Journal of Research in Pharmacy

Research Article

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Prospects for repurposing FDA-approved medications as Omicron spike/ACE-2 protein complex disruptors

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Received: 10 February 2023 / Revised: 15 March 2023 / Accepted: 15 March 2023

ABSTRACT: The interaction of viruses with the host cell surface proteins is a critical step in disease pathogenesis. The interaction of SARS-CoV-2 spike protein and human ACE-2 (Angiotensin-converting enzyme 2) protein, which is similar to the ligand-receptor binding, initiates viral attachment, facilitates cellular viral entry, and subsequent replication in the human body leading to potentially fatal illnesses such as acute respiratory distress syndrome, and multi-organ failure. The Omicron variant, known as B.1.1.529, is a novel SARS-CoV-2 variant of concern, contains thirty distinct mutations, fifteen of which occur in the spike protein. With the high number of mutations in the spike protein, it is more likely to increase transmissibility and increase the ability to cause a severe form of the disease. The variant is believed to affect even the vaccinated individuals. Hence, there is an urgent need to search for more suitable pharmacotherapy to treat this infection. In this view, the study was aimed to screen the existing FDA (Food and Drug Administration)-approved drugs as a potential protein-protein complex disruptor against Omicron spike/ACE-2 protein complex through virtual screening using molecular docking and dynamic simulation. Initially, 2137 small molecules were selected from the FDA-approved drugs database and virtually screened against Omicron spike/ACE-2 complex. Based on higher docking score, interactions with 'hotspot' residues, and binding free energies three drugs namely Floctafenine, Metaraminol and Vilanterol were selected for further molecular dynamics analysis to predict the stability of the complex. Floctafenine complex showed a higher RMSD (Root Mean Square Deviation) value than Omicron spike/ACE-2 protein complex and it reduces the hydrogen bonding interactions between the complex proteins. Floctafenine will play as PPI (protein-protein interaction) disruptor for virus attachment/cellular entry and act as an initial demonstration for the repurposing of existing small molecules for alternative and cost-effective antiviral therapy for the treatment of disease caused by of Omicron variant of SARS-CoV-2.

KEYWORDS: Omicron spike variant; Angiotensin-Converting Enzyme 2 (ACE-2); Protein-protein interaction; Complex disruptors; FDA drugs

1. INTRODUCTION

Coronavirus disease (COVID-19) is a life-threatening severe global pandemic caused by SARS-CoV-2 (Severe acute respiratory syndrome coronavirus 2) virus [1]. Based on the reports of World Health Organization (WHO), more than 269 million people are being affected by severe acute respiratory syndrome, and nearly 5.3 million deaths have been recorded across the world [2]. Global expansion has thus far been dispersed across multiple pandemic waves in a variety of countries. Each wave was defined by the introduction of novel SARS-CoV-2 variants, several of which subsequently became dominant in local

How to cite this article: Chandrasekan J, Parasuraman P, Theivendren P, Sundar K, Ammunje D, Rex D. Kunjiappan S. Prospects for repurposing FDA-approved medications as Omicron spike/ACE-2 protein complex disruptors. J Res Pharm. 2023; 27(4): 1605-1614.

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ISSN: 2630-6344

http://dx.doi.org/10.29228/jrp.445

epidemics or on a global scale [3]. Despite the appearance of an asynchronous wave chronology and variant distribution, numerous variants emerged that dominated the global pandemic event, most notably the variants of concerns (VOCs) are Alpha, Beta, Gamma, and Delta [4].

Recently, South Africa reported the identification of a new variant of SARS-CoV-2, Omicron (B.1.1.529) to the WHO [5]. The epidemiological studies in South Africa identified three distinct peaks in reported cases, the latest of which was predominantly due to the Delta variant [6]. The first known case of infection by B.1.1.529 (Omicron) variant was reported to WHO from South Africa on November 24, 2021 [7]. In recent weeks, infections due to omicron have been increased steadily around the world [8]. Currently, the Omicron variant has been detected in more than 90 countries, including Australia, Botswana, Brazil, Canada, the European Union, Hong Kong, Israel, Japan, Nigeria, India, the United Kingdom, and the United States [9]. According to the WHO report, the variant has a large number of mutations, some of which are concerning. Preliminary evidence suggests an increased risk of re-infection with this variant, as compared to other variants of SARS-CoV-2. The Omicron variant has high numbers of mutations of their spike protein with the potential to increase transmissibility, confer resistance to therapeutics, or partially escape infection- or vaccine-induced immunity [10].

Virus entry inside the cell is facilitated by interaction of viral protein with a receptor in the host. In SARS-CoV-2, interaction between SARS-CoV-2 spike glycoprotein and the host ACE-2 (Angiotensin-converting enzyme 2) protein facilitates virus entry and results in acute respiratory distress syndrome which could lead to multi-organ failure [11]. Despite the fact that non-pharmaceutical therapies and immunizations are utilized to minimize illness spread and severity, the disease is spreading globally [12]. Due to the frequent emergence of novel variants with varying degrees of severity, the identification and development of new chemical entities capable of effectively resisting these progressions become a vital need. Recently, majority of drug discovery targets are mainly focused on one of the five protein families: protein-protein interactions, enzymes (kinases and proteases), ion channels, nuclear hormone receptors, and transcription factors [13]. In the development of pathogenesis of many pathogens, protein-protein interactions play a key role as mediators of signal transductions. In this connection, targeting PPIs has been recognized as one of the very difficult drug discovery processes [14]. However, in recent years, targeting PPIs has received significant attention and emerged as an intriguing target for drug development, especially against infectious diseases; some of them have entered clinical studies, and some of are approved for marketing [15, 16]. Further, the development of PPIs as stabilizers and disruptors has emerged as a new window of opportunity for pharmaceutical research. Here, we used a similar integrative in silico approach to investigate the druggable sites in the PPIs of Omicron spikes and Human ACE-2 and identified important active site 'hotspot' residues in the protein complex formation. Furthermore, a virtual screening approach with FDA (Food and Drug Administration)-approved medicines and the subsequent molecular simulation studies at the active site interface, identified a small number of possible PPI disruptors with a high proclivity for destabilizing the integrity and complex formation

2. RESULTS and DISCUSSION

The structure of the novel coronavirus spike protein receptor-binding domain, which is complexed with its receptor ACE-2, has been retrieved from Protein Data Bank (PDB ID: 6LZG). Following retrieval, the mutated amino acids in the Omicron spike protein were substituted at their appropriate positions (G339D, S371L, S373P, S375F, K417N, N440K, G446S, S447N, T478K, E484A, Q493K, G496S, Q498R, N501Y, & Y505H) in the C-terminal domain of SARS-CoV-2 (SARS-CoV-2-CTD) spike (S) protein in complex with human ACE-2 (hACE-2). For equilibration, the constructed Omicron spike/ACE-2 complex structure was simulated for 100ns. The terminal trajectory frame that resulted from the simulation was chosen for further investigation and analysis.

The Discovery Studio Visualizer was used to demonstrate the interaction between Omicron and the ACE-2 complex. The hydrogen bond, electrostatic interaction, and hydrophobic interaction were responsible for the vast majority of the interactions. It was observed that the primary amino acid residues for hydrogen bonding were mediated by the altered residues of the omicron spike, specifically ASN477, LYS493, ARG498, TYR501, and HIS505 (as well as others). Additionally, mutant residues LYS493, ALG498, and TYR501 mediate electrostatic interaction, whereas mutant residues TYR501 and HISR505 facilitate hydrophobic interaction. Table 1 and Figure 1 show a detailed list of interactions, with the most significant ones highlighted in asterisk (*). Mutant residues LYS493, ARG498, and TRY501 were found to participate in both hydrogen and electrostatic interactions. Additionally, the amino acid TYR501 contributes to each of the three types of interaction.

Table 1. Protein-Protein interactions between Omicron spike protein /human ACE-2 protein complex refined through molecular dynamic simulations

Hydrogen bond interactions		
Omicron-Spike Residue	**ACE-2 Residue**	**Distance**
LYS493*	ASP38	2.50
ARG498*	ASP355	2.75
LYS444	GLU329	2.84
TYR449	ASP38	2.04
LYS493*	HIS34	2.44
ARG498*	ASP355	2.24
ARG498*	ASN330	2.49
THR500	ASP355	1.56
HIS505*	GLU37	2.75
TYR501*	TYR41	2.18
ASN477*	GLN24	1.83
TYR449	GLN42	2.06
Electrostatic Interaction		
Omicron-Spike Residue	**ACE-2 Residue**	
LYS493*	ASP38	
ARG498*	ASP355	
ARG403	GLU37	
LYS493*	GLU35	
ARG498*	ASP355	
TYR501*	LYS353	
Hydrophobic interaction		
Omicron-Spike Residue	**ACE-2 Residue**	
TYR489	LYS31	
TYR501*	LYS353	
HIS505*	LYS353	
TYR501*	TYR41	

*Majorly contributing residues

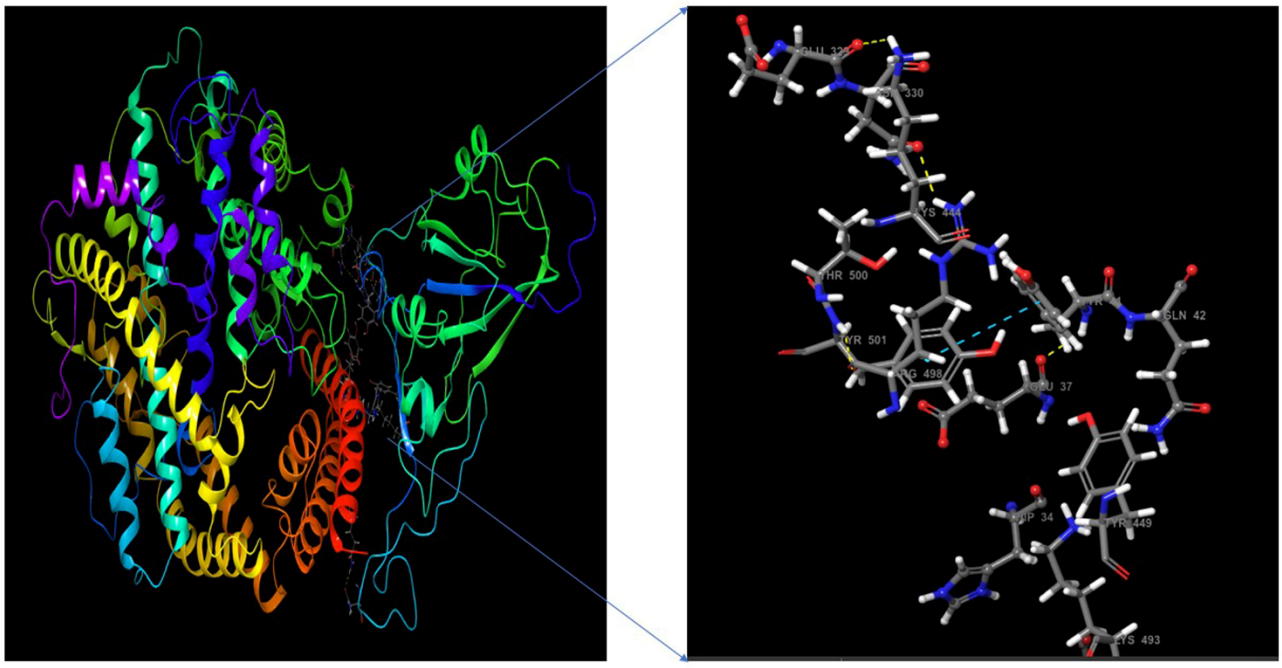

Figure 1. Interaction between Omicron spike/ACE-2 protein complex.

Further, the pre-residual energy contribution of each amino acid for complex formation between Omicron spike and ACE-2 was calculated using the ANCHOR webserver. The results indicate that the Omicron-Spike residues LYS493, AGR498, ARG403, and LYS444, as well as the ACE-2 residues ASP355, GLU35, and ASP38, were the most critical residues for complex formation (Table 2). It is important to note that two of the altered residues from the Omicron spike, "LYS 493" and "ARG 498," have the highest binding energy of the four. It may be inferred that "LYS 493" and "ARG498" were the two essential residues that are more crucial in complex formation than the previously identified variants.

Table 2. Pre-residue energy contribution of key amino acid residues obtained through ANCHOR analysis for equilibrated simulation trajectory of Omicron-Spike/ACE-2 complex

Omicron-Spike Residues	Binding free energy (Kcal.mol^{-1})	ACE-2 Residues	Binding free energy (Kcal.mol^{-1})
LYS493*	-10.3	ASP355*	-5.8
ARG498	-3.6	GLU35*	-5.6
ARG403	-2.5	ASP38	-4.2
LYS444	-2.3	GLU329	-0.9
		GLU37	-0.7

*Majorly contributing residues

Prediction of druggable sites was carried out in order to identify potential complex disruptors of the Omicron Spike/ACE-2 complex, which was then tested. The anticipated druggable Hotspot residues were determined based on the SASA (solvent-accessible surface area) and binding free energy of the amino acid residues, respectively. After evaluating all the interacting residues at the interface, it was observed that the amino acid LYS493 had the lowest binding free energy and the highest SASA, followed by LYS444, ARG498, and ARG 403. In ACE-2, GLU35 has a higher SASA than ASP355, ASP38, and THR27 (Table 3). A few of the most critical amino acid residues include LYS493, GLU35, and ASP355, which are positioned among these eight major amino acid hotspots (Figure 2). It may be concluded that if the "HIT molecule" interacts with any of the key 'hotspot' residues listed above, the activity of complex disruptors would be maximized.

Table 3. Potential binding sites ("hotspots") residues for disruptors binding obtained through Pre-residues energy contribution and Solvent-accessible surface area (SASA) of Omicron-Spike/ACE-2 complex

Omicron-Spike Residues	Binding free energy (Kcal.mol^{-1})	ΔSASA	ACE-2 Residues	ΔSASA	Binding free energy (Kcal.mol^{-1})
LYS493*	-10.3	78.9	ASP355*	36.6	-5.8
LYS444	-2.3	51.4	GLU35*	45.9	-5.6
ARG498	-3.6	42.8	ASP38	35.8	-4.2
ARG403	-2.5	17.4	THR27	60.1	-1

*Majorly contributing residues

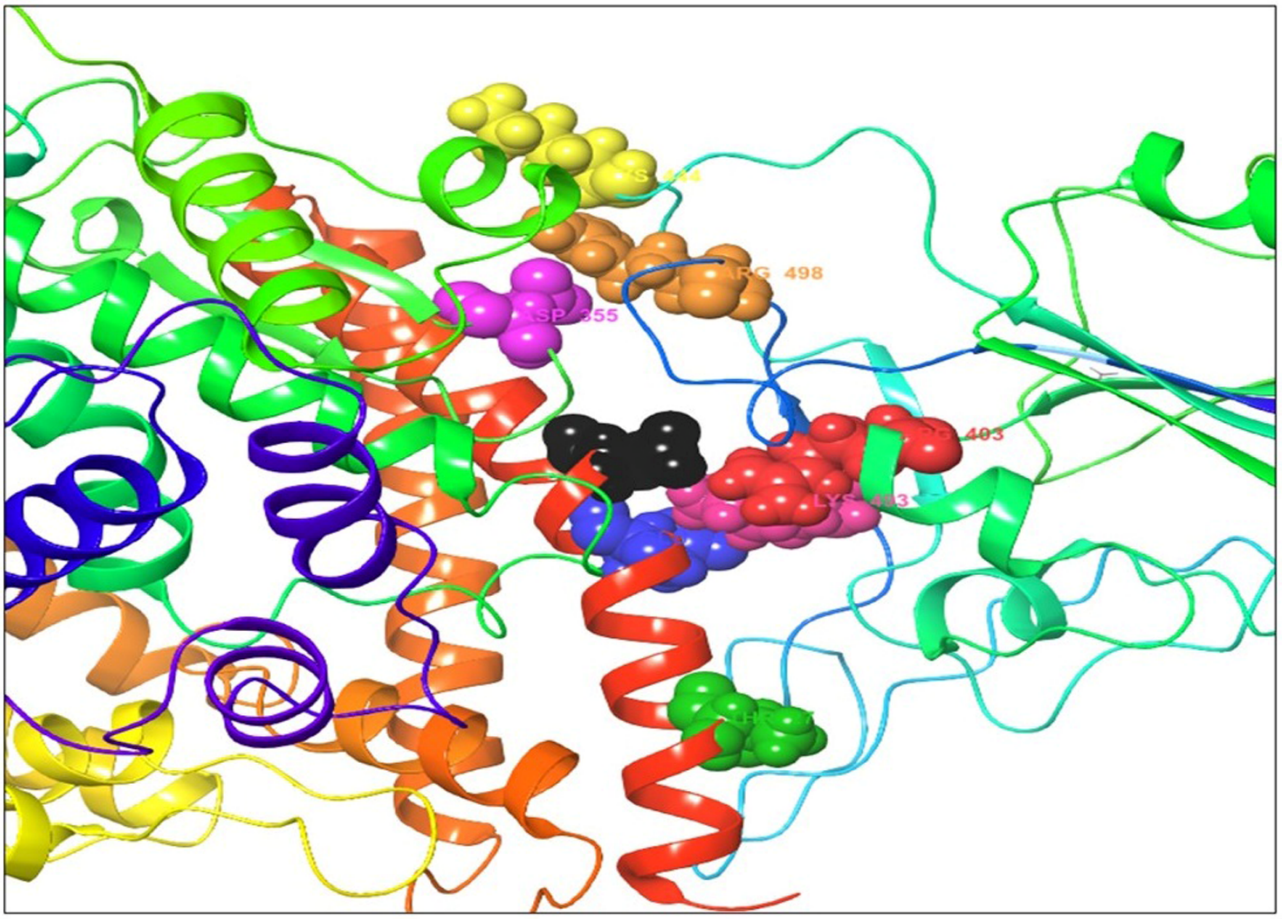

Figure 2. Position of eight major amino acid 'hotspot' residues in the Omicron spike /ACE-2 protein complex.

Further, we screened FDA-approved drugs using the extra precision docking program developed by Schrodinger in order to identify potential Omicron spike/ACE-2 complex disruptors. The primary results of the docking program were scrutinized based on the Docking score, and the top ten FDA drugs were inspected further for their interaction with the key 'hotspot' residues, and the third level of scrutiny was carried out based on the binding free energy obtained through MM GBSA (Molecular mechanics with generalised Born and surface area solvation), which was carried out in parallel, represented in Table 4. We chose three medications, based on the results of three filters: Vilanterol, Floctafenine, and Metaraminol (Chemical structures were depicted in Figure 3).

Table 4. Extra-precision docking and binding free energy (MM GBSA) results of top 10 FDA-approved drugs at the Omicron-Spike/ACE-2 complex interface

S.No	FDA Drugs	Docking Score	Glide G score	Interaction Residues	Nature of Interaction	MM GBSA dG Bind
1	Alendronic acid	-8.33	-8.41	A: GLU 35*	H-Bond Salt bridge	-2.06
				A: GLN 42	H-Bond	
				A: LYS 68	H-Bond Salt bridge	
				B: LEU 492	H-Bond	
				B: LYS 493*	H-Bond	
				B: SER 494	H-Bond	
2	Pamidronate	-8.08	-8.14	A: GLU 35*	Salt bridge	0.52
				A: GLN 42	H-Bond	
				B: LYS 493*	Salt bridge H-Bond	
				B: SER 494	H-Bond	
3	Norepinephrine	-7.14	-7.18	A: GLU 35*	H-Bond Salt bridge	-23.33
				A: GLN 42	H-Bond	
				B: LEU 492	H-Bond	
4	Vilanterol	-6.81	-6.81	A: GLU 35*	H-Bond Salt bridge	-53.83
				A: GLU 75	H-Bond	
				B: CYX 488	H-Bond	
				B; PHE 490	H-Bond	
5	Pravastatin	-6.72	-6.72	A: GLN 42	H-Bond	-37.12
				A: LYS 68	H-Bond	
				A: ASN 49	H-Bond	
6	Canagliflozin	-6.69	-6.69	A: LYS 68	Pi-Cation	-53.03
				B: GLY 447	H-Bond	
				B: ASN 448	H-Bond	
				B: TYR 449	Pi-Pi Stacking	
7	Epinephrine	-6.63	-6.66	A: GLU 35*	H-Bond Salt bridge	-25.15
				A: GLN 42	H-Bond	
8	Baclofen	-6.35	-6.35	A: GLU 35*	H-Bond Salt bridge	-19.63
				A: GLN 42	H-Bond	
				A: LYS 68	Salt bridge	
9	Floctafenine	-6.07	-6.07	B: LEU 492	H-Bond	-43.14
				A: LYS 68	Salt bridge	
				B: LYS 493	H-Bond	
				B: SER 494	H-Bond	

10	Metaraminol	-6.02	-6.05	A: GLU 35 B: TYR 449 B: LYS 493 B: SER 494	Salt bridge Pi-Pi Stacking H-Bond H-Bond	-24.53

*Majorly contributing residues

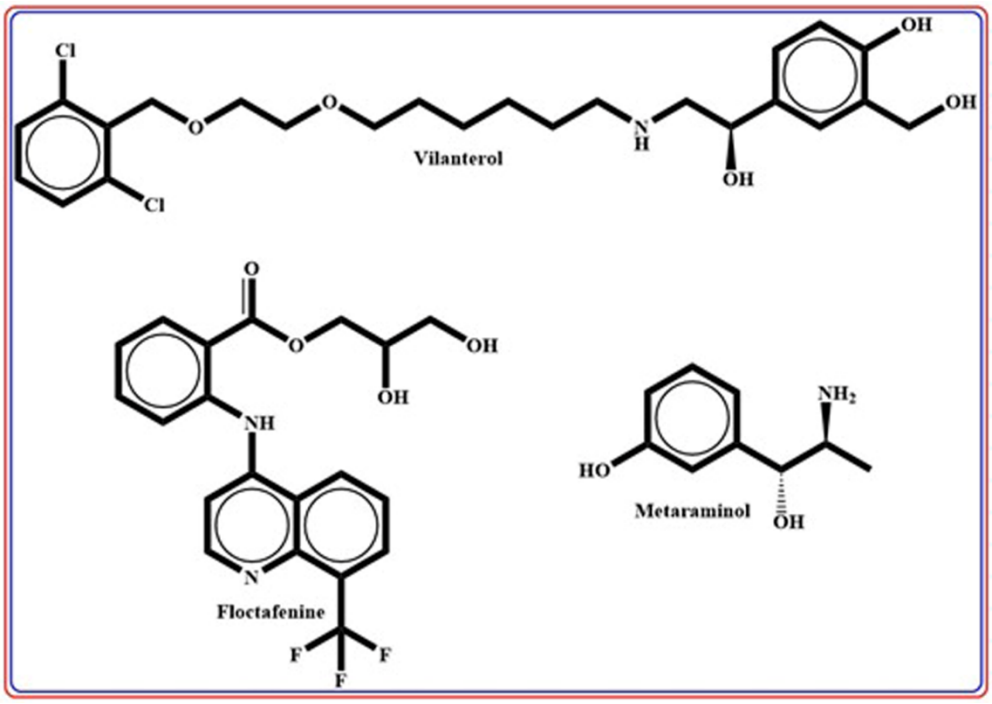

Figure 3. Selected FDA-approved drugs Vilanterol (a), Floctafenine (b), and Metaraminol (c)

Vilanterol is a long-acting beta2-adrenergic agonist used in combination with other bronchodilators for the management of chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema. Vilanterol had a docking score of -6.81 and binding free energy of -53.03, mediating an H-bond interaction with ACE-2's 'hotspot' residue GLU35. Floctafenine is an anti-inflammatory analgesic similar in action to aspirin. On the other hand, Floctafenine, an anti-inflammatory analgesic agent with a docking score of -6.07 and mediated an H-bond interaction with Omicron spike's 'hotspot' residue LYS493 with a binding free energy of -43.14. Whereas, Metaraminol an adrenergic agonist has a docking score of -6.02 and has a binding free energy of -24.53, and interacts with hotspot residues GLU35 and LYS493 (Figure 4 & 5). These three drugs were selected for further molecular dynamic simulation studies for analyses of the RMSD backbone and H-bonding with complex proteins.

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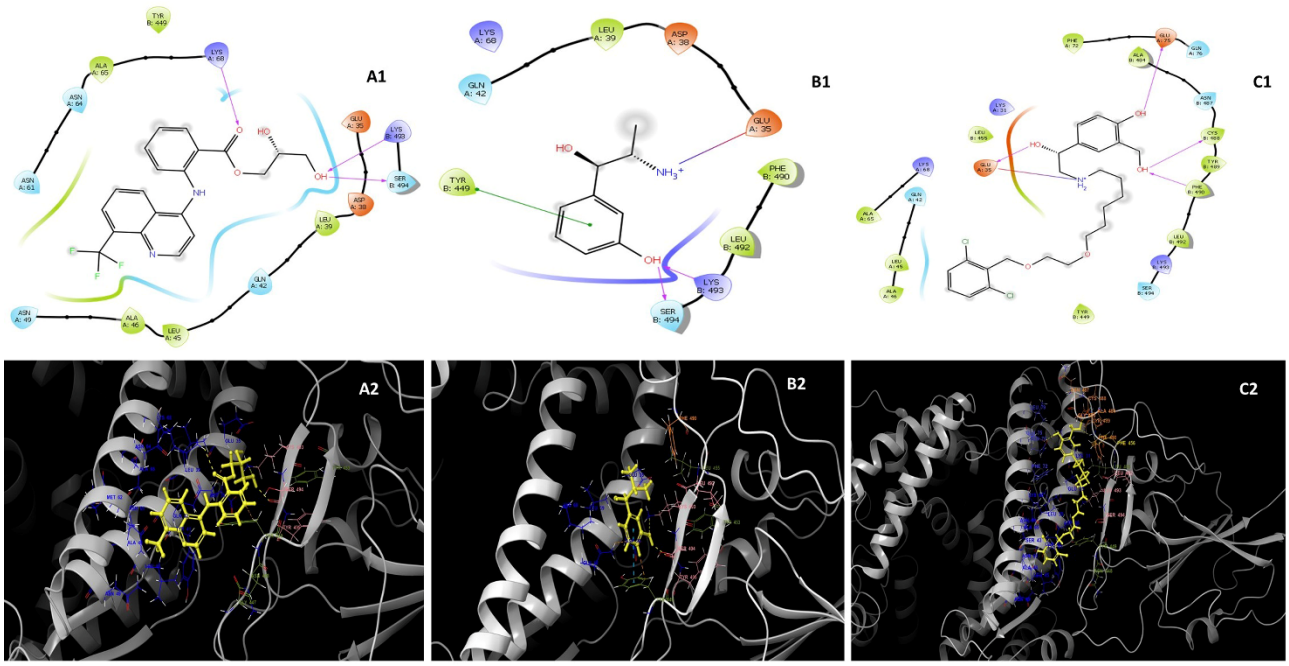

Figure 4. 2D and 3D representation of intermolecular interaction between Floctafenine (A1 and A2), Metaraminol (B1 and B2), Vilanterol (C1 and C2) with Omicron spike/ACE2 protein complex.

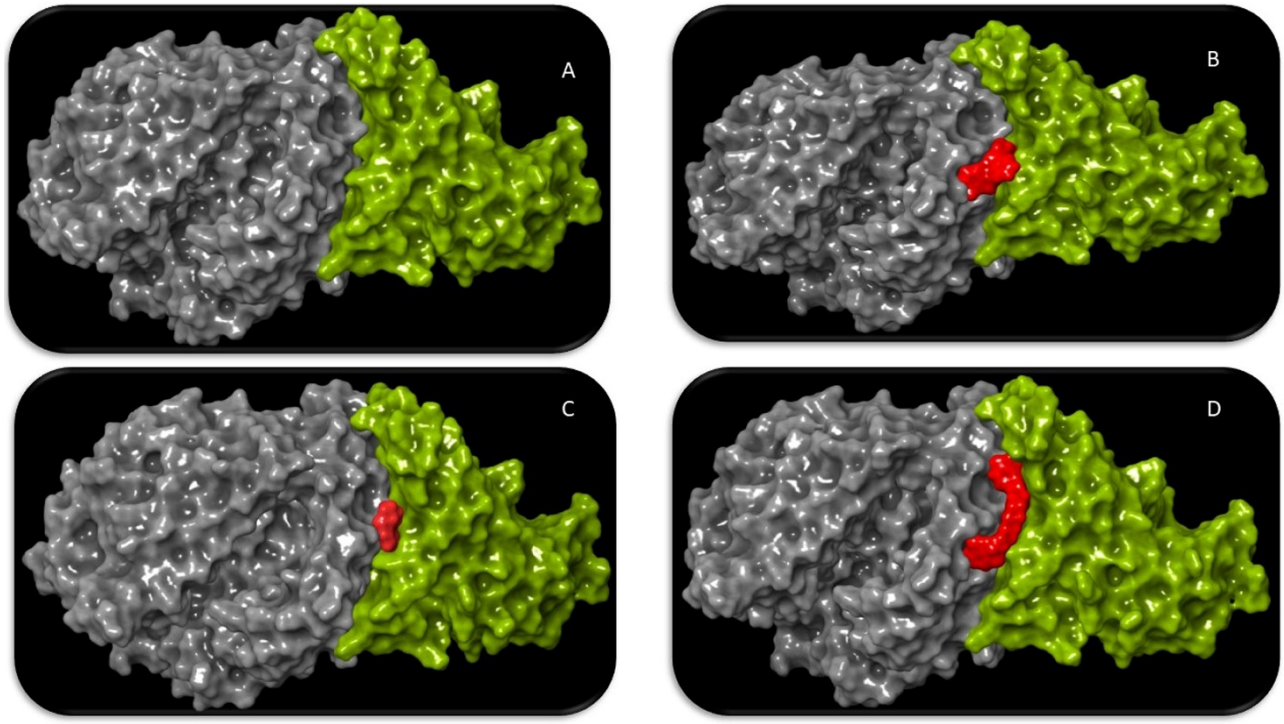

Figure 5. Protein interface representation of Omicron spike/ACE-2 protein complex (a), Floctafenine with Omicron spike/ACE-2 protein complex (b), Metaraminol with Omicron spike/ACE-2 protein complex (c) Floctafenine with Omicron spike /ACE-2 protein complex (d)

In order to analyze the structural consequences of Omicron spike/ACE-2 complex on ligand binding at the protein-protein interaction interface, the selected FDA-approved drugs, Vilanterol, Metaraminol, and Floctafenine in a complex with Omicron spike/ACE-2 was subjected to MD simulation. The stability of the complex was evaluated by measuring the backbone RMSD values obtained during the course of the 100ns by MD production run. The average backbone RMSD of the Omicron spike/ACE-2 complex was 0.688nm,

whereas the Vilanterol, Metaraminol, and Floctafenine complexes, were 0.637nm, 0.645nm, and 0.746nm, respectively (Table 5). It was interesting to note that, Floctafenine complex rendered a substantial increase in the RMSD at the end of 20ns. Thereby depicting the disruption of regular complex formation. In addition, average H-bond analysis reveals that there is a significant reduction in the number of H-Bonds compared to the native complex structures (Supplementary Figure 1).

Table 5. Molecular dynamics simulation trajectory analysis of native system and Complexes generated through docking at the complex interface of Omicron-spike/ACE-2 protein complex

S. No	Complex System	Average backbone RMSD (nm)
1	Omicron-Spike/ ACE-2 (Complex)	0.637
2	Vilanterol-Complex	0.636
3	Metaraminol-Complex	0.645
4	Floctafenine-Complex	0.746

3. CONCLUSION

The results of this study predicted three small-molecule disruptors, namely Vilanterol, Metaraminol, and Floctafenine, which displayed a higher docking score, interactions with 'hotspot' residues, and binding free energies against Omicron spike/ACE-2 protein complex. Particularly, Floctafenine showed a higher RMSD value against the active site of the Omicron spike/ACE-2 protein complex and it reduces the hydrogen bonding interactions between the complex proteins. The overall analysis suggests that Floctafenine has a high propensity to destabilize the complex and it can be anticipated to act as a disruptor for Omicron spike protein/ACE-2 protein interaction. The current study is the first to try a computational binding analysis of Omicron-Spike protein with Human ACE-2 using molecular docking and a dynamic simulation approach to discover potential disruptors with the existing therapeutic options. These predicted disruptors can be ideal candidates for further investigation as possible treatments of Omicron variant of SARS-CoV-2 infection.

4. MATERIALS and METHODS

4.1. Retrieval, modelling, and refinement of protein structures

The X-ray crystallographic structure of the receptor-binding domain of SARS-CoV-2 spike protein and Human ACE-2 complex was retrieved from the protein data bank, PDB entry ID: 6LZG (https://www.rcsb.org). Following that, mutant residues were substituted in the spike protein to model the Omicron spike. Following replacement, the complex was processed in the Schrodinger suite's "Protein preparation wizard" for missing side chains, bond order deviations, side-chain fixing, and loop refinement before being subjected to energy minimization using the OPLS4 force field. A Ramachandran plots Phi/Psi distribution was used to validate the processed complex. GROMACS (GROningen Machine for Chemical Simulations) 2019.2 software was then used to simulate the defined complex for 100ns. We extracted and processed the 1000th frame of the MD trajectory for protein refinement and additional docking investigations. Discovery Studio Visualizer BIOVIA 2020 was used to visualize intermolecular interactions [17].

4.2. Identification of druggable binding sites in the Omicron Spike/ACE-2 Protein complex

Prior to molecular docking, the druggable target binding sites and 'hotspot' residues in the Omicron Spike/ACE-2 protein-protein complex were evaluated using the ANCHOR webserver (http://structure.pitt.edu/anchor), which measures changes in Solvent Accessible Surface Area (SASA) of each side chain as well as its binding energy. This facilitates the identification of important 'hotspot' residues for small molecule inhibition [18].

4.3. Molecular docking and the calculation of the Molecular Mechanics – Generalized Born Surface Area (MM-GBSA)

The flexible docking program was run in extra precision mode with the Schrodinger software's Glide module (https://www.schrodinger.com/products/glide). The grid was generated at the active site

interface using information obtained from the ANCHOR web server and then docked with selected FDA-approved drugs. The docking complexes were ranked according to their docking score, nature, and number of interacting residues at the active site.

The effect of solvent on the binding free energies of ligands (ΔG bind) was estimated using the Prime MM-GBSA tool of the PRIME v3.5 module, Schrodinger süite (Schrödinger, LLC, New York, NY, 2019-1) [19]. In brief, the Glide XP docked poses of FDA-approved drug candidates were minimized, and total free binding energies were computed by using the VSGB as a solvent model, OPLS-3e as a force field. The binding free energies were calculated using the following equation:

$$\Delta G \text{ bind} = \Delta EMM + \Delta GSolv + \Delta GSA$$

Where, ΔEMM is the difference between the minimized energies of Omicron-spike/ ACE-2 protein-Inhibitor complex and the sum of minimized unbound Omicron-spike/ACE-2 complex and its inhibitor, ΔGSolv is the difference between the GBSA solvation energies of Omicron spike/ ACE-2 protein-Inhibitor complex and the sum of GBSA solvation energies of unbound Omicron spike/ACE-2 complex and its inhibitor, and ΔGSA is the difference between the surface area energies of Omicron spike/ACE-2 complex and its inhibitor, and the sum of the surface area of unbound protein and its inhibitor.

4.4. Molecular dynamics (MD) simulation

The molecular dynamics simulation was assessed to conclude the binding stability, conformation, and interaction modes between the selected FDA drugs (ligands) and Omicron-Spike/ACE-2 interface [20]. The complex files were subjected to molecular dynamics studies using GROMACS 2019.2 software [21]. The selected ligands topology was downloaded from the PRODRG server [22]. For molecular dynamic simulation, the first vacuum was minimized using the steepest descent algorithm for 5000 steps. The complex structure was solvated in a cubic periodic box of 0.5 nm with a simple point charge (SPC) water model. The complex system was subsequently maintained with an appropriate salt concentration of 0.15M by adding a suitable amount of Na+ and Cl− counter ions. Each complex was allowed a simulation time of 100 ns from the NPT (Isothermal-Isobaric, constant number of particles, pressure, and temperature) equilibration was subjected in NPT ensemble for the final run. Trajectory analysis was performed by using the GROMACS simulation package through the online server "WebGRO for Macromolecular Simulations (https://simlab.uams.edu)".

4.5. Molecular mechanics Poisson–Boltzmann surface area (MMPBSA) calculation

The protein-ligand binding free energy of each complex was estimated using the MMPBSA technique. The g_mmpbsa tool developed for GROMACS was used to estimate the binding free energy [23].

Acknowledgements: The authors thank Dr. Meenakshisundaram Balasubramaniam, Assistant Professor at the University of Arkansas for Medical Sciences, Little Rock, Arkansas, USA, Ms. Ewa Babkiewicz, and Dr. Piotr Maszczyk, Department of Hydrobiology, Faculty of Biology, University of Warsaw, Warsaw, Poland, for timely help and support.

Author contributions: Concept – J.C., P.P., S.K.; Design – J.C., D.A.B., D.N.A.; Supervision – S.K.; Resources – K.S., P.T.; Materials: J.C., P.P., S.K.; Data Collection and/or Processing – J.C., P.P. S.K.; Analysis and/or Interpretation – J.C., P.P., T.P., K.S.; Literature Search – J.C., P.P., D.N.A., D.A.P., K.S.; Writing – J.C.; Critical Reviews – P.P., S.K., K.S., T.P., D.A.B.

Conflict of interest statement: The authors report no financial interest that might pose a potential, perceived or real conflict of interest.

REFERENCES

[1] Faheem BKK, Sekhar KVGC, Kunjiappan S, Jamalis J, Balaña-Fouce R, Tekwani BL, Sankaranarayanan M. Druggable targets of SARS-CoV-2 and treatment opportunities for COVID-19. Bioorg Chem 2020; 104:104269. https://doi.org/10.1016/j.bioorg.2020.104269.

[2] Saied EM, El-Maradny YA, Osman AA, Darwish AM, H Abo Nahas H, Niedbała G, Piekutowska M, Abdel-Rahman MA, Balbool BA, Abdel-Azeem AM. A comprehensive review about the molecular structure of severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2): Insights into natural products against COVID-19. Pharmaceutics 2021; 13(11):1759. https://doi.org/10.3390/pharmaceutics13111759.

[3] Durmaz V, Köchl K, Krassnigg A, Parigger L, Hetmann M, Singh A, Nutz D, Korsunsky A, Kahler U, König C, Chang L, Krebs M, Bassetto R, Pavkov-Keller T, Resch V, Gruber K, Steinkellner G, Gruber CC. Structural bioinformatics analysis of SARS-CoV-2 variants reveals higher hACE2 receptor binding affinity for Omicron B.1.1.529 spike RBD compared to wild type reference. Sci Rep. 2022;12(1):14534. https://doi.org/10.1038/s41598-022-18507-y.

[4] Dubey A, Choudhary S, Kumar P, Tomar S. Emerging SARS-CoV-2 Variants: Genetic Variability and Clinical Implications. Curr Microbiol 2022; 79(1):20. https://doi.org/10.1007/s00284-021-02724-1.

[5] CDC COVID-19 Response Team. SARS-CoV-2 B.1.1.529 (Omicron) Variant - United States, December 1-8, 2021. MMWR Morb Mortal Wkly Rep. 2021 Dec 17;70(50):1731-1734. https://doi.org/10.15585/mmwr.mm7050e1.

[6] Sahoo JP, Samal KC. World on alert: WHO designated South African new COVID strain (Omicron/B. 1.1. 529) as a variant of concern. Biot Res Today 2021; 3(11):1086-1088.

[7] Poudel S, Ishak A, Perez-Fernandez J, Garcia E, León-Figueroa DA, Romaní L, Bonilla-Aldana DK, Rodriguez-Morales AJ. Highly mutated SARS-CoV-2 Omicron variant sparks significant concern among global experts–What is known so far? Travel Med Infect Dis 2022; 45:102234. https://doi.org/10.1016/j.tmaid.2021.102234.

[8] Quarleri J, Galvan V, Delpino MV. Omicron variant of the SARS-CoV-2: a quest to define the consequences of its high mutational load. Geroscience. 2022;44(1):53-56. https://doi.org/10.1007/s11357-021-00500-4.

[9] He X, Hong W, Pan X, Lu G, Wei X. SARS-CoV-2 Omicron variant: characteristics and prevention. Med Comm 2021; 2(4):838-845. https://doi.org/10.1002/mco2.110.

[10] Sarkar R, Lo M, Saha R, Dutta S, Chawla-Sarkar M: S glycoprotein diversity of the Omicron variant. Med Rxiv 2021. https://doi.org/10.1101/2021.12.04.21267284.

[11] Khan S, Rafat D, Khan AU, Rahman SZ, Farhat N. Application of saliva in COVID-19 diagnosis: Challenges and opportunities. Bangladesh J Med Sci 2021; 20(4):697-699. https://doi.org/10.3329/bjms.v20i4.54122.

[12] Zhang Y, Quigley A, Wang Q, MacIntyre CR. Non-pharmaceutical interventions during the roll out of covid-19 vaccines. BMJ. 2021;375:n2314. https://doi.org/10.1136%2Fbmj.n2314.

[13] Alexander SP, Kelly E, Mathie A, Peters JA, Veale EL, Armstrong JF, Faccenda E, Harding SD, Pawson AJ, Southan C, Buneman OP, Cidlowski JA, Christopoulos A, Davenport AP, Fabbro D, Spedding M, Striessnig J, Davies JA, Ahlers-Dannen KE, Alqinyah M, Arumugam TV, Bodle C, Dagner JB, Chakravarti B, Choudhuri SP, Druey KM, Fisher RA, Gerber KJ, Hepler JR, Hooks SB, Kantheti HS, Karaj B, Layeghi-Ghalehsoukhteh S, Lee JK, Luo Z, Martemyanov K, Mascarenhas LD, McNabb H, Montañez-Miranda C, Ogujiofor O, Phan H, Roman DL, Shaw V, Sjogren B, Sobey C, Spicer MM, Squires KE, Sutton L, Wendimu M, Wilkie T, Xie K, Zhang Q, Zolghadri Y. THE CONCISE GUIDE TO PHARMACOLOGY 2021/22: Introduction and Other Protein Targets. Br J Pharmacol. 2021 Oct;178 Suppl 1(Suppl 1):S1-S26. https://doi.org/10.1111/bph.15537.

[14] Chang CK, Lin SM, Satange R, Lin SC, Sun SC, Wu HY, Kehn-Hall K, Hou MH. Targeting protein-protein interaction interfaces in COVID-19 drug discovery. Comput Struct Biotechnol J. 2021;19:2246-2255. https://doi.org/10.1016/j.csbj.2021.04.003.

[15] Cabri W, Cantelmi P, Corbisiero D, Fantoni T, Ferrazzano L, Martelli G, Mattellone A, Tolomelli A. Therapeutic peptides targeting PPI in clinical development: Overview, mechanism of action and perspectives. Front Mol Biosci 2021; 8: 697586. https://doi.org/10.3389/fmolb.2021.697586.

[16] Mannes M, Martin C, Menet C, Ballet S. Wandering beyond small molecules: peptides as allosteric protein modulators. Trends Pharmacol Sci 2022; 43(5):406-423. https://doi.org/10.1016/j.tips.2021.10.011.

[17] Mohan UP, Kunjiappan S, Pichiah PT, Arunachalam S. Adriamycin inhibits glycolysis through downregulation of key enzymes in *Saccharomyces cerevisiae*. 3 Biotech 2021; 11(1):15. https://doi.org/10.1007/s13205-020-02530-9.

[18] Veeramachaneni GK, Thunuguntla V, Bobbillapati J, Bondili JS. Structural and simulation analysis of hotspot residues interactions of SARS-CoV 2 with human ACE2 receptor. J Biomol Struct Dyn 2020; 39(11):4015-4025. https://doi.org/10.1080/07391102.2020.1773318.

[19] Bhachoo J, Beuming T. Investigating protein–peptide interactions using the Schrödinger computational suite. Modeling peptide-protein interactions. Methods Mol Biol 2017; 1561:235-254. https://doi.org/10.1007/978-1-4939-6798-8_14.

[20] Kalimuthu AK, Panneerselvam T, Pavadai P, Pandian SRK, Sundar K, Murugesan S, Ammunje DN, Kumar S, Arunachalam S, Kunjiappan S. Pharmacoinformatics-based investigation of bioactive compounds of Rasam (South Indian recipe) against human cancer. Scientific Rep. 2021; 11(1):21488. https://doi.org/10.1038/s41598-021-01008-9.

[21] Markov S, Petkov P, Pavlov V. Large-Scale Molecular Dynamics Simulations on Modular Supercomputer Architecture with Gromacs. In: International conference on Variability of the Sun and sun-like stars: from asteroseismology to space weather: 2019. Springer, pp. 359-367.

[22] Van Aalten DM, Bywater R, Findlay JB, Hendlich M, Hooft RW, Vriend G. PRODRG, a program for generating molecular topologies and unique molecular descriptors from coordinates of small molecules. J Comput Aided Mol Des 1996; 10(3):255-262. https://doi.org/10.1007/bf00355047.

[23] Pandian SRK, Pavadai P, Vellaisamy S, Ravishankar V, Palanisamy P, Sundar LM, Chandramohan V, Sankaranarayanan M, Panneerselvam T, Kunjiappan S. Formulation and evaluation of rutin-loaded solid lipid nanoparticles for the treatment of brain tumor. Naunyn-Schmiedeberg's Arch Pharmacol 2021; 394(4):735-749. https://doi.org/10.1007/s00210-020-02015-9.