Section A-Research paper
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Cellulose acetate phthalate (CAP) as an adjuvant for the treatment of severe acute respiratory syndrome coronavirus type 2: A molecular docking study

Naveen Khatri[1], Prabhu. M[2], Dr. Dharmendra Bhati[3], Dr. Vimal Kumar Bharti[4], Shubhangee Tomar[5], Prof. Minakshi P. Sathe[6], Prof. (Dr.) Mrunal K Shirsat[7], Meenambiga Setti Sudharsan*[8]

[1] College of Pharmacy Pt BD Sharma University of Health Sciences, Rohtak, Haryana, India
[2] Associate Professor, School of Pharmacy, Sri Balaji Vidyapeeth Deemed to be University, Pondicherry
[3] Assistant Professor in Chemistry Department, Government College, Jewar
[4] Associate Professor, S.D. College of Pharmacy & Vocational Studies, Bhopa Road, Muzaffarnagar. U.P 251001
[5] Associate Professor, Gujarat Technological University
[6] Associate Professor, Gondwana University
[7] Professor/Principal, SBSPMs B-Pharmacy College Ambejogai District-Beed-431517
[8] Assistant Professor, Department of Bioengineering, Vels Institute of Science Technology and Advanced Studies, Pallavaram, Chennai-600117

Corresponding Author Details:
Meenambiga Setti Sudharsan
Assistant Professor, Department of Bioengineering, Vels Institute of Science Technology and Advanced Studies, Pallavaram, Chennai-600117
Email id: meenambiga.se@velsuniv.ac.in

Abstract

Experts are still very worried about the COVID-19 pandemic that the SARS-CoV-2 outbreak produced a year later. Unexpectedly, the primary protease is a significant target because of its role in viral transmission. There is currently little substantial evidence pertaining to the off-label applications of pharmaceutical adjuvants. An industrial polymer called cellulose acetate phthalate, or CAP as it is more often known, is utilized in the enteric coating of tablets and capsules. In several studies, it has been shown that CAP possesses anti-HIV properties via the co-receptor site. As a consequence, an *in-silico* method was used in the present investigation to assess CAP's efficacy against the protease M^{pro} of SAR-primary CoV-2. Auto Dock was used to test a few CAP compounds against SAR-CoV-2, and Discovery Studio Visualizer was used to create 3D and 2D interaction photos. The binding energies for CAP were 3.05 kcal/mol, 3.78

kcal/mol, and 3.01 kcal/mol for site-specific docking, blind docking, and docking with a N3 inhibitor, respectively. It was also possible to view how the amino acids interacted with the CAP structure using the discovery studio visualizer. Intriguingly, the results from the discovery studio visualizer showed that it established H-bonds with Mpro residues, TYR37, TYR101, and LYS100 during blind docking, and with LYS88, TYR101, and LYS100 during site-specific docking. More research is required to establish CAP's synergistic effectiveness as an anti-viral agent, but the findings indicated that it binds to allosteric sites non-competitively and that it may function in conjunction with other anti-viral drugs.
Keywords: COVID-19 pandemic, anti-HIV property, Cellulose Acetate Phthalate, Protease Mpro

Introduction

Over 200 nations have been impacted by the corona virus illness epidemic that started in Wuhan, China in late 2019 and is also referred to as COVID-19. The Coronaviridae family of viruses includes the crown-shaped ribonucleic acid (RNA) known as coronavirus. The coronaviruses that cause SARS and MERS have caused pandemics in the last 20 years, with death rates of 10% and 37%, respectively. (Rabi and others, 2020) In Wuhan, China, in December 2019, a novel coronavirus with a likely bat origin led to a global epidemic of human lung disease.2020 (Wu et al.; Zhou et al.) The World Health Organization (WHO) originally identified the harmful substance as 2019-novel coronavirus (2019-nCoV). The virus is known as Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) (host) because its RNA genome shares 82.30 percent of its identity with SARS coronavirus (SARS-CoV) and has a similar pathology. Rabi and colleagues 2020; R. Lu et al., 2020) The sickness was known as Corona Virus Disease 2019 (COVID-19) (WHO, 2020). The World Health Organization (WHO) proclaimed the COVID-19 epidemic a worldwide public health emergency on January 30, 2020, and on March 11, 2020, the outbreak was confirmed as a pandemic 2020. Given that their host genomes (SARS-CoV and SARS-CoV-2) are identical, their pathophysiologies are comparable.(Rabi and others, 2020)

A sore throat, cough, headache, myalgia, weariness, fever, and dyspnea are a few symptoms.Lovato and colleagues 2020 The SARS-CoV, which has infected more than 8098 individuals in 26 countries and has been linked to a much higher fatality rate (12%), was discovered by scientists in 2003. Compared to the SRAS-CoV, the COVID-19 exhibited a reduced death rate (9%).In 2020, Shereen et al. The sickness takes 1–14 days to manifest, and after 6-7 days it may cause pneumonia, other problems, or even death. Health issues are brought on by very high concentrations of tumour necrosis factor, interleukin (IL)-10, IL7, IL2, macrophage inflammatory protein 1A, monocyte chemoattractant protein 1, and inducible protein 10.2020 (Huang et al.) There have also been several instances of people who are asymptomatic or don't have a fever.S. Lu and others, 2021 Severe illness has also been linked to increased levels of creatinine, prothrombin time, lactate dehydrogenase (LDH), alanine transaminase (ALT)/aspartate transaminase (AST), and creatine kinase (CPK). Patients are diagnosed using sputum, throat swabs, bronchoalveolar lavage, endotracheal aspirates, as well as

molecular and immunological studies.Abbasi-oshaghi and colleagues, 2020 Preliminary analyses of illness conditions have employed imaging technologies including X-rays and CT scans.2020 (Singhal) Many efforts have been made to treat COVID-19 up to this point, including The treatment of COVID-19 patients with a drug combination of lopinavir and ritonavir, which has previously been used to treat individuals with HIV, SARS CoV, or the Middle East respiratory sickness (MERS) coronavirus, was the subject of many early research results.(Liang et al., 2020; Chu et al., 2004) Other coronavirus therapeutic targets have been identified, but the major protease (Mpro), also known as 3-chymotrypsin-like protease (3CLpro), has emerged as the most well-known.(2003) Anand et al. The big polypeptide produced from viral RNA is spliced by the Mpro at 11 different locations, usually from Leu to Gln (Ser, Ala, and Gly). These vital splicing sites differ from those seen in humans. Enzyme inhibition may restrict viral pathogenesis, making it a potential SARS-CoV-2 therapeutic target. 2020 (Jin et al.)

The development of pharmaceuticals may alter as a result of computational biology and bioinformatics, which also have the potential to accelerate and reduce the cost of medication development. RDD helps to facilitate and speed up the drug design process, which uses a number of methods for finding novel molecules. Docking pharmaceuticals with receptors is one of these methods. The location of medication action is a receptor, and it is this site that is ultimately responsible for the therapeutic outcome. Docking is the process by which two molecules cling to one another in three dimensions.(Leite et al., 2007; Christensen et al., 2007; Baskaran & Ramachandran, 2012) Numerous studies utilising integrated computational methods have highlighted the possibility of repurposing licenced and well-known medications against SARS-CoV-2 pharmacological targets, either alone or in combination, to combat COVID-19 virulence, providing strong evidence that the use of computational approaches facilitated the understanding and utilisation of compounds to a whole new level. In another work, in-silico techniques were employed to identify many plant chemicals as possible SARS-CoV-2 Mpro inhibitors. In-silico tests were performed on Bictegravir, Dolutegravir, Paritaprevir, and Raltegravir mimics against 3CLpro and 2'-OMTase.Khan and others (R. J., 2021; S. A., 2021) Another research showed that the natural substances Darunavir, Remdesivir, and Saquinavir, which are derived from coumarin and flavone, inhibit 3CLpro.(Naik et al., 2020; R. J. Khan et al., 2021; S. A. Khan et al., 2021) Bonducellpin D, Oolonghomobisflavan-A, and other strong plant-derived candidates have shown potential Mpro inhibition.Bhardwaj et al. and AB et al., 2020

Excipients as adjuvants or as antagonists of the allosteric sites in COVID-19, on the other hand, have not been the subject of any significant research. Adjuvants are used in a variety of pharmaceutical products, including vaccinations, certain drugs, chemotherapy, and other things, and it wouldn't be erroneous to say that these compounds boost the effectiveness of pharmaceutical products based on their results. (Zheng et al., 2021; Denduluri et al., 2021; Hsu & Hwang, 2019; Sarris et al., 2009) Other sites other than active sites are those known as allosteric sites. These locations may act as binding sites and control how proteins function.Srinivasan and colleagues (2014); Gurnera & Berezovsky (2016) Excipients and other compounds with antiviral activity may thus be important tools in the battle against COVID-

19.(Sarkar et al., 2021; El-Megharbel et al., 2021) In order to prevent infection by STD pathogens like HIV-1, we conducted computational-based investigations on covid-19 Mpro with cellulose acetate phthalate (CAP), which is commonly used for enteric coating of tablets and capsules.(*Lee JC: Cellulose Acetate Phthalate. In Handbook of Pharmaceutical Excipients: American Pharmaceutical Association Pub.; 199491-93*, n.d.)

Material and methods

Ligand preparation and optimization

The two-dimensional (2D) structure of CAP and MOL data were created using Chemdraw software. The MOL cannot be used directly for docking studies and needs be converted to.pdb files using the free babel programme.

Mpro molecule preparation

We used a -4-oxo-1-[(3r)-2oxopyrrolidin-3-yl] for the molecular docking experiments on the 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). Methylbut-2-enyl)-l-leucinamide peptide from Protein Data Bank (PDB) with PDB ID 6LU7 and crystal resolution 2.16 (Jin et al., 2020). To begin, all HOH molecules were removed using the Auto Dock Tool (ADT), hydrogen polarities were assigned to the protein, Kollman charges were added, and polar hydrogen atoms were then inserted. The 6LU7 protein structure file and the prepared protein both received Gasteiger charges. PDB to 6LU7 conversion (PDBQT) (Naik et al., 2020; Ram et al., 2021)

Analysis of In-silico interaction

Tools MGL The interaction energies between pharmaceuticals and COVID-19 proteins were predicted using Autodock 4.2 software techniques. Lamarckian genetic analysis (LGA) was used to examine interactions. The following equation was utilised by AutoDock to calculate the binding energy (DG) between a ligand and a receptor.

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

The dispersion of two gaussian functions is referred to as ΔG_{gauss}. $G_{repulsion}$: the square of the distance is repelled if the distance is larger than a threshold value. G_{hbond}: a ramp function that may be used to model metal ion interactions. $\Delta G_{hydrophobic}$: ramp function, G_{tors}: proportional to the number of rotatable bonds.(Morris et al., 1998)

In addition, water (HOH) was eliminated when the native PDB file of the selected 3D structure of the COVID-19 protein, i.e., primary protease (PDB: 6LU7), was modified. The pharmaceutical compounds were given hydrogen atoms, Kollman unified charges, default solvation parameters, and a Gasteiger charge for each of the three docking studies. In the first docking experiment, which used blind docking, the grid box was made to fully enclose the protein. A grid point's X, Y, and Z axes were configured to have values of 1160 X 1260 X 1260. The default setup has a grid point spacing of 0.575. The X, Y, and Z axes of a grid point were changed to 440 X 440 X 480 for the second docking experiment. The default setup has a grid point spacing of 0.375. The X, Y, and Z axes of a grid point were changed to 680 X 200 X 680 for the third docking experiment. The default setup has a grid point spacing of 0.375. Flexible

docking computations between protein-drug molecules were performed using the Lamarckian Genetic Algorithm (LGA).(2009) Morris et al. The default LGA settings were set to 150, 2,500,000, 27,000, 0.02, 0.8, and 0.2 for population size, energy evaluations (ga pop size), mutation rate, crossover rate, and step size, respectively. Ten LGA runs at most were permitted. After the docking procedures were successfully completed, the obtained conformations of specific SARS-CoV-2 proteins and drug complexes were thoroughly examined for the formation of various types of interactions using molecular visualisation software called Discovery Studio 2019. (Jamal and others, 2021)

Results

We discovered that CAP interacts with COVID-19 proteins in some manner after looking at molecular interaction results generated from docking tests with different drugs. It is possible to evaluate molecular docking data by taking into account the final intermolecular energy, inhibition constants, and formation of hydrogen bonds during the interaction between drugs and receptor molecules.(Ferreira et al., 2015)

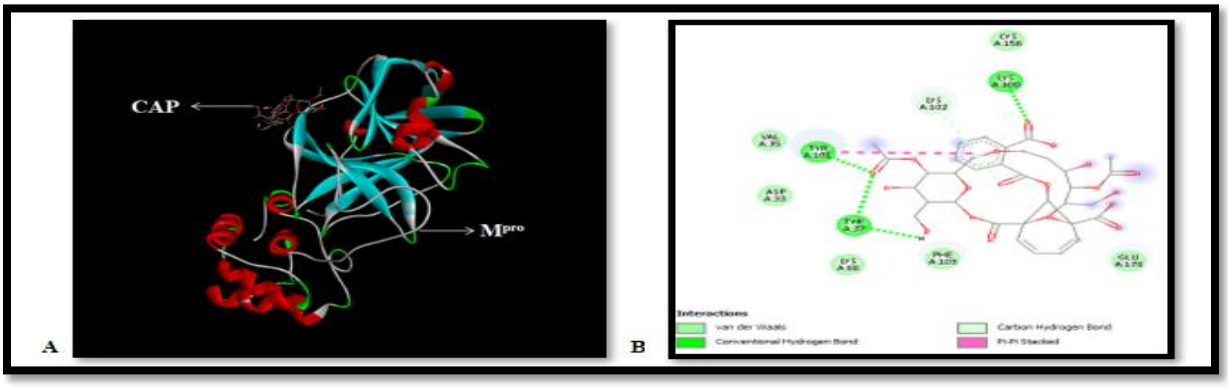

Fig.1 (A) CAP interaction with M^{pro} in blind docking (b) 2D structure of CAP and surrounding amino acid residues involved in interaction during blind docking

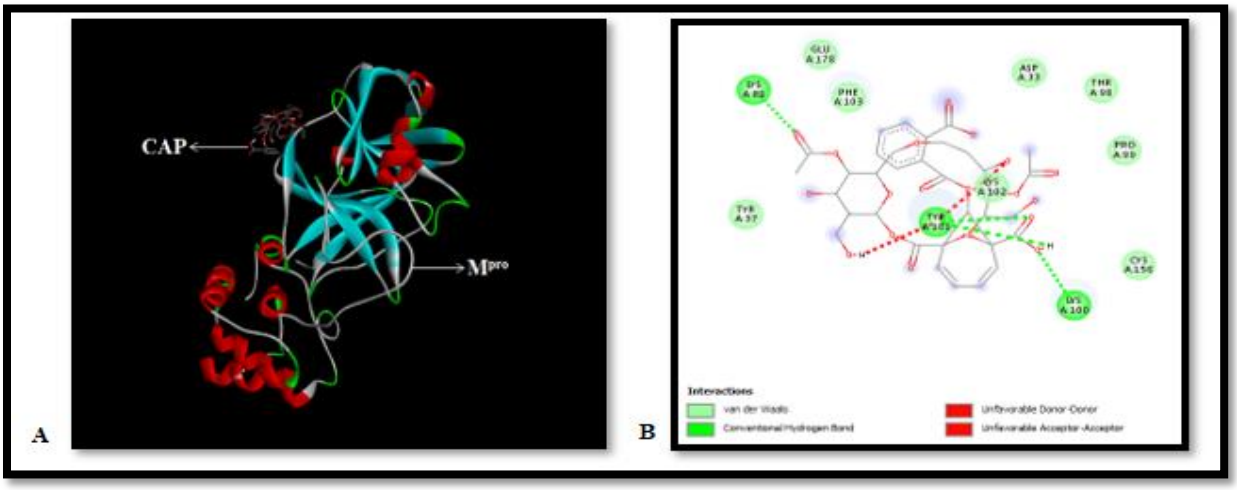

Fig.2 (A) CAP interaction with M^{pro} in site specific docking (B) 2D structure of CAP and surrounding amino acid residues involved in interaction during site specific docking

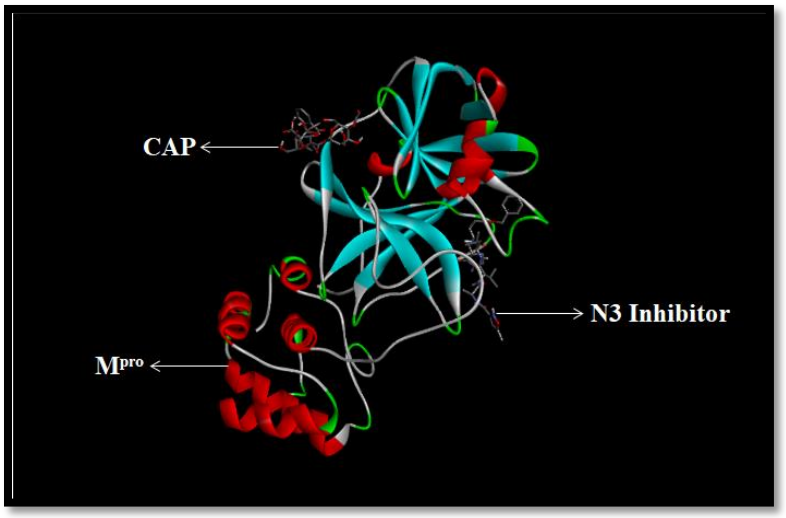

Fig.3- CAP interaction with M^{pro} in the presence of N3 inhibitor
***Fig. 1,2 and 3 were created by using the BIOVIA discovery studio visualizer 21.1.0.0**

During blind docking, the CAP ligand was found to interact and form conventional hydrogen bonds with TYR37, TYR101, and LYS100; 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 CAP has interacted and formed 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. 1A & B), site specific (Fig. 2A & B), and in the presence of N3 inhibitor docking (Fig. 3).

Discussion

The primary protease interacted with CAP, as shown by the interaction energies calculated from in-silico testing utilising CAP against COVID-19 major protease (PDB: 6LU7). According to CAP test findings, CAP made the HIV-1 inactive by blocking the co-receptor binding site on the virus's envelope glycoprotein gp120, while keeping the major cellular receptor CD4 accessible. This was noticed by reviewing earlier evidence on CAP activity against HIV virus.(Neurath et al., 2001; H et al., 1996) (The anti-HIV properties of cellulose) As a consequence, HIV-1 IIIB was suppressed synergistically.(2002) Neurath et al. In a similar vein, the findings of our study showed that CAP interacted with the Mpro, but not at the active sites, but rather at the allosteric sites, with about the same binding energy in both blind docking and in the presence of a N3 inhibitor.

Our research raises a number of possibilities because when CAP is administered together with other medications, it may have a synergistic impact since CAP binds to allosteric sites while the other medications attach to active sites. The allosteric sites don't need nearly as much high binding energy as the active sites do, which suggests that CAP with low binding energy may still exert its effects. Due to its low binding energy, CAP won't compete with the major medications for the active sites. It's interesting to note that, generally speaking, allosteric sites are less susceptible to mutation than active sites. Therefore, the treatment of the covid-19 may benefit

from CAP interaction with the allosteric sites. The protein may be partially regulated via allosteric sites.

Conclusion

The coronaviruses that cause SARS and MERS have caused pandemics in the last 20 years, with death rates of 10% and 37%, respectively. The antiviral effectiveness of several medications against the corona virus is being studied. Potentially useful as a medicinal excipient is cellulose acetate phthalate (CAP). It has modest antiviral action, according to reports. Using Protease M^{pro} as an in-silico model, we examined the antiviral efficacy of CAP against the COVID-19 virus in the current work. According to the data, CAP and other anti-viral medications may work together as an adjuvant in a synergistic manner. Future studies may be able to partially or completely control the covid-19 M^{pro} protein by CAP interaction with allosteric regions. In order to prove the antiviral ability of CAP as an adjuvant by using relevant animal models against COVID-19 virus, we advise further study.

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