Molecular Docking Studies on the Anti-viral Activity of Cellulose Acetate Phthalate (CAP) Against SARS-CoV-2 by Protease Mpro

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Abstract

Even after a year, the COVID-19 pandemic produced by the SARS-CoV-2 remains a major source of concerns for scientists. Surprisingly, the primary protease is a key target because of its role in viral propagation. As a result, no significant study in the field of adjuvant has been done too far. CAP stands for “Cellulose Acetate Phthalate”, an industrial polymer utilized in the enteric coating of tablets and capsules. CAP has been shown in certain trials to have anti-HIV properties by using the co-receptor location. Thus, CAP was tested against SAR-primary CoV-2's protease Mpro using in silico methods in the present study. Auto Dock was used to evaluate selected CAP molecules against SAR-CoV-2, and Discovery studio visualizer was used to create 3D and 2D interaction photos. CAP's binding energies were -3.05kcal/mol, -3.78kcal/mol, and -3.01kcal/mol during blind docking, site specific docking, and docking with a N3 inhibitor, respectively. Additionally, the discovery studio visualizer was utilized to look at interacting amino acids and 3D structures. Interestingly, the data from the discovery studio visualizer showed that it established H-bonds with Mpro residues, TYR37, TYR101, and LYS100 during blind docking and LYS88, TYR101, and LYS100 during site specific docking. The findings indicated that CAP binds non-competitively to co-receptor sites and that it may have synergistic effects with other medicines or medications. As a result, it's a good candidate for further testing in the lab and in the clinic.

Introduction

The outbreak of corona virus disease (also known as COVID-19) in Wuhan, China in late 2019 sparked a global public health crisis that has affected over 200 countries. Coronavirus is a crown-like ribonucleic acid (RNA) that belongs to the Coronaviridae family. In the previous two decades, the coronaviruses that cause SARS and MERS have created pandemics, with fatality rates of 10% and 37%, respectively.¹ In December 2019, a new coronavirus with a probable bat origin caused a worldwide outbreak of human lung illness in Wuhan, China.²⁻³ The causative agent was first identified as 2019-novel coronavirus (2019-nCoV) by the World Health Organization (WHO). Because its RNA genome shares 82.30 percent of its identity with SARS coronavirus (SARS-CoV) and has a similar pathogenesis, the virus is known as Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) (host).^{1,4} Corona Virus Disease 2019 (COVID-19) was the name given to the illness (WHO, 2020). On January 30, 2020, WHO declared the COVID-19 epidemic a global public health emergency, and on March 11, 2020, the outbreak was verified as a pandemic. 2020, according to the World Health Organization. SARS-CoV and SARS-CoV-2 have a similar pathophysiology since their genomes are identical (host).¹

Symptoms include a sore throat, cough, headache, myalgia, fatigue, fever, and dyspnea.⁵ In 2003, scientists identified the SARS-CoV, which has infected over 8098 people in 26 countries and has been associated to a significantly higher mortality rate (12%). The COVID-19 had a lower mortality rate (9%) than the SRAS-CoV. (2003).⁶ It takes 1–14 days for the illness to develop, and after 6–7 days, it can lead to pneumonia, complications, and even death. Extremely high amounts of Interleukin (IL)-10, IL7, IL2, macrophage inflammatory protein 1A, monocyte chemoattractant protein 1, inducible protein 10,

granulocyte-macrophage colony-stimulating factor, and tumour necrosis factor cause health problems.⁷ In addition, there have been many cases of individuals who are asymptomatic or do not have a temperature.⁸ Elevated levels of creatinine, prothrombin time, Lactate dehydrogenase (LDH), Alanine transaminase (ALT)/Aspartate transaminase (AST), and Creatine kinase (CPK) have also been associated to severe sickness. Sputum, throat swabs, bronchoalveolar lavage, and endotracheal aspirates, as well as molecular and immunological tests, are used to diagnose patients.⁹ Imaging technologies such as X-rays and CT scans have been used in preliminary assessments of disease situations.¹⁰ To date, a lot of work has been done to treat covid-19, such as Several preliminary study findings investigated the potential of a medication combination of Lopinavir and Ritonavir to cure COVID–19 afflicted persons, which has previously been used to treat people infected with HIV, SARS CoV, or the Middle East respiratory syndrome (MERS) coronavirus.¹¹⁻¹² Though there have been other coronavirus therapeutic targets found, the main protease (Mpro), also known as 3-chymotrypsin-like protease (3CLpro), has become the most well-known.¹³ The Mpro splices the large polypeptide derived from viral RNA at 11 distinct places, mostly from Leu to Gln (Ser, Ala and Gly). These crucial splicing sites aren't the same as the ones present in humans. Enzyme inhibition may limit viral pathogenesis, making it a viable treatment target for SARS-CoV-2. Furthermore, a mechanism-based peptide-like inhibitor (N3) was found utilising computer-aided drug design, and the crystal structure of the SARS-CoV-2 Mpro in connection with this chemical was determined.¹⁴

Computational biology and bioinformatics have the potential to change not just the way medicines are developed, but also to speed up and lower the cost of drug development. RDD assists in the facilitation and acceleration of the drug design process, which involves a variety of techniques for discovering new compounds. One of these techniques is the docking of medicinal drugs with receptors. A receptor is the site of drug action, and it is this site that is ultimately accountable for the therapeutic effect. The phenomenon of two molecules fitting together in three-dimensional space is called docking.¹⁵⁻¹⁷

The prospect of repurposing licensed and well-known medicines against SARS-CoV-2 pharmacological targets, either alone or in combination, to combat COVID-19 virulence has been highlighted by recent studies utilising integrated computational methods. In silico methods were used to identify many plant compounds as potential inhibitors of the Mpro of SARS-CoV-2. Bictegravir, dolutegravir, paritaprevir, and raltegravir mimics were tested against 3CLpro and 2'-OMTase using in silico methods.¹⁸⁻¹⁹ In another study, natural compounds derived from coumarine and flavone, darunavir, remdesivir, and saquinavir, were demonstrated to inhibit 3CLpro.¹⁸⁻²⁰ Other plant-derived powerful possibilities, such as bonducellpin D, oolonghomobisflavan-A, and others, have shown potential inhibition of Mpro.²¹⁻²²

However, no substantial work was found in covid-19 for adjuvant trials. Adjuvants are employed in many pharmaceutical goods, such as vaccines, certain medications, chemotherapy, and other things, and based on their outcomes, it wouldn't be incorrect to claim that substances that increase the impact of pharmaceutical products are referred to as adjuvants.²³⁻²⁶ As a result, drugs with antiviral activity might be significant resources in the fight against covid-19.²⁷⁻²⁸ In a study of pharmaceutical excipients,

researchers discovered that cellulose acetate phthalate (CAP), which is commonly used for enteric coating of tablets and capsules, is a potential microbicide option for the prevention of infection by STD pathogens such as HIV-1.²⁹ As a result, we conducted computational-based investigations of CAP to see how it affects Mpro in this study.

Results And Discussion

After examining molecular interaction findings produced from docking experiments with various medications, we observed that CAP interacts with COVID-19 proteins in some way. The final intermolecular energy, inhibition constants, and creation of hydrogen bonds during the interaction between medications and receptor molecules might all be utilised to assess molecular docking data.³⁰

During blind docking, the CAP ligand was found to interact and form conventional hydrogen bonds with TYR37, TYR101, and LYS100 (fig 1(a)); formed a carbon hydrogen bond with LYS100 as shown in fig.1(b); and based on the data obtained from blind docking, it was observed that it was interacting and forming conventional hydrogen bonds with LYS88, TYR101, and LYS100.

The binding energy and inhibition constant of the CAP ligand were determined to be '-3.05 kcal/mol and 5.86mM', '-3.78 kcal/mol and 1.69mM', and '-3.01 kcal/mol and 6.25mM', respectively, for blind (fig. 1(a) & (b)), site specific (fig.2(a) & (b)), and in the presence of N3 inhibitor docking (fig. 3).

Conclusion

The interaction energies evaluated from in-silico tests using CAP against COVID-19 major protease (PDB: 6LU7) revealed that the main protease interacted with CAP. CAP renders HIV-1 inactive by inhibiting the co-receptor binding site on the virus's envelope glycoprotein gp120, while leaving the main cellular receptor CD4 accessible, according to CAP test results (cellulose's anti-HIV action).³²⁻³³ Thus, a synergistic suppression of HIV-1 IIIB has been shown.³⁴

Similarly, the expected results in our investigations revealed that CAP coupled with the co-receptor binding site with about the same binding energy in both blind docking and in the presence of a N3 inhibitor. As a result, the CAP may have a synergistic effect with COVID-19 medicines. However, it is recommended that further research should be done to confirm the antiviral and synergistic effects of CAP against COVID-19.

Materials And Methods

Ligand preparation and optimization

Chemdraw software was used to generate the two-dimensional (2D) structure of CAP, as well as MOL data. The MOL must be converted to.pdb files using openbabel software because it cannot be used

directly for docking studies.

Mpro molecule preparation

COVID-19 Mpro crystal structure in the presence of the peptide inhibitor N3 (n- [(5-methylisoxazol-3-yl) carbonyl]) alanyl-l-valyl-n~1~-((1r,2z) -4-(benzyloxy). We utilized a -4-oxo-1-[(3r)-2oxopyrrolidin-3-yl] for the molecular docking experiments. PDB ID 6LU7 and crystal resolution 2.16 for methylbut-2-enyl)-l-leucinamide) peptide from Protein Data Bank (PDB).¹⁴ Initially, the Auto Dock Tool (ADT) was used to eliminate all HOH molecules, assign hydrogen polarities to the protein, and added Kollman charges and polar hydrogen atoms. The prepared protein and the 6LU7 protein structure file were likewise charged with Gasteiger charges. Conversion of PDB to 6LU7 (PDBQT) done.^{20,35}

Analysis of In-silico interaction

MGL tools Autodock 4.2. software approaches were used to predict the interaction energies between medicinal compounds and COVID-19 proteins. Interactions were analysed using the Lamarckian genetic approach (LGA). AutoDock uses the method below to compute the ligand and receptor interaction binding energy (DG):

$$\Delta G_{\text{binding}} = \Delta G_{\text{gauss}} + \Delta G_{\text{repulsion}} + \Delta G_{\text{hbond}} + \Delta G_{\text{hydrophobic}} + \Delta G_{\text{tors}}$$

The dispersion of two gaussian functions is referred to as ΔG_{gauss} . $\Delta G_{\text{repulsion}}$: the square of the distance is repelled if the distance is larger than a threshold value. ΔG_{hbond} : a ramp function that may be used to model metal ion interactions. $\Delta G_{\text{hydrophobic}}$: ramp function, ΔG_{tors} : proportional to the number of rotatable bonds.³⁶

Additionally, water (HOH) was removed during the modification of the native pdb file of the chosen 3D structure of COVID-19 protein, i.e., main protease (PDB: 6LU7). For all three docking experiments, the medicinal compounds were given hydrogen atoms, Kollman unified charges, default solvation parameters, and a Gasteiger charge. The grid box was designed to encompass the maximal area of the protein in the first docking experiment, resulting in blind docking. In the X, Y, and Z axes of a grid point, the values were set to 1160 X 1260 X 1260. The grid point spacing was set at 0.575 in the default configuration. In the second docking experiment, the X-, Y-, and Z-axis of a grid point were adjusted to 440 X 440 X 480. The grid point spacing was set at 0.375 in the default configuration. In the third docking experiment, the X-, Y-, and Z-axes of a grid point were adjusted to 680 X 200 X 680. The grid point spacing was set at 0.375 in the default configuration. The Lamarckian Genetic Algorithm (LGA) was used to compute protein–drug molecule flexible docking calculations.³⁷ For population size (ga pop size), energy

evaluations (ga num generation), mutation rate, crossover rate, and step size, the default LGA parameters were set to 150, 2,500,000, 27,000, 0.02, 0.8, and 0.2, respectively. A maximum of ten LGA runs were allowed. After the docking steps were completed successfully, the obtained conformations of selected SARS-CoV-2 proteins and drug complexes were subjected to additional analysis and were thoroughly examined for the formation of various types of interactions using Discovery Studio 2019 molecular visualization software.³⁸

Declarations

Author contributions statement:

A.S. Concept and Design of the Manuscript

P.A. Verification of data and Editing of Manuscript

U. Prepared content of Manuscript

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Figures

a

b

Figure 1

(a) CAP interaction with Mpro in blind docking (31) (b) 2D structure of CAP and surrounding amino acid residues involved in interaction during blind docking.

Figure 2

(a) CAP interaction with Mpro in site specific docking (31) (b) 2D structure of CAP and surrounding amino acid residues involved in interaction during site specific docking

Figure 3

CAP interaction with M^{pro} in the presence of N3 inhibitor (31) *The images (fig.1-3) were created by using the BIOVIA discovery studio visualizer 21.1.0.0