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IN-SILICO REPURPOSING OF FDA-APPROVED HEPATITIS C DRUGS, VELPATASVIR AND BOCEPREVIR, AGAINST THE OMICRON VARIANT SPIKE GLYCOPROTEIN

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Abstract

The rapid emergence of the SARS-CoV-2 Omicron variant, carrying more than 50 mutations including over 30 within the spike (S) glycoprotein, has challenged existing vaccines and therapeutics. Although several drugs alleviate COVID-19 symptoms, none fully eliminate the virus. Repurposing FDA-approved antivirals provides a fast and cost-effective strategy to identify new therapeutic candidates. Owing to genomic and replication similarities between hepatitis C virus (HCV) and SARS-CoV-2, we assessed the inhibitory potential of two FDA-approved HCV drugs, boceprevir (NS3/4A protease inhibitor) and velpatasvir (NS5A inhibitor), against the Omicron spike using molecular docking. In the absence of an experimentally determined Omicron spike structure, a homology-modeled 3D structure (97.5% sequence identity) was generated and validated through GMQE, QMEAN, Ramachandran, and ERRAT analyses. Active-site residues, including Omicron-specific mutations (LEU365, PRO367, GLN403), were identified via CASTp for docking studies. Both drugs exhibited strong binding affinities, with docking scores of –11.7 kcal/mol (boceprevir) and –12.4 kcal/mol (velpatasvir), and binding free energies of –8.42 and –9.15 kcal/mol, respectively. Interaction analyses revealed stable hydrogen bonding, hydrophobic contacts, and van der Waals interactions with mutational hotspots critical for spike–ACE2 engagement. These findings suggest that velpatasvir and boceprevir may impede Omicron infectivity, warranting further in vitro, in vivo, and clinical validation.

1. Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) disease-2019 (COVID-19) outbreak, first identified in Wuhan, China in December 2019 [1] rapidly evolved into a global pandemic, affecting over 356 million people and causing more than 5.6 million deaths as of January 26, 2022 [2]. COVID-19 was declared a Public Health Emergency of International Concern by the World Health Organization (WHO) on January 30, 2020 [3, 4]. Like other RNA viruses, SARS-CoV-2 undergoes continuous genetic variation through mutations, giving rise to variants with altered transmissibility, virulence, and immune escape potential [5]. To prioritize global monitoring and research, WHO classified these as Variants of Interest (VoI) or Variants of Concern (VoC), with five major VoCs identified to date: Alpha (United Kingdom, September 2020), Beta (South Africa, May 2020), Gamma (Brazil, November 2020), Delta (India, October 2020), and Omicron (B.1.1.529, multiple countries, November 2021) [6-8].

The Omicron variant is distinguished by over 50 mutations, more than 30 of which occur in the

spike (S) glycoprotein, a critical determinant of viral entry and the main target for neutralizing antibodies and vaccines [9, 10]. Structural changes in the spike protein's receptor-binding domain (RBD) may enhance binding to the human angiotensin-converting enzyme 2 (ACE2) receptor, potentially increasing transmissibility and impacting the efficacy of current vaccines and therapies [9, 11].

Given the rapid spread of COVID-19 and the absence of specific vaccines or drugs during the early outbreak, repurposing FDA-approved antivirals through in-silico screening emerged as an urgent strategy. Computational docking against SARS-CoV-2 spike proteins and the human ACE2 receptor, a known viral entry point, offers a rapid approach to identify potential therapeutics. The spike protein alone can mediate cell infection and is a key target for neutralizing antibodies in previously infected individuals. [12-14]. The SARS-CoV-2 spike (S) protein is crucial for viral entry and represents a major target for antivirals and vaccines. Its interaction with ACE2 enables cell infection, with ACE2 alone sufficient for viral entry [13, 15, 16]. SARS-CoV-2, a single-stranded RNA virus with a 29,903-nucleotide genome (GenBank No. MN908947), invades human cells through S protein binding to ACE2, similar to SARS-CoV [17-20]. SARS-CoV-2 infects cells via the ACE2 receptor [16, 21], Its RNA-dependent RNA polymerase (RdRp) synthesizes complementary RNA and is a key target for antiviral drug development [22, 23]. The Omicron variant carries ~50 mutations, over 30 in the spike protein, the main vaccine target [24].

Drug repurposing offers a rapid strategy against SARS-CoV-2, as FDA-approved drugs already have established safety, pharmacokinetics, and lower development costs. Studies report the use of traditional Chinese medicines and antivirals such as oseltamivir, remdesivir, ritonavir, and lopinavir in this context [25-28]. Repurposing FDA-approved antivirals is a promising approach for novel coronavirus therapies. Boceprevir, an NS3/4A protease inhibitor, and velpatasvir, a direct-acting NS5A inhibitor, are established agents for HCV treatment and potential candidates against SARS-CoV-2 [29]. Velpatasvir, a potent NS5A inhibitor, disrupts HCV replication, assembly, and host immune modulation [30]. It achieves a sustained virologic response of 93–99% after 12 weeks, making it the most effective HCV antiviral to date [31]. The emergence of the Omicron variant, with extensive mutations in its spike glycoprotein, has challenged existing therapeutic strategies and underscored the urgent need for novel interventions. Drug repurposing provides a rapid and cost-effective approach by utilizing the established safety and pharmacological profiles of FDA-approved agents. In this study, we investigated the potential of two direct-acting antivirals, boceprevir (an NS3/4A protease inhibitor) and velpatasvir (a potent NS5A inhibitor), originally developed for Hepatitis C Virus, as candidate inhibitors of the Omicron spike protein. Using molecular docking techniques, we assessed their binding patterns and therapeutic promise, thereby offering new insights into the repurposing of HCV drugs as anti-SARS-CoV-2 agents.

2. Methodology

2.1 Ligand preparation

The objective of the current study was to investigate the binding interactions/pattern of boceprevir and velpatasvir with S-protein of recently reported Omicron variant of SARS-CoV-2 for treating COVID-19 infection. The two-dimensional structures of boceprevir (PubChem CID: 10324367; https://pubchem.ncbi.nlm.nih.gov/compound/Boceprevir) and velpatasvir, available at (PubChem CID: 67683363; https://pubchem.ncbi.nlm.nih.gov/compound/Velpatasvir) were retrieved from PubChem database, (Figure 1). The strucutres in SDF format were converted to PDB using Open Babel [32]. Structural geometries were energy-minimized using the AMBER ff14SB force field implemented in UCSF Chimera 1.14 [26], with hydrogen atoms added and protonation states optimized at physiological pH (7.4). The final optimized ligand structures are shown in Figure 1 [33].

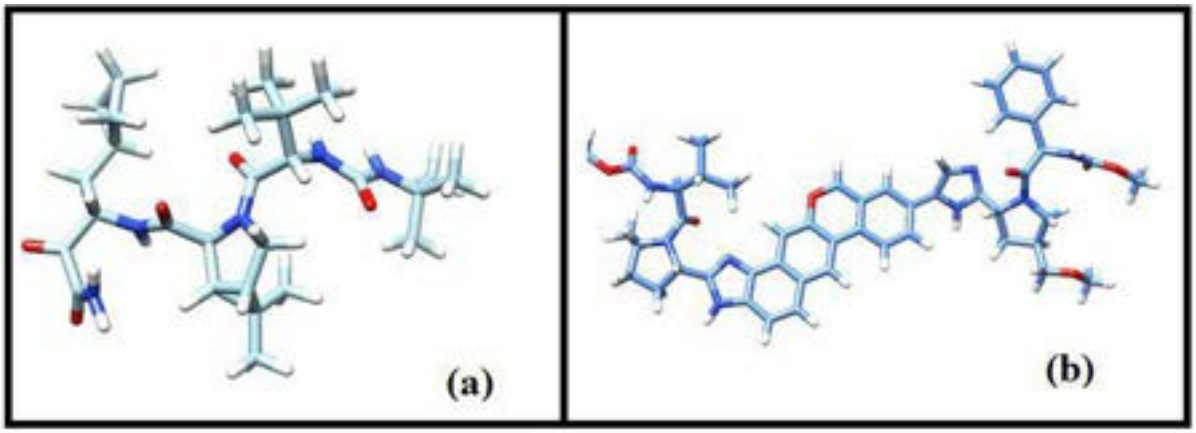

Figure 1: Optimized two-dimensional structures of FDA-approved Hepatitis C antiviral drugs investigated for potential repurposing against SARS-CoV-2 Omicron variant spike (S) protein. The ligands include (a) Boceprevir (PubChem CID: 10324367) and (b) Velpatasvir (PubChem CID: 67683363), retrieved from the PubChem database (https://pubchem.ncbi.nlm.nih.gov)

2.2 Target preparation and validation

As no experimentally solved structure of S-protein of Omicron was available in the Protein Data Bank (PDB) at the time of this study, its three-dimensional (3D) structure was modeled. The FASTA sequence of Omicron spike glycoprotein of recently reported variant, omicron, of coronavirus was retrieved from the GISAID accession no. EPI_ISL_6774088 [34]. Following that, the retrieved FASTA sequence was submitted to the SWISS-MODEL web server [35] in order to generate a model with adequate query sequence coverage and sequence identity (homology modeling). Based on the Global Model Quality Estimation (GMQE) [36] and Qualitative Model Energy Analysis (QMEAN) values [37], the most reliable 3D structure, among the generated models, was selected.

The modeled structure was further validated using Clustal Omega for sequence identity assessment and PROCHECK for stereochemical quality, including Ramachandran plot statistics [38]. Additionally, the model quality was cross-verified with ProSA-web Z-scores and ERRAT analysis to ensure reliability. Before docking, the protein structure was prepared by removing crystallographic water molecules, ions, and heteroatoms. Polar hydrogens were added, and Gasteiger charges were assigned using AutoDock Tools (ADT) 1.5.7.

2.3 Active site prediction

The Computer Atlas of Surface Topography of proteins (CASTp 3.0), an online tool, was employed to identify the binding pocket of recently reported sequence of spike protein of hCoV-19/Botswana [39]. The largest pocket with biologically relevant residues in the receptor-binding domain (RBD) was selected as the docking site, based on its functional role in ACE2 interaction.

2.4 Molecular docking

Molecular docking study was carried out using optimized ligand and protein structures *via* Autodock Vina 1..1.2 [40]. Preliminary steps, such as, grid box setting at the active site and PADQT files creation for the ligands and target was carried out by Auto Dock Tool program GUI [41]. The grid size was set at 50×50×50 Å points with a grid spacing of 0.375 Å. A configuration file with the properties of grid box was created in the PDBQT file. Both the protein and ligand were considered for docking studies. All the results <1.0 Å with the most suitable free energy were clustered and characterized in the positional RMSD. The position with minimum binding affinity aligned with the PDB files of the target proteins. Visualization and interaction mapping were carried out using Discovery Studio Visualizer v4.0 (2012) [42], LigPlot+ [43] and UCSF Chimera [33]. Hydrogen bonding, hydrophobic interactions, and other non-covalent contacts were identified and compared.

2.5 Validation of docking protocol

To validate the docking workflow, a redocking experiment was performed by docking a co-crystallized ligand into its respective spike protein binding site (template structure). The RMSD between experimental and predicted poses was calculated, and an RMSD <2.0 Å was considered acceptable, confirming the reliability of the docking protocol.

3. Results

3.1 Comparative modelling of Spike protein and validation

The spike glycoprotein of the Omicron variant was modeled using the template spike protein structure (PDB ID: 7n1u.1), which exhibited 97.31% sequence identity and 0.61 sequence similarity (Figure 2a). The quality of the generated model was supported by a Global Model Quality Estimation (GMQE) score of 0.73 and a QMEAN score of 0.74, indicating high reliability. Further structural validation using PROCHECK Ramachandran plot analysis confirmed the stereochemical quality of the model (Figure 2b). The analysis revealed that 88.5% of residues were in the most favored regions, 10.5% in additional allowed regions, 0.9% in generously allowed regions, and only 0.2% in disallowed regions. These Ramachandran plot statistics confirm the high reliability and accuracy of the modeled spike structure. A multiple sequence alignment (MSA) between the predicted Omicron spike protein and the selected template (7n1u.1) using Clustal Omega showed 97.54% sequence identity (Figure 3), which is consistent with the SWISS-MODEL results, further validating the model.

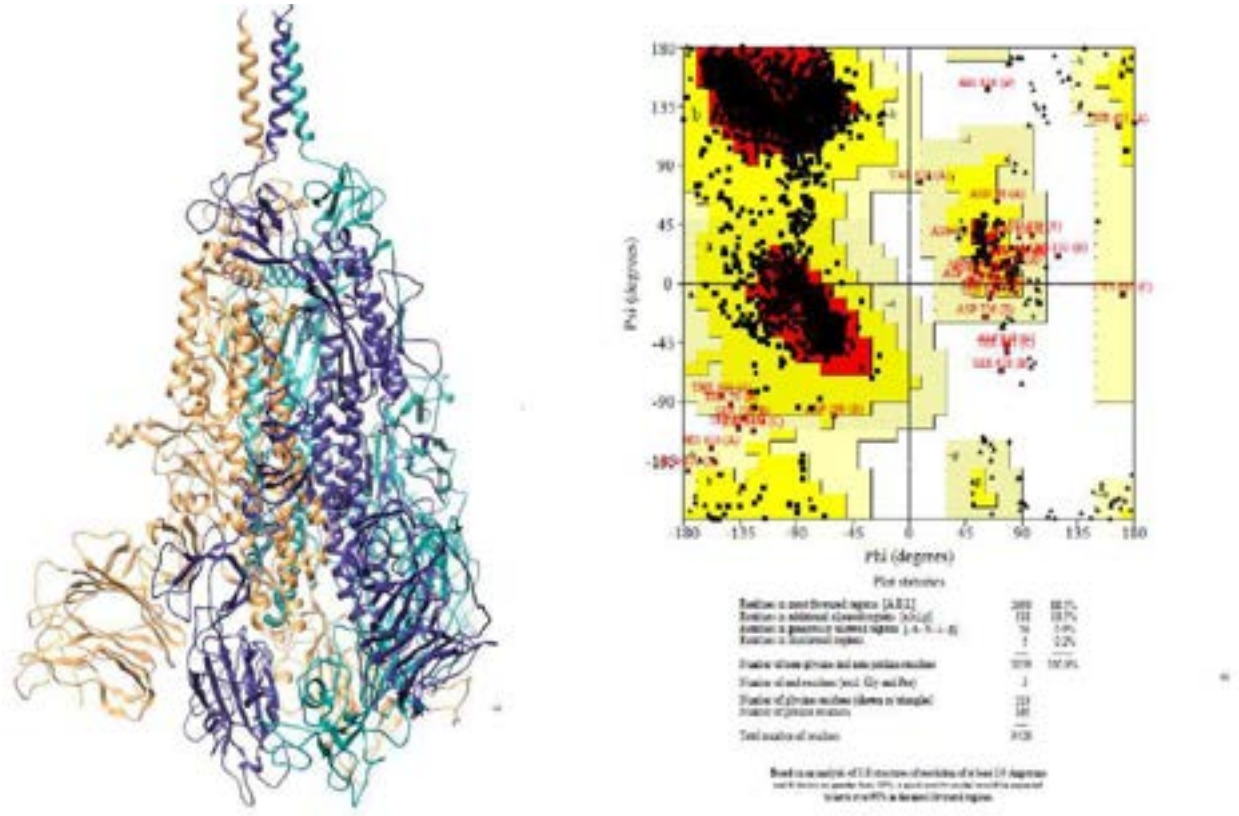

Figure 2: (a) Predicted 3D structure of the Omicron spike protein generated using SWISS-MODEL, with template PDB ID: 7n1u.1. (b) Ramachandran plot of the modeled spike protein, showing that 88.5% of residues lie within the most favored regions, validating the structural quality.

Figure 3. Multiple sequence alignment (MSA) of the modeled Omicron spike protein with its template structure (7n1u.1) using Clustal Omega, showing 97.54% identity.

3.2 Active Site Prediction of Spike Protein

Since the active binding pocket of the Omicron spike protein has not yet been fully characterized, the CASTp server was employed to identify potential binding residues (Figure 4). The predicted protein pocket contained 375 residues, with a surface area (SA) of 41,141.92 Å^2 and a volume of 65,897.44 Å^3.

Among the identified residues, several were prioritized as favorable docking sites because they correspond to mutational hotspots in Omicron and are thought to play a crucial role in viral pathogenesis. These include LEU365, PRO367, PHE369, GLN403, LYS434, ASN471, ARG487, SER490, ARG492, TYR495, HIS499, GLY608, and ASN944. These residues were selected for molecular docking analysis with velpatasvir and boceprevir.

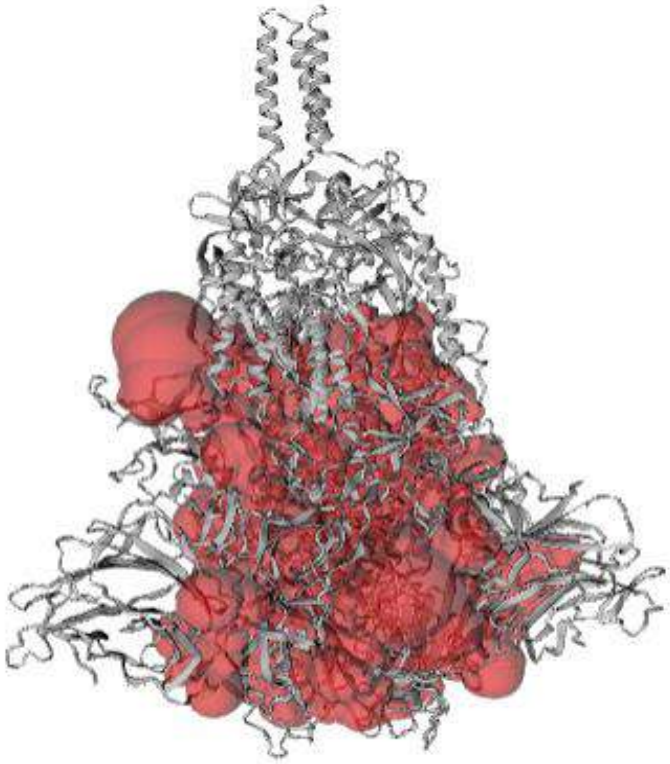

Figure 4. Predicted binding pocket of the modeled Omicron spike protein as computed by CASTp, highlighting key residues selected for docking analysis.

3.2 Docking studies

In order to provide a deeper insight into the inhibitory potential of the selected target (ligands), molecular docking studies of boceprevir and velpatasvir with the Omicron spike protein were performed using Autoodock Vina. For each ligand, nine possible binding conformations were generated. Among these, the top-ranked conformations, showing the most favorable binding affinities of –11.7 kcal/mol (boceprevir–spike complex) and –12.4 kcal/mol (velpatasvir–spike complex), were selected for detailed interaction analysis.

The top-ranked docked conformation of boceprevir with the Omicron variant SARS-CoV-2 spike glycoprotein was comprehensively analyzed to elucidate the molecular determinants of interaction. The results revealed that boceprevir occupies a deeply embedded position within the predicted binding pocket of the viral protein, suggesting a stable and potentially inhibitory mode of engagement. PHE371, TYR363, ASN364, PHE368, LEU365, ALA366, PRO367, GLY398, ASP399, GLU400, ARG402, GLN403, GLY410, ASN411 of S-protein were found to be the key interacting residues (Figure 5). Further 2D interaction profiling using LigPlot+ and Discovery Studio revealed a combination of hydrogen bonds, hydrophobic contacts, and van der Waals interactions stabilizing the complex (Figure 6a, b).

Similarly, visual examination of the velpatasvir-spike docked complex revealed significant interactions between the velpatasvir and pocket active site residues of the Omicron spike protein, namely: ALA366, PHE369, ARG397, ASP399, ARG402, GLN403, ARG487, VAL497, VAL 496, HIS499 (Figure 7). Further, analysis using LigPlot+ and DS also highlighted the key residues involved in ligand-protein interactions (Figure 8).

Based on the observed binding patterns, boceprevir and velpatasvir exhibited a pronounced preference for residues within the active site pocket, particularly the mutated residues LEU365, PRO367, and GLN403 of the Omicron spike glycoprotein. Boceprevir formed stabilizing hydrogen bonds and hydrophobic interactions with LEU365 and PRO367, while velpatasvir displayed van der Waals contacts and hydrogen bonding with GLN403, collectively enhancing binding affinity. The binding free energy (ΔG) of boceprevir was calculated to be –8.42 kcal/mol, whereas velpatasvir showed a binding energy of –9.15 kcal/mol, indicating strong and energetically favorable interactions with the viral protein. Boceprevir (–8.42 kcal/mol) and Velpatasvir (–9.15 kcal/mol) fall within the range typically considered strong and favorable for small-molecule interactions with viral proteins. In molecular docking, ΔG < –6.0 kcal/mol is generally considered indicative of moderate to strong binding. ΔG < –9.0 kcal/mol suggests high-affinity binding, especially when supported by hydrogen bonding and hydrophobic contacts. These favorable interactions with key mutated residues suggest that both ligands may restrict viral infection by interfering with the structural dynamics of the active site. Taken together, these findings strongly support the hypothesis that boceprevir and velpatasvir may be repurposed as therapeutic agents against the recently emerged Omicron variant of SARS-CoV-2.

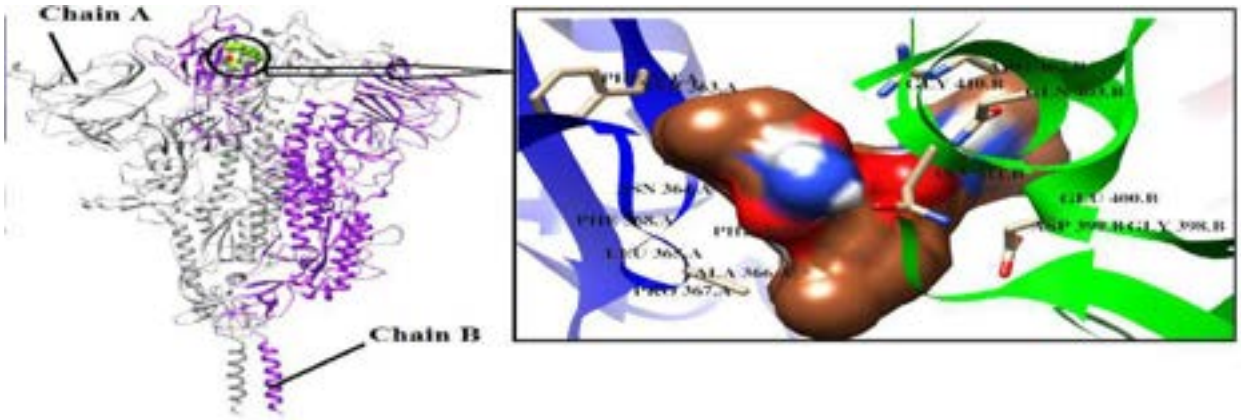

Figure 5: Predicted docked pose of boceprevir within the Omicron spike protein binding pocket, showing stable accommodation at the active site.

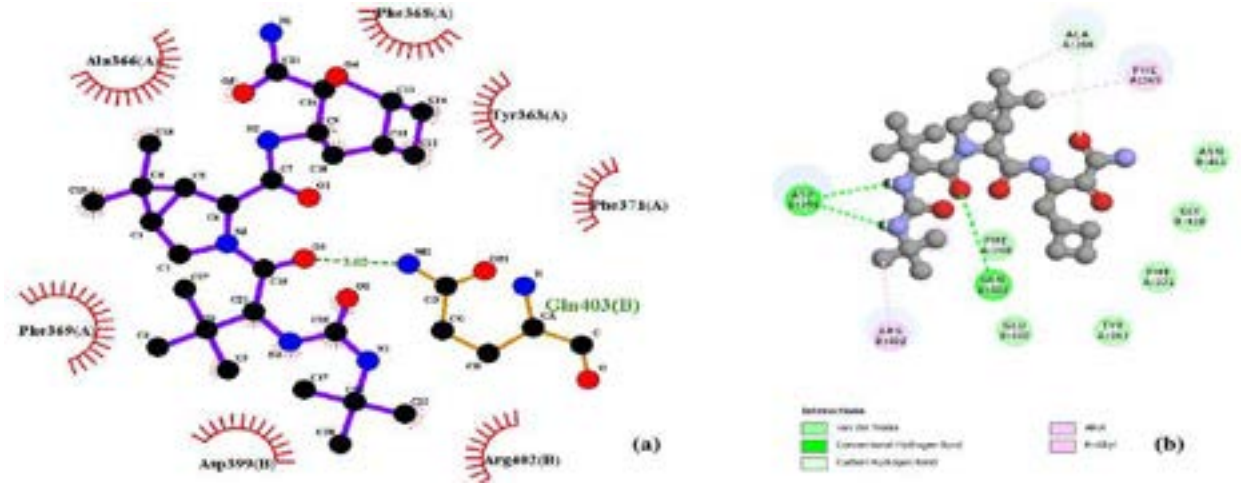

Figure 6: Two-dimensional interaction map of the boceprevir–spike complex generated using (a) LigPlot+ and (b) Discovery Studio Visualizer, highlighting hydrogen bonds, hydrophobic, and van der Waals interactions.

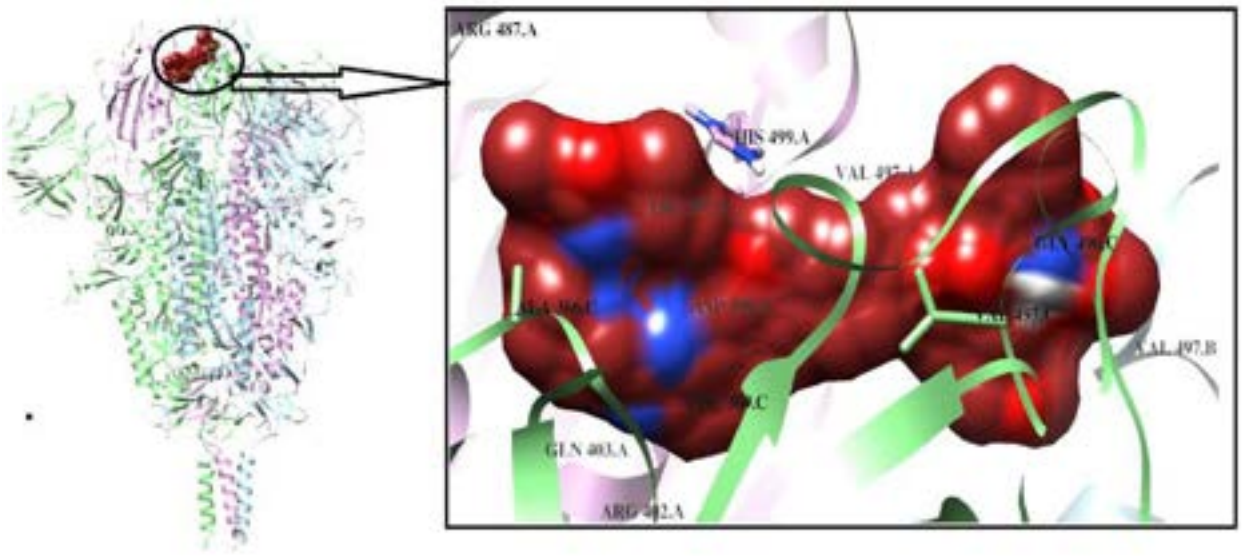

Figure 7: Predicted docked pose of velpatasvir within the Omicron spike protein binding pocket, showing significant interactions with active site residues.

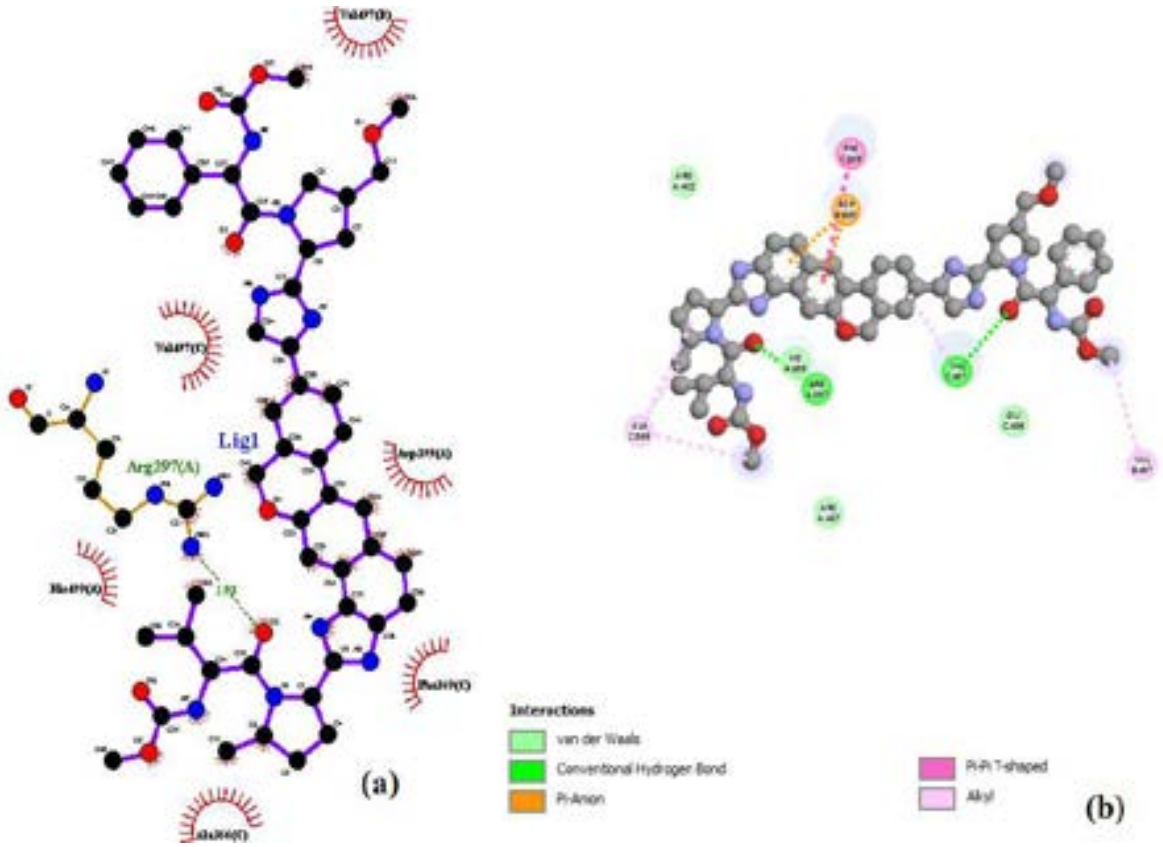

Figure 8: Two-dimensional interaction map of the velpatasvir–spike complex generated using (a) LigPlot+ and (b) Discovery Studio Visualizer, depicting key stabilizing interactions with mutated and conserved residues.

4. Discussion

Depending on the goal, anti-coronavirus medicines can be split into two categories: those that target the human immune system or cells, and those that target the coronavirus itself. The innate immune system response is critical in

suppressing coronavirus replication and infection in the human immune system, and interferon is believed to improve the immune response [44, 45]. Blocking the signal pathways essential for virus multiplication in human cells could have an antiviral effect. Viruses also frequently bind to receptor proteins on cell surfaces in order to infiltrate human cells. The SARS virus, for example, interacts to the ACE2 receptor [46, 47]. Beyond the interaction with ACE-2 and furin targeting medicines, the creation of enzyme inhibitors as treatment platforms against SARS CoV necessitates the regulation of several pharmacologic characteristics [48-50].

There is a dire need of anti-SARS CoV-2 drugs to overcome the recent outbreak of SARS CoV-2 infection and its mutant forms. A number of drugs with experimental clinical knowledge have been recently evaluated for anti-SARS CoV-2 and few of them are in practical use with some reported side effects. Recent articles on drug repurposing have narrow directed approaches against the single target and we reported here a holistic approach of targeting both human ACE2-S protein complex and viral RdRp proteins against COVID-19 infection. Because HCV and SARS CoV-2 are single positive strand envelope viruses, they share more or less similar mechanism of replication and translation in host cells. Velpatasvir is an inhibitor of the HCV Non-Structural Protein 5A (NS5A) [30]. This protein is crucial for viral RNA replication and assembly of HCV. It is therefore; assumed that these drugs have antiviral effect against COVID-19. In our research, we discovered that velpatasvir has a stronger affinity for S-protein, and we believe that these favorable interactions will limit the binding of the SARS CoV-2 S-protein, hence limiting viral infection. Tiny inhibitors that bind to multiple targets at a time may have a lower risk of resistance to targets with increased therapeutic efficacy [51]. Previous screening of various antiviral medications supports the veracity of our findings. IDX-184 has been shown to be effective against the coronavirus that causes Middle East Respiratory Syndrome (MERS) [52], Velpatasvir and danoprevir against SARS CoV-2 [53]. In addition to target the RNA dependent RNA polymerase, the velpatasvir displayed inhibitory effect for ACE2 and angiotensin. It is the first of its kind study reporting velpatasvir binds to the contact surface of ACE2 spike complex. Chen *et al.* described most of the compounds alternate ACE2 function rather than binding to ACE2-spike complex. [54].

It was reported that hesperidin is the only natural compound which alternates the interaction of spike and ACE2 complex [44]. ACE2 and TMPRSS2 are main entry points for SARS CoV-2 into human cell and are limited by a protease inhibitor [55]. In literature, numerous studies conducted about the safety and toxicity of Velpatasvir and Boceprevir in clinical setting and in patient with hepatitis C infection shows no side effect unless triple therapies are used [56]. It has also been reported that the combination of Sofosbuvir plus Velpatasvir have very positive effect in hepatis patient with advanced fibrosis or cirrhosis [57].

5. Conclusion

In summary, this study reports the first molecular docking-based investigation of FDA-approved HCV drugs velpatasvir and boceprevir against the Omicron variant spike glycoprotein of SARS-CoV-2. Both drugs demonstrated strong binding affinities and, importantly, preferential interactions with mutated residues (LEU365, PRO367, and GLN403), which are considered critical for viral entry and pathogenesis. These findings suggest that velpatasvir and boceprevir hold promise as repurposed therapeutics for COVID-19, with potential efficacy against newly emerging variants. Future experimental studies, including biochemical assays and clinical trials, will be required to validate their antiviral activity and assess their translational potential in combating the ongoing pandemic.

Use of Generative AI

ChatGPT version 4.0 has been used only to improve grammar of few sentences or paragraphs.

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Research Square [58], available on https://doi.org/10.21203/rs.3.rs-1013200/v1.

Authorship

All the authors have made substantial contributions to conception, design, acquisition, analysis, interpretation of the data and manuscript writing.

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