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The Suggestion of a Drug for COVID-19 with Molecular Docking

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ABSTRACT

Background and objectives: This study aimed to study the interaction between the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein complex and seven drugs that inhibit the angiotensin-converting enzyme 2.

Methods: Plots of protein-ligand interaction were obtained using the LigPlot software. In addition, binding energies in kcal/mol, hydrophobic interactions, and hydrogen bonds were determined. Autodock software v.1.5.6 and AutoDock Vina were used for the analysis of molecular docking processes.

Results: The only structure that interacted with the SARS-CoV-2 spike protein was anakinra.

Conclusion: Anakinra was the only drug that interacted with the SARS-CoV-2 spike protein. This could be further investigated for finding a temporary alternative medicine for the treatment of coronavirus disease 2019.

Keywords: Molecular Docking Simulation, SARS-CoV-2, Software.

INTRODUCTION

In December 2019, a novel coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was reported in Wuhan, China. This new type of coronavirus can transmit from animals to humans. The spike (S) glycoprotein in this single-stranded RNA virus is divided into two subunits: S1 and S2. The S1 subunit is responsible for receptor binding, and the S2 subunit causes infection (1). Dry cough, fever, and restlessness are the most common symptoms of SARS-COV-2 infection (2). Viral spikes could be seen as 20-nm-long surface projections under an electron microscope (3). The virus uses the angiotensin-converting enzyme 2 (ACE2) receptor to facilitate viral entry into target cells. Studies have shown that S proteins in SARS-COV-2 and SARS-COV had about 76.5% similarity in their amino acid sequence (4). Conversion of angiotensin 2 to angiotensin 1, which prevents vascular inflammation, is one of the activities of the ACE2 enzyme (5).
Hydroxychloroquine has been regarded as the drug of choice for the treatment of rheumatoid arthritis. A shared phenomenon between rheumatoid arthritis and SARS-COV-2 infection is the elevation of B and T lymphocytes (6). This study aimed to study the interaction between the SARS-CoV-2 S protein complex and various ACE2 inhibitors that are commonly prescribed for inflammation including chloroquine antivirals (7-9), camostat, lamivudine, pepstatin (10, 11), losartan (6), ribavirin (12), and hydroxychloroquine (13,14).

MATERIALS AND METHODS

Drugs were prepared using ChemDraw 8.0. The SARS-CoV-2 S glycoprotein (5wrg) from the Protein Data Bank (PDB) was used in molecular docking and dynamic simulation studies. Input protein structures were prepared by removing nonfunctional water molecules and adding hydrogen atoms. The molecular docking process was carried out using the AutoDock software (version 1.5.6) (Table 1) and AutoDock Vina (Figure 1). The global optimum binding position search was performed using a Lamarckian genetic algorithm. The drugs' torsion angles were identified, and hydrogen atoms were added to the macromolecule. Bond distances were modified, and solvent parameters were added to the 3D structure of the enzyme. The Gasteiger method was used to calculate partial charges. Docking parameters were as follows: population size of 150, the maximum number of energy assessment range of 25.0000, the maximum generation number of 27,000, the mutation rate of 0.02, and the crossover rate of 0.8. Other docking parameters were set to the software default values. After docking, the drugs were ranked according to their docked energy as implemented in the AutoDock software. The residue ASN 479 in the protein binding site was also chosen due to its possible specific hydrogen bonds. This residue was set as a flexible residue, while the other residues were kept as rigid residues. Approximately, to get the most reliable results possible, 100 cycles were performed to get a final binding position. The docking procedure was run, and the maximum negative final docking energy was calculated. During the docking simulation, population size and max steps were set to 150 and 100, respectively. The central grid was at the experimentally determined binding sites.
The LigPlot software was implemented for molecular docking to obtain protein-ligand interaction diagrams. This program automatically generates schematic diagrams of protein-ligand interactions for a given protein in a PDB file (Figure 2). Residues were identical for all seven drugs. The SARS-CoV-2 S protein structure was constituted of strong hydrogen bonds and hydrophobic interactions that were observed in the protein-drug structure.

RESULTS

The docking study showed that the interaction of drugs with protein and residues was complex. The results showed that the best condition studied was the one which appropriately fitted to the protein binding site and formed the protein-drug complex. Therefore, optimal interactions and docking results were defined. Docking and molecular dynamic simulations were used in the molecular modeling protocol in silico, which depicted that the ASN479 group could have favorable interactions with the S1 subunit of SARS-CoV-2 S protein.
The molecular modeling revealed that the orientation with plots, where the ASN residue 479 was placed, showed interaction with drugs (Figure 1). In this position, asparagine within the SARS-CoV-2 S protein was close to the

residues that were connected by hydrophobic interactions and hydrogen bonds.
In the case of anakinra, TYR442, TRP476, LEU478, LYS439, and ASP480 interacted with ASN479 by hydrophobic interactions (Figure 2a).

Table 1-The binding energy between SARS-CoV-2 spike protein and the tested drugs

Drug	Binding energy (Kcal/mol)	References (RMS)	Ki (mM)
Anakinra	**-0.35**	**307.04**	**558.08**
Chloroquine	**-2.93**	**7.17**	**311.03**
Comostat	**17.73**	**304.78**	**0**
Favipiravir	**-2.97**	**313.83**	**6.6**
Lamirudine	**-2.93**	**312.36**	**7.07**
Lostartan	**-4.29**	**309.06**	**6.18**
Ribavirin	**-1.46**	**309.37**	**84.99**

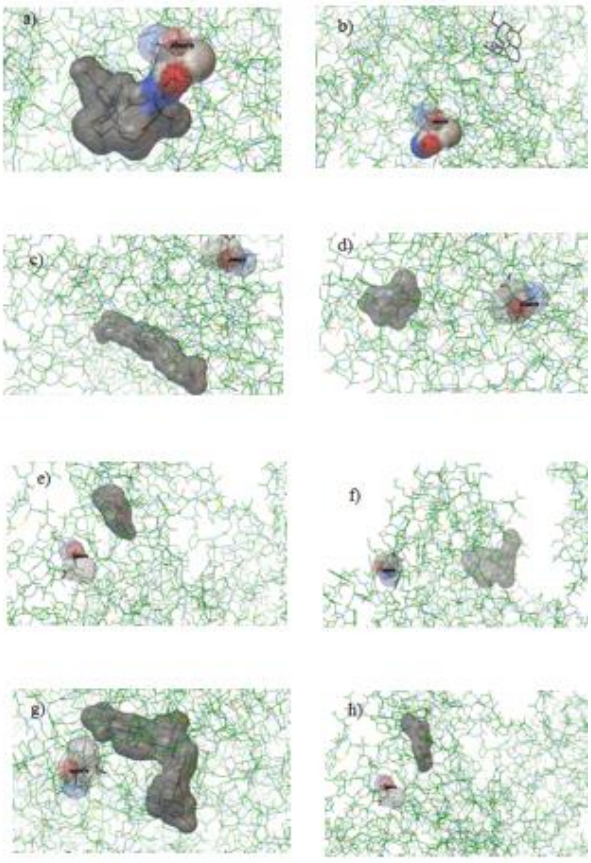

Figure 1- The plots generated by Autodock Vina software. Complex interactions between SARS-CoV-2 spike protein and a) anakinra (binding energy=-7.4 kcal/mol), b) chloroquine (binding energy=-7.2 kcal/mol), c) camostat (binding energy=-8.8 kcal/mol), d) favipiravir (binding energy=-5 kcal/mol), e) lamivudine (binding energy=-6 kcal/mol), f) losartan (binding energy=-6.7 kcal/mol), g) pepstatin (binding energy=-9.5 kcal/mol), and h) ribavirin (binding energy=-6.9 kcal/mol)

In chloroquine, TYR440, ASP480, LEU478, and TYR442 interacted with ASN479 by hydrophobic interactions (Figure 2b). In camostat, LEU478, ASP480, and TYR440 interacted with ASN479 by hydrophobic interactions (Figure 2c).

In favipiravir, TYR442, TYR440, and LEU478 interacted with ASN479 by hydrophobic interactions (Figure 2d). In lamivudine, TYR442, TYR440, and ASP480 interacted with ASN479 by hydrophobic interactions (Figure 2e).

In losartan, TYR440, ASP480, LEU478, and TYR442 interacted with ASN479 by hydrophobic interactions (Figure 2f). In ribavirin, TYR440, ASP480, LEU478, and TYR442 interacted with ASN479 by hydrophobic interactions (Figure 2h). Moreover, the results of the analyses done by LigPlot software showed the presence of hydrogen bonds between the drugs and the S protein. The orientations of these residues with the drugs were depicted by Autodock Vina (Figure 1).

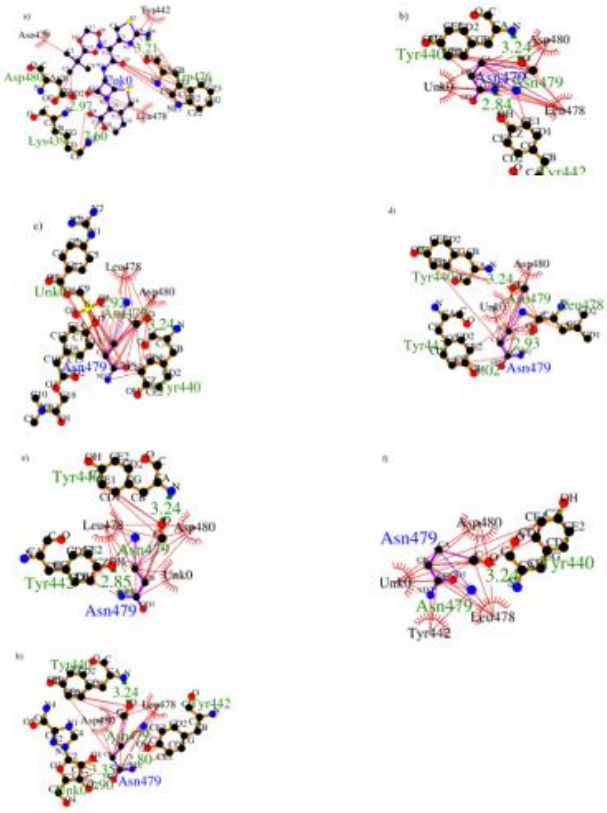

Figure 2-The plots generated by the LigPlot⁺ program. Hydrogen binding (blue line) and hydrophobic interactions (red line) pockets of SARS-CoV-2 spike protein-drugs complexes; a) anakinra, b) chloroquine, c) camostat, d) favipiravir, e) lamivudine, f) losartan, and h) ribavirin

DISCUSSION

The role of interleukin-6 (IL-6) in the pathogenesis of several diseases including multiple myeloma, post-menopausal osteoporosis, and chronic autoimmune diseases has been demonstrated. Thus, potent IL-6 receptor antagonists are commonly used as an effective therapeutic tool (4).

On the other hand, the renin-angiotensin system (RAS), which is a peptide-based system, has been classically recognized as a complex linear humoral system that controls cardiovascular, renal, and adrenal functions (1). The circulatory protease, renin, is a key enzyme of the RAS, which is secreted into the blood. The RAS is involved in respiratory illnesses, such as acute respiratory distress syndrome (ARDS) and acute lung injury during sepsis (5). Pulmonary edema, severe hypoxia, and accumulation of inflammatory cells are hallmarks of ARDS (10). One of the most common indications of ARDS is a strong inflammatory response, which is characterized by the release of proinflammatory cytokines (5). The effects of RAS on the cardiovascular system, particularly on blood pressure, vasoconstriction, cell growth, and cardiac

remodeling have been well-documented (6).
The purpose of this present study was to find potential anti-SARS-CoV-2 S protein drugs. As confirmed by persistently higher levels of IL-6, activated inflammation may have extensive and profound clinical implications for the treatment of arthritis (15, 16). Even when virologically contained, treated HIV-infected individuals have considerably higher IL-6 levels in plasma compared to well-matched uninfected controls (17). Cytokines are pleiotropic and influenced by the concentrations, presence, or absence of other cytokines. Once produced, these factors may act individually or together and directly or indirectly on infected cells, activating cellular components of the intrinsic system and/or promoting specific T- and B-cells' adaptive responses to mediate anti-microbial effects (18-23).

CONCLUSION

Analysis of the number of hydrogen and hydrophobic bonds between the tested drugs and the S protein showed that the complex has a high number of intermolecular Van der Waals bonds, indicating the high affinity of the S protein for TYR442, TRP476, LEU478, LYS439, and ASP480. Theoretically, losartan had the lowest binding energy in the docking simulations. However, comparing reference RMSs to expression standard deviation and the consideration of inhibitor constant, lamivudine, followed by favipiravir, and chloroquine could be the most effective. Nevertheless, anakinra was the only drug that interacted with SARS-CoV-2 S protein in the simulations obtained by AutoDock Vina.

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DECLARATIONS

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this article.

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