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Molecular Docking Study of Several Antiviral Drugs to Defeat COVID-19

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Abstract

Corona virus is one of the significant pathogens that destructs the human respiratory functioning. Deaths and casualties caused by coronaviruses (CoVs) include the severe acute respiratory syndrome (SARS)-CoV and the Middle East respiratory syndrome (MERS)-CoV. The aim of the work was to compare several antiviral drugs and find out which is the most active drug that might be used in treatment for COVID -19. In this study Molecular Docking approach was used to determine the binding affinities of 62 antiviral molecules. The study was carried out using Molegro Virtual Docker 6.0 with PDB 2GTB procured from RCSB Protein Data Bank. Simeprevir and Telaprevir were discovered to be most potent having high MolDock and Rerank scores of -225.158, -78.4383 and -209.467, -136.155 respectively. Further studies may be conducted to design more potent analogue and defeat COVID-19.

Keywords: Molecular Docking, Corona Virus, PDB, Molegro Virtual Docker.

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1. Introduction

Coronavirus is one of the significant pathogens that fundamentally focuses on the human respiratory framework.[22] Past flare-ups of coronaviruses (CoVs) incorporate the severe acute respiratory syndrome (SARS)-CoV and the Middle East respiratory syndrome (MERS)-CoV which have been beforehand portrayed as operators that are an incredible threat to general well-being.[3]A group of patients were admitted to emergency clinics with an underlying finding of pneumonia of an obscure etiology in late December 2019. These patients were epidemiologically connected to a seafood and wet animal wholesale market in Wuhan, Hubei Region, China.[17]

2. History of COVID-19 infections

In December 2019, the first cases were reported.[24]From December 18, 2019 through December 29, 2019, five patients were hospitalized with intense respiratory trouble condition and one of these patients died.[21]

By January 2, 2020, 41 conceded emergency clinic patients had been recognized as having lab affirmed COVID-19 contamination, not exactly 50% of these patients had fundamental illnesses, including diabetes, hypertension, and cardiovascular sickness.[10]These patients were presumed to be contaminated in that medical clinic, likely because of nosocomial disease. It was presumed that the COVID-19 is definitely not a super-hot spreading infection (spread by one patient to numerous others), but instead likely spread because of numerous patients getting infected at different areas all through the emergency clinic through obscure components. What's more, just patients that became clinically ill were tried, accordingly there were likely a lot more patients that were apparently infected.

By January 22, 2020, an aggregate of 571 cases of the 2019-new coronavirus (COVID-19) were accounted in 25 provinces in China.[16]

China's National Health Commission revealed the details of the initial 17 deaths up to January 22, 2020. On January 25, 2020, an aggregate of 1975 cases were affirmed to be infected with the COVID-19 in territory China with a sum of 56 deaths.[26]

Another report on January 24, 2020 evaluated the combined occurrence in China to be 5502 cases.[19] As of January 30, 2020, 7734 cases have been affirmed in China and 90 different cases have additionally been reported from various nations that incorporate Taiwan, Thailand, Vietnam, Malaysia, Nepal, Sri Lanka, Cambodia, Japan, Singapore, Republic of Korea, United Arab Emirates, US, The Philippines, India, Australia, Canada, Finland, France, and Germany. The case casualty rate was determined to be 2.2% (170/7824).[2]

At the time of preparing this manuscript (May 13, 2020), the World Health Organization reported 4 088 848 as total confirmed cases with 82 591 new cases in 24 hours and 283 153 total deaths with 4261 deaths in 24 hours.[12]

2.1 Symptoms of COVID-19 infections

The period from the beginning of COVID-19 indications to death went from 6 to 41 days with a median of 14 days. This period is subject to the age of the patient and status of the patient's immune system. It was shorter among patients>70-years old compared to those below the age of 70.26

The most common symptoms at onset of COVID-19 infection are fever, cough, and fatigue, while other symptoms include sputum production, headache, haemoptysis, diarrhoea, dyspnoea, and lymphopenia. [21,10,26,4]

Clinical features uncovered by a chest CT scan showed pneumonia, however, there were irregular features, for example, RNAaemia, acute respiratory distress syndrome, acute cardiac injury, and incidence of grand-glass opacities that prompted death.[10]

Some cases reported multiple peripheral ground-glass opacities in subpleural regions of both lungs[15] that likely induced both systemic and localized immune response that prompted to increased inflammation. Unfortunately, treatment of some cases with interferon inhalation showed no clinical impact and rather seemed to worsen the condition by progressing pulmonary opacities.[15]

Also, in view of results from chest radiographs upon confirmation, a portion of the cases show an invade in the upper lobe of the lung that is related with expanding dyspnea with hypoxemia.[20] Significantly, though patients infected with COVID-19 showed gastrointestinal symptoms like diarrhea, on the other hand a low level of MERS-CoV or SARS-CoV patients experienced similar GI distress. Hence, it is imperative to test fecal and urine samples to reject a potential elective course of transmission, explicitly through health care workers, patients and so on.[1, 14]

2.2 Pathogenesis

Patients infected with COVID-19 demonstrated higher leukocyte numbers, abnormal respiratory discoveries, and expanded degrees of plasma pro-inflammatory cytokines. One of the COVID-19 case reports demonstrated a patient at 5 days of fever presented with a cough, coarse breathing sounds of both lungs, and a body temperature of 39.0 °C. The patient's sputum demonstrated positive real time polymerase chain reaction results that affirmed COVID-19 infection.[15] The laboratory investigations indicated leucopenia with leukocyte tallied up to 2.91 × 10^9 cells/L of which 70.0% were neutrophils. Moreover, an estimation of 16.16 mg/L of blood C-reactive protein was noted which is above the ordinary range (0–10 mg/L). High erythrocyte sedimentation rate and D-dimer were also observed.[15]

The primary pathogenesis of COVID-19 disease as a respiratory system targeting virus was severe pneumonia, RNAaemia, combined with the incidence of ground-glass opacities, and acute cardiac injury.[10]

2.3 Transmission

Genomic sequence analysis of COVID-19 demonstrated 88% identity with two bat-derived severe acute respiratory syndrome (SARS)- like coronaviruses,[18, 27] showing that mammals are the most probable connection between COVID-19 and people. Individual to individual transmission happens essentially by means of direct contact or through droplets spread by coughing or sneezing from an infected individual. In a small report directed on women in their third trimester who were affirmed to be infected with the

coronavirus, there was no proof that there is transmission from mother to child. Nonetheless, all pregnant women experienced cesarean segments, so it stays indistinct whether transmission can happen during vaginal birth. This is significant on the grounds that pregnant women are moderately more susceptible to infection by respiratory pathogens and severe pneumonia.[6]

The binding of a receptor expressed by host cells is the initial step of viral infection followed by fusion with the cell membrane. It is contemplated that the lung epithelial cells are the primary target of the infection. Hence, it has been accounted for that human-to-human transmissions of SARS-CoV happens by the binding between the receptor-binding domain of virus spikes and the cellular receptor which has been distinguished as angiotensin-converting enzyme 2 (ACE2) receptor.[27, 13]Critically, the sequence of the receptor-binding domain of COVID-19 spikes is similar to that of SARS-CoV. This information unequivocally recommends that passage into the host cells is doubtlessly by means of the ACE2 receptor.[27]

2.4 Phylogenetic Analysis

According to World Health Organization (WHO) COVID-19 has been classified as a β-CoV of group 2B.[11]Ten genome sequences of COVID-19 received from a total of nine patients showed 99.98% sequence identity.[18] Another study showed that was 99.8–99.9% nucleotide identity isolated from five patients and the sequence results revealed the presence of a new beta-CoV strain.[21]The genetic sequence of the COVID-19 exhibited more than 80% identity to SARS-CoV and 50% to the MERS-CoV,[21,18]and both SARS-CoV and MERS-CoV were originated in bats.[8]Thus, the evidence from the phylogenetic analysis indicates that the COVID-19 belongs to the genus beta coronavirus, which includes SARS-CoV, that infects humans, bats, and wild animals.[28]

COVID-19, being the seventh member of the coronavirus family that infects humans and has been classified under the orthocoronavirinae subfamily. The COVID-19 is thus categorized as a biological group within the subgenus sarbecovirus.[28]Based on the genetic sequence identity and the phylogenetic reports, COVID-19 is quite different from SARS-CoV and it can thus be considered

as a new beta coronavirus that infects humans. COVID-19 is most likely developed from bat origin corona viruses. Another piece of evidence that supports the COVID-19 is of bat origin is the presence of a high degree of homology of the ACE2 receptor from a variety species of animals, thus indicating that these animal species can be considered as possible intermediate hosts or animal models for COVID-19 infections.[27] Moreover, these viruses have a single intact open reading frame on gene 8, which further indicates that COVID-19 is of bat-origin CoVs. However, the amino acid sequence of the tentative receptor-binding domain is similar to that of SARS-CoV, which indicated that these viruses might use the same receptor.[21]

2.5 Therapeutics or Treatment Options

At present, there are no particular antiviral medications or vaccine against COVID-19 disease for potential treatment of people. The main choice accessible is utilizing broad-spectrum antiviral drugs like Nucleoside analogues and also HIV-protease inhibitors that could lessen infection disease until the particular antiviral becomes available.[16]The treatment that have so far been endeavored indicated that 75 patients were administrated existing antiviral drugs. The course of treatment included twice a day oral administration of 75 mg oseltamivir, 500 mg lopinavir, 500 mg ritonavir and the intravenous administration of 0·25 g ganciclovir for 3–14 days.[7]Another report indicated that the broad spectrum antiviral remdesivir and chloroquine are profoundly compelling in the control of 2019-nCoV contamination in vitro. These antiviral compounds have been utilized in human patients with a safety track record. Subsequently, these remedial specialists can be considered to treat COVID-19 infection.[25]

3. Materials and Methods

For the study, data sets of 62 molecules of antiviral origin were taken from the earlier reported work done by De Clercq[9] and Chadhuri.[5] Chem Draw Ultra 8.0 was used for the sketching of the molecules with the help of drawing tools in the software. The sketched 2D structures were transformed into 3D structures using module of the program followed by energy minimization and

saving them into .mol format. Protein 2GTB[23]was obtained from RCSB website. Followed by its correction by addition of missing hydrogen atoms and correction of wrong bond orders and the charges.

Then Docking was carried out using Molegro Virtual Docker 6.0 via the Docking Wizard followed by validation where in the superimposition of cognate ligand to that of co-crystallized ligand was evaluated.

4. Results & Discussion:

Molecular docking study revealed that most active compound Simeprevir and Telaprevir bind to the active site of the protein [PDB code: 2GTB]. Simeprevir has a high Moldock score of -225.158 and Rerank Score of -78.4383 with interaction Glu166 that matched to that of co-crystallized ligand in PDB. The table below shows the scores and interactions that matched to the co-crystallized ligand of the top 10 molecules.

Table1: scores and interactions that matched to the co-crystallized ligand of the top 10 molecules

Sl. No.	Name of compound	Moldock score	Rerank score	H-bond	H- bond Interactions
01	Simeprevir	-225.158	-78.4383	-1.80887	Glu166
02	Telaprevir	-209.467	-136.155	-5.23425	Glu166
03	Saquinavir	-197.903	-130.649	-6.29496	Glu166,Asn142
04	Ritonavir	-197.575	-72.3414	-8.42434	Glu166,Gly143
05	Lopinavir	-191.354	-32.8035	-8.81497	Glu166,His164
06	Darunavir	-190.131	-142.613	-6.45388	Glu166
07	Atazanavir	-182.192	-62.8551	-7.27341	Glu166,His164
08	Daclatasvir	-180.632	76.6135	-5.27467	Gly143
09	Boceprevir	-178.528	-116.14	-5.98347	Glu166,Gln189
10	Maraviroc	-175.994	-123.204	-2.33554	Glu166

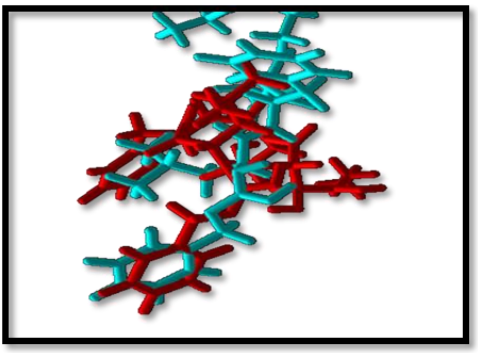

Figure 01: Validation showing Superimposition

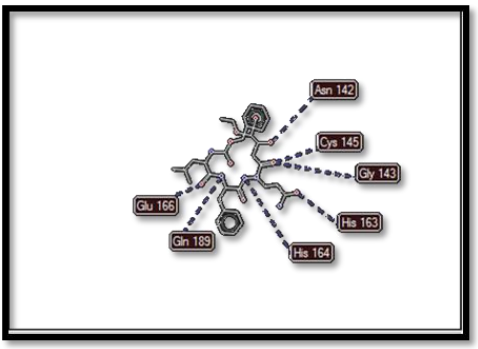

Figure 02: H-Bond Interactions in the PDB

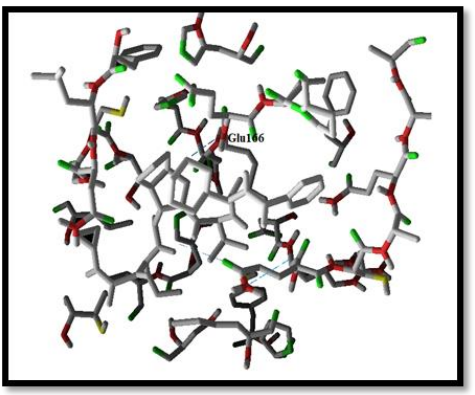

Figure 03: Image showing binding of Simeprevir

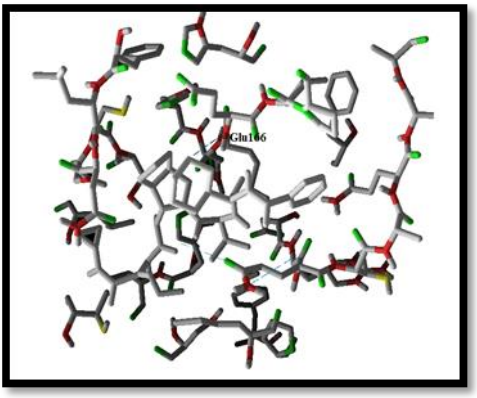

Figure 04: Image showing binding of Telaprevir

5.Conclusion

On the basis of docking study, it can be concluded that drugs like Simeprevir and Telaprevir are the most potent top two compounds against the SARS corona virus. Further in-vitro and in-vivo studies may be conducted to design more potent analogues and the clinical trials may be conducted to evaluate its efficacy.

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Conflicts of Interest

Authors have no Conflict of Interest

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