV-2 sequence (GenBank: MN908947) and construct the SARS-CoV-2 spike protein. The protein was then run through a restriction minimization process utilizing Schrodinger Docking Suits® Protein Preparation which allows side chains to be placed in the most energetically favorable conformation (Fig. 1B).

In an effort to stop the Spike-ACE2 interaction, several sites have been determined and targeted on the Spike protein for docking studies. Three of these sites are located at the interaction points specifically where hydrogen bonding is calculated as the main intermolecular force of the Spike-ACE2 interaction and a fourth allosteric site has been determined by surface mapping of the protein.

The locations of the binding sites have been chosen as these would cause the most destruction in ACE2 interactions. The sites are labeled as site 1–4 and information on the sites can be seen in Supplemental (Table S1, Fig. S1). The results from the SARS-CoV-2 spike glycoprotein are reported in Table 1.

3.2. $3CL^{PRO}$ main protease

Structural alignments have revealed that the SARS-CoV-2 protease is highly conserved for that of the SARS (PDB: 1LVO) main protease at 98% ID [11]. The $3CL^{PRO}$ main protease was run through a restriction minimization process utilizing Schrodinger Docking Suits® (Fig. S3A). Previous studies have revealed in the SARS protease mutation of the residue His162 renders the enzyme inactive. The SARS-CoV-2 homologous residue is His163 (Site 1 center: x = −17.59, y = 15.81, z = 63.53) (Fig. S3B) which has been used as the central point for molecular docking calculations. The active site also revealed a second Histidine (center: His41 Site 2 center: x = −13.81, y = 19.72, z = 71.91) (Fig. S3C) that seems to play a role in the interactions of the bound ligand in the 6LU7 structure, so this was targeted as a second center point for the molecular docking calculations. The results from the SARS-CoV-2 3CL protease are reported in Table 2.

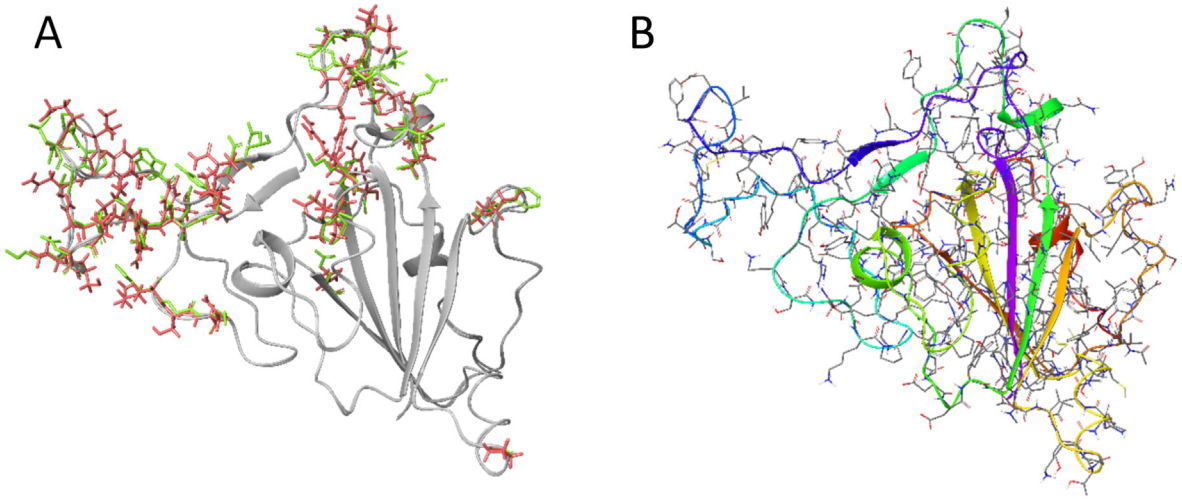

Fig. 1. A) Modeled SARS-CoV-2 Spike Glycoprotein overlaid with the SARS-CoV (PDB: 2GHV) unique amino acids are shown. Variable amino acid residue side chains are shown: Green: SARS-CoV Red: SARS-CoV-2. **B)** Minimized final structure of modeled SARS-CoV-2 spike glycoprotein. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Table 1
Highest scoring molecules for SARS-CoV-2 Spike Glycoprotein.

Site #	DrugBank ID	Docking Score (kcal/mol)	Name	Indication
1	DB06441	−7.234	Cangrelor	$P2Y_{12}$ Inhibitor
1	DB00157	−7.038	Dpnh (NADH)	Supplement Mental Health
2	DB03147	−11.089	Flavin Adenine Dinucleotide (FAD) Adeflavin	B2 Deficiency
2	DB11705	−7.687	Iomeprol	Contrast Medium
3	DB01992	−11.555	Coenzyme A	Supplement
4	DB01133	−9.364	Tiludronate	Paget's disease
4	DB03147	−9.353	Flavin Adenine Dinucleotide (FAD) Adeflavin	B2 Deficiency

Table 2
Highest scoring molecules for SARS-CoV-2 $3CL^{PRO}$ Main Protease.

Site #	DrugBank ID	Docking Score (kcal/mol)	Name	Indication
1	DB00157	−11.016	Dpnh (NADH)	Supplement Mental Health
1	DB00558	−8.843	Zanamivir	Antiviral Drug
1	DB00188	−8.654	Bortezomib	Anti-Cancer
1	DB01232	−7.285	Saquinavir	HIV Protease Inhibitor
2	DB03147	−10.339	Flavin Adenine Dinucleotide (FAD) Adeflavin	B2 Deficiency
2	DB06441	−10.269	Cangrelor	$P2Y_{12}$ Inhibitor
2	DB08889	−8.924	Carfilzomib	Anti-Cancer
2	DB00224	−8.199	Indinavir	HIV Protease Inhibitor
2	DB14761	−7.215	Remdesivir	Antiviral

4. Conclusion

Molecular docking has been employed for the search of possible medications that are contained in the approved bioactive compound database. The hit compounds reported here have potential to inhibit the SARS-CoV-2 spike protein and the $3CL^{PRO}$ main protease but are not guaranteed to have any activity; however, this lays the groundwork for computational drug discovery for new compounds to reduce transmission and symptoms of SARS-CoV-2. We have used structural homology modeling to determine a dock-able target for the SARS-CoV-2 spike protein and have utilized the newly characterized $3CL^{PRO}$ main protease in our docking models.

We have several exciting hits on the $3CL^{PRO}$ main proteinase. Zanamivir is an approved medication for the treatment of influenza A and B viruses [12]. Indinavir and Saquinavir have been shown to treat and prevent HIV. Remdesivir is an antiviral compound in experimental stages that has shown activity against the SARS-coronavirus, Ebola virus, and possibly the SARS-CoV-2 [13–15]. It is also exciting to uncover that Flavin Adenine Dinucleotide (FAD) Adeflavin, B2 Deficiency medicine, and Coenzyme A, a coenzyme, may also be potentially used for the treatment of SARS-CoV-2 infections.

CRediT authorship contribution statement

Donald C. Hall: Writing - original draft. **Hai-Feng Ji:** Writing - review & editing, Writing - original draft.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tmaid.2020.101646.

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