MOLECULAR DOCKING STUDY OF NOVEL COVID-19 PROTEASE WITH CURRENT CLINICAL MANAGEMENT AGENTS

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ABSTRACT

Objective: The first case of a new strain of coronavirus (CoV), usually known as CoV disease (COVID)-19, was recognized in Wuhan city of China, in December 2019. Till today, there are no specific treatments available against COVID. During literature searching, it was observed that drugs such as remdesivir, hydroxychloroquine, and chloroquine as their therapeutic options to stop the progress of COVID-19 infections. In the present study, the molecular docking study was performed to understand the binding pattern of selected drugs.

Methods: Molecular docking methods were carried out using molecular virtual Docker software using COVID-19 protease (PDB ID 6LU7), and interactions of these three drugs were visualized.

Conclusion: All three drugs have shown binding interactions with an active site. We assume that these inhibitory activities helped us to identify the possible drug mechanism and further designing of new molecules or investigate the potential use of other available drugs.

Keywords: Coronavirus, Chloroquine, Hydroxychloroquine, Molecular docking, Protease, Remdesivir.

INTRODUCTION

In the last month of 2019, the first case of a new type of coronavirus (CoV), which is now known as severe acute respiratory syndrome (SARS)-CoV-2, was identified and reported in the Wuhan City of China. Later on, in Guangdong state of China, its human-to-human transmission was first confirmed [1]. After this incidence, in the very first week of March 2020, the World Health Organization has announced it as a global public health emergency. According to reports, this deadly virus has infected almost 210 countries and territories worldwide. The total number of confirmed CoV disease (COVID)-19 infections is more than 2.8 million, and around 193 lakh (it is equal to 0.193 million) death occurred in the whole world. It was observed that around 3% of cases are more serious and the virus is spreading at a rapid rate through air distance, airborne transmission, duration on objects, and surfaces, respectively [2]. However, in the meanwhile, the various drug discovery organizations and academics are continuously working on the development of suitable vaccine and other therapies to effectively treat this epidemic and diminish death cases. In this direction, the crystal structure of the COVID-19 main protease in complex with a peptidomimetic inhibitor (PDB code 6LU7) was developed [3,4]. In many reports, it was studied that CoVs are the members of the retrovirus family and contain its genomic data in form of a long RNA strand. This genome contains a replication/transcription complex which is responsible for synthesizing new virions, and two proteases, respectively. The proteases are well known for their actions. They act through cutting the polyproteins into their functional pieces [5]. Here, in present study, we have performed the molecular docking study of three drugs, such as remdesivir, hydroxychloroquine, and chloroquine against COVID-19 infections. One of the major reasons behind the selection of these three drugs is the ability of remdesivir to inhibit viral replication through termination of RNA transcription. It has also expressed its action against SARS-CoV-2 in vitro methods along with inhibition of activities of other similar beta-CoVs. Apart from this, both hydroxychloroquine and chloroquine are under investigation in clinical trials for pre-exposure and post-exposure prophylaxis of SARS-CoV-2 infection. In India, the drug hydroxychloroquine is approved by the Indian Council of Medical Research for the treatment of COVID-19 patients [6,7]. These three drugs are well known for their anti-viral and anti-malarial activities, respectively. Their structures, along with their Expanded Lipinski’s rule properties, are shown in Table 1 [8].

METHODS

Molecular structure and optimization

The structure of these three drugs, namely, remdesivir, hydroxychloroquine, and chloroquine was drawn by Chem Draw Professionals v15.0.0.106. The geometrical isomers structure of these drugs was further optimized by Chem Bio Draw three-dimensional (3D) Ultra v12.0. All energy minimized structures are saved as in pdb format.

Protein preparation

To identify the desired protein, an extensive literature survey was carried out using the PubChem database. On the basis of the obtained information, the desired protein was identified and downloaded from the PDB database (https://www.rcsb.org/). The PDB ID 6LU7 was used for our study, and necessary protein preparation steps were carried out using the Molegro Virtual Docker software [9]. The covalently bound peptidomimetic ligand was isolated, and docking was performed in the absence of water molecules. Simulations performed with and without ligand binding to explain the role of COVID-19 protease of the main content of these three drugs. These algorithms utilize a cavity detection algorithm (cavity) to identify the active region to bind of drug (ligand). Screening of the most stable form of ligand combined with MM2 as energy minimizes to get conformational search for generating ligand poses consistent in the active form of the receptor.
RESULTS AND DISCUSSION

Drug likeness parameters according to Pfizer’s rule of five, such as mol. wt, logP, hydrogen bond acceptor, hydrogen bond donors, and no. of rotatable bonds of the selected drugs were predicted in silico using pKCSM software, are shown in Table 1, and it was observed that calculated parameters were found within the optimum range. The 3D structures of all selected compounds are also represented in Fig. 1.

Next, in this study, we used that X-ray structure of the COVID-19 main protease in complex with an inhibitor N3 (PDB code 6LU7) was downloaded from protein data bank for molecular docking. The total structure weight of this protein is around 34506.34 DA with 2.1 Å resolutions. The molecular docking study was performed using MVD software (https://omictools.com) to investigate the molecular interaction between selected drugs and protease enzyme. The software has identified five protected areas of the enzymatic flap, as represented in Fig. 2. The target protein was further refined using protein preparation option, and 3D energy minimized structures of the designed ligands were superimposed using the software, as shown in Fig. 3. The best-scoring pose of cocrystallized ligand in pdb 6UL7 is shown in Fig. 3. The docking poses of representative compounds are shown in Fig. 4.

Table 1: In silico predicted physicochemical parameter

| Name and structure of compound | M.Wt. | log P | RB^a | HBA^b | HBD^b | PSA^e |
|-------------------------------|-------|-------|------|-------|-------|-------|
| Remdesivir                    | 602.58| 2.31  | 13   | 13    | 4     | 242.38|
| Hydroxychloroquine            | 335.87| 3.78  | 9    | 2     | 4     | 143.02|
| Chloroquine                   | 319.88| 4.81  | 8    | 3     | 1     | 138.23|
| Cocrystallized ligand         | 680.80| 2.08  | 17   | 9     | 5     | 286.07|

HBA: Hydrogen bond acceptor, HBD: Hydrogen bond donors, RB: Rotatable bond
Table 2: The sum of the energies resulting from the interaction of selected drugs and protease enzymes

| Ligand                  | Mol dock score | Rerank score | HBond | Electrostatic bond | Interactions                                                                 |
|-------------------------|----------------|--------------|-------|-------------------|-----------------------------------------------------------------------------|
| Cocrystallized ligand   | −232.04        | −178.63      | −13.22| 0                 | H Bonding Interactions: Phe 140, Ser 144, His 164, Glu 166, Gln 189 and Thr 190. Steric Interactions: Thr 26, Gly 143, His 163, Met 165, and Phe 181. |
| Remdesivir              | −163.62        | −116.14      | −8.44 | 0                 | H Bonding Interactions: Leu 141, Ser 144 and Cys 145. Steric Interactions: Thr 25, His 41, Leu 141, Ser 144, Cys 145, His 163, Met 165, Glu 166, and Gln 189. |
| Hydroxychloroquine      | −114.45        | −75.54       | −9.72 | 0                 | H Bonding Interactions: Tyr 54, Leu 141, Ser 144, Cys 145, and Gln 189. Steric Interactions: Met 49, Gly 143, His 164, Met 165, Phe 181, Asp 187, and Gln 189. |
| Chloroquine             | −110.25        | −70.44       | −8.14 | 0                 | H Bonding Interactions: Gly 143, Ser 144, and Cys 145. Steric Interactions: Leu 141, Gly 143, Ser 144, Cys 145, His 163, His 164, Met 165, and Gln 189. |

The obtained mol dock score is a representation of hydrogen bonding, steric, and other interactions between enzyme and drugs and plays a crucial role to define enzymatic catalysis. Based on the results of the present study, it can be concluded that these clinical management agents can interfere with the important amino acids in the enzymatic cavity to inhibit the protease enzyme virus. In the future, this study will help the scientist for drug development against COVID-19.