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A computational evaluation of structural stability of omicron and delta mutations of SARS-CoV-2 spike proteins and human ACE-2 interactions

Kehinde A. Idowu *, Collins Onyenaka, Omonike A. Olaleye

Department of Pharmaceutical and Environmental Health Sciences, College of Pharmacy and Health Sciences, Texas Southern University, 3100 Cleburne St, Houston, TX, 77004, USA

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ABSTRACT

Several more infectious SARS-CoV-2 variants have emerged globally since SARS-CoV-2 pandemic and the discovery of the first D614G variant of SARS-CoV-2 spike proteins in 2020. Delta (B.1.617.2) and Omicron (B.1.1.529) variants have proven to be of major concern out of all the reported variants, considering their influence on the virus’ transmissibility and severity. This study aimed at evaluating the impact of mutations on these two variants on stability and molecular interactions between the viral Spike protein and human angiotensin converting enzyme-2 (hACE-2). The spike proteins receptor binding domain (RBD) was docked with the hACE-2 using HADDOCK servers. To understand and establish the effects of the mutations on the structural stability and flexibility of the RBD-hACE-2 complex, molecular dynamic (MD) simulation of the docked complex was performed and evaluated. The findings from both molecular docking analysis and binding free energy showed that the Omicron (OM) variant has high receptiveness towards hACE-2 versus Delta variant (DT), thereby, responsible for its increase in transmission. The structural stability and flexibility evaluation of variants’ systems showed that mutations on DT and OM variants disturbed the stability of either the spike protein or the RBD-hACE-2 complex, with DT variant having greater instability impact. This study, therefore, assumed this obvious instability observed in DT variant might be associated or responsible for the reported severity in DT variant disease over the OM variant disease. This study provides molecular insight into the effects of OM and DT variants on stability and interactions between SARS-CoV-2 protein and hACE-2.

1. Introduction

As of August 24, 2022, about 598,180,048 cases of SARS-CoV-2 infections have been recorded (https://coronavirus.jhu.edu/map.html). This huge spread of the virus could be associated with emerging changes/variation in the virus genetic content because of mutation, resulting to emergence of several variants of the virus. Study has shown that the virus RNA, rapidly mutate in host cells [1], thereby produces the diverse variants of the virus. Of the different classifications of SARS-CoV-2 variants by WHO, variants of concern (VOC) have been the most infectious and virulent variants [2]. WHO defined VOC as variants with a) modification in their genetic code that alters SARS-CoV-2 characteristics, b) variants that cause notable viral transmission, and severe COVID-19 epidemiology, and c) reduced drugs/vaccines efficiency [2].

Presently, five SARS-CoV-2 variants fall under the VOCs, namely, Alpha (lineage B.1.1.7) (Domingo & Benito, 2021), Beta (lineage B.1.351) (Reincke et al., 2022), Gamma (lineage P.1) (Nonaka et al., 2021), Delta (lineage B.1.617.2) [3], and Omicron (lineage B.1.1.529) [4] VOCs. Out of these, Delta (B.1.617.2) and Omicron (B.1.1.529) variants have proven to be of major concern, considering their influence on the virus’ transmissibility and severity [5]. Delta variant (lineage B.1.617.2) was discovered in countries within few months and WHO labeled the B.1.617.2 sublineage on May 11, 2021, as a VOC delta variant [6]. By the end of third quarter of 2021, delta variant has become the global dominant VOC [2,4,7]. The predominant mutation in the spike protein of the B.1.617 sublineage includes D614G, L452R, and P681R (Fig. 1 and Table 1). A study by Mlcochova et al. showed that the variant is eight-fold less susceptible to antibodies produced by vaccines and six times less sensitive to serum antibodies from recuperating persons when compared to its wild type [3].

Omicron variant (lineage B.1.1.529) is another VOC. It was detected by the Network for Genomic Surveillance in South Africa on November 24, 2021 [9] and was named by the WHO (WHO, 2021d). The three

* Corresponding author.
E-mail address: Kehinde.idowu@tsu.edu (K.A. Idowu).

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The UCSF Chimera software package [23]. The structures of the proteins Spike RBD for each variant with hACE-2 was done using Haddock molecular docking server [24], with default docking parameters. The docked complexes were then subjected to molecular dynamics simulations.

### 2.2. Molecular dynamic (MD) simulations

The MD simulation was performed as described by Idowu et al. with little modification [19]. The simulations were performed using the GPU version provided with the AMBER package (AMBER 18) [25], in which the FF18SB variant of the AMBER force field [26] was used to describe the systems.

The Leap module of AMBER 18 allowed for the addition of hydrogen atoms and Na+ and Cl− counter ions to complexes, to neutralize all solutes. They were performed for 1000 steps using the steepest descent method followed by 1000 steps of conjugate gradients. An additional full minimization of 1000 steps were further carried out using the conjugate gradient algorithm without restraint. A gradual heating MD simulation from 0 K to 300 K was executed for 50 ps, such that the systems maintained a fixed number of atoms and fixed volume. The systems’ solutes were imposed with a potential harmonic restraint of 10 kcal/mol and

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**Table 1**

| Variants | Sequence | Amino acid/position | Mutation |
|----------|----------|---------------------|----------|
| Wild type (WT) | NCBI: P0DTC2 | T19R, G142D, Δ156-157, R185G, Δ213-214, L145R, Δ439-440, Δ501-502, N679K, P681H, Q498R, N501Y, Y505H, T547K, K417 N, N440K, G446S, S477 N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, N764K, D950 N | |
| Delta Variant (B.1.617.2) | NCBI: QWK65230.1 | T19R, G142D, Δ156-157, R185G, Δ213-214, L145R, Δ439-440, Δ501-502, N679K, P681H, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, N764K, D950 N, G908R, T910N | |
| Omicron (B.1.529) | GSAID: R408B60_BHP_3321001247/202 | A67V, Δ69-70, T91V, G142D, Δ143-145, N211I, Δ214-215, V215L, P216T, G339D, S371L, S373P, S375F, S477N, K417N, Δ440K, Δ446S, Δ577N, T478K, E484A, Q493R, Δ496S, Q498R, Δ501Y, Y505H, Δ547K, D614G, H655Y, N679K, P681H, N764K, D950N, N969K, L981F |

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**Fig. 1.** A comparison of Delta and Omicron variant spike mutation [8]. OM spike protein’s variation is determined by 30 mutations (3 small deletions and 1 insertion).
collision frequency of 1.0 ps. Following heating, an equilibration estimating 500 ps of each system was conducted; the operating temperature was kept constant at 300 K. Additional features such as several atoms and pressure were also held constant, mimicking an isobaric-isothermal ensemble. The system’s pressure was maintained at 1 bar using the Berendsen barostat [28,29].

The total time for the MD simulations conducted was 50 ns. In each simulation, the SHAKE algorithm was employed to constrict hydrogen atoms’ bonds [30]. The step size of each simulation was 2fs, and an SPFP precision model was used. The simulations coincided with the isobaric-isothermal ensemble (NPT), with randomized seeding, the constant pressure of 1 bar maintained by the Berendsen barostat [29], a pressure-coupling constant of 2 ps, a temperature of 300 K and Langevin thermostat [31] with a collision frequency of 1.0 ps.

2.3. Post-dynamic analysis

Analysis of Root Means Square Deviation (RMSD), Radius of Gyration (RoG), and Solvent Accessible Surface Area (SASA) was done using the CPPTRAJ module employed in the AMBER 18 suit. All raw data plots were generated using python 3.9 on Anaconda3 software.

2.4. Binding free energy calculations

To estimate and compare the systems’ binding affinity, the free binding energy was calculated using the Molecular Mechanics/GB Surface Area method (MM/GBSA) [32]. Binding free energy was averaged over 50000 snapshots extracted from the 50ns trajectory. The free binding energy (ΔG) computed by this method for each molecular species (complex, ligand, and receptor) can be represented as:

\[ \Delta G_{\text{bind}} = G_{\text{complex}} - G_{\text{receptor}} - G_{\text{ligand}} \]  

\[ \Delta G_{\text{bind}} = E_{\text{gas}} + G_{\text{sol}} - TS \]  

\[ E_{\text{gas}} = E_{\text{int}} + E_{\text{ele}} + E_{\text{vdw}} \]  

\[ G_{\text{sol}} = G_{\text{GB}} + G_{\text{SA}} \]  

\[ G_{\text{SA}} = \gamma S_{\text{SASA}} \]  

\[ E_{\text{gas}} \] denotes the gas-phase energy, which consists of the internal energy \( E_{\text{int}} \), Coulomb energy \( E_{\text{ele}} \) and the van der Waals energies \( E_{\text{vdw}} \). The \( E_{\text{gas}} \) was directly estimated from the FF14SB force field terms. Solvation free energy, \( G_{\text{sol}} \) was estimated from the energy contribution from the polar states, \( G_{\text{GB}} \), and non-polar states, \( G_\text{n} \). The non-polar solvation energy, \( G_{\text{SA}} \) was determined from the solvent-accessible surface area (SASA), using a water probe radius of 1.4 Å. In contrast, the polar solvation, \( G_{\text{GB}} \), the contribution was estimated by solving the GB equation. S and T denote the total entropy of the solute and temperature, respectively.

3. Results and discussion

In this study, the result of molecular docking analysis of the two variants and wild type of SARS-CoV-2 with hACE-2 showed that the OM variant has highest docking score of \(-134.4 \) kcal/mol, while DT variant showed a lower score of \(-59.2 \) kcal/mol (Fig. 2). A molecular docking score is therefore a measurement of the fitness of a molecule/ligand into the catalytic active/binding site pocket of an enzyme or protein, and the more negative the value, the better the fitness of the molecule [33; Shode et al., 2021]. This scoring functions allowed the estimation and prediction of the binding affinities of individual molecules [34]. This result corroborates the finding of Kumar et al. that earlier reported OM exhibited highest docking score of \(-539.81 \) kcal/mol, higher than the docking score reported for the DT variant \((-529.62 \) kcal/mol) [8]. Furthermore, the trend in our result is similar to the trend reported in the finding of Hwang et al. that reported docking energy of 340.0 kcal/mol for the WT, 25.2 kcal/mol for the DT, and \(-382.1 \) kcal/mol for the OM variant [35]. This indicates that the OM variant is more receptive to the host receptor, hACE2 than the DT. This result might be the first clue to explain the higher infectivity/transmission of SARS-CoV-2 observed in OM variant over the DT variant.

3.1. Prediction of the binding energy between variant spike RBD and hACE-2

Molecular dynamics is a popular computational method for calculating the binding affinity and probing energy interaction. In this study, molecular mechanics/generalized born surface area (MMGBSA) computational technique was employed to estimate the binding free energies (ΔG<sub>bind</sub>) between the variants and wild type spike proteins toward hACE-2. The molecular dynamic simulation of the RBD–hACE-2 docking complexes was used for the predictions of binding affinity between the hACE2 receptor and two variant and WT. Table 2 showed the thermodynamic binding energy profiles for the variants toward hACE-2. The estimated ΔG<sub>bind</sub> result showed the binding free energy for RBD and hACE-2 is stronger in OM variant \((-43.591 \) kcal/mol) than the DT variant \((-19.743 \) kcal/mol) and WT \((-29.700 \) kcal/mol). Our finding is similar to the reports of previous studies that showed the binding affinity

![Fig. 2. Molecular Docking scores SARS-CoV-2 Spike glycoprotein Variants a) Wild-type (WT), b) Delta-type (DT) and c) Omicron type (OM) toward hACE-2.](image-url)
between hACE-2 and the RBD of the OM variant to be stronger than that of the WT and DT variant [35–37]. For instance, Hwang et al. reported the binding energy was –894.4 kcal/mol for the WT, –980.8 kcal/mol for the DT variant, and –1444.5 kcal/mol for the OM variant [35]. The result of our binding energy together with the molecular docking result, further suggests that the OM variant is more receptive to hACE2 than the DT, and might be associate or responsible for the greater transmission of the virus observed in OM variant than DT variant and WT.

3.2. Protein-protein molecular interactions

A typical receptor-ligand interaction examined the molecular interactions between the bound ligand and the amino acid residues at the binding sites of the protein [38,39]; Obakachi et al., 2022). However, in this study we evaluate the protein-protein molecular interactions between the interacting amino acid residues of the spike RBD and the hACE-2. Fig. 3 showed the interaction poses of the RBD-hACE-2 complexes for the variants and WT after 50 ns MD simulation. Table 3 summarized the number and type of interactions that exist within each complex. For the WT complex, a total of 21 interactions (17 hydrogen bonds and 5 hydrophobic bonds) was observed. However, the presence of mutations on the DT spike protein lowers the number of interactions in the DT spike protein-hACE-2 complex to a total of 16 bonds (9 hydrogen and 7 hydrophobic bonds). Furthermore, the DT mutations significantly lower the hydrogen bond in the complex from 17 in WT to 9 in DT. The reduction in interaction, undoubtedly, is responsible for the lowered docking score and binding affinity reported for DT in this study. For the OM variants, insignificant reduction in the number of interactions, 19 (10 hydrogen and 9 hydrophobic bonds) was observed. However, a significant increase in strong hydrophobic interaction/bond was recorded compared to the WT (5 hydrophobic bond). This study suggests that the increase in the number of strong hydrophobic bonds in OM variant might be the reason for high binding energy and docking score reported in this study and other related studies.

3.3. Structural stability and flexibility evaluation of variants’ systems

The structural stability of the protein complexes was measured following experimental simulation of the spike protein RBD (for both variants and WT) together with the hACE-2. To confirm the dynamic of the complexes, 50 ns MD simulations was performed. Binding of a molecule (either drugs or protein) to a specific biological target is usually associated with structural and conformational changes, which in

![Fig. 3. Interacting Amino residues between the Variants' Spike proteins and hACE-2.](image-url)
most cases influence the biological activity of that target [40–42]. To establish the stability and accurate equilibration of the investigated complexes, RMSD, RoG, RMSF and SASA of alpha carbon (Ca) atoms were monitored and analyzed along with the entire duration of 50 ns of the MD simulation for the WT, DT and OM. These parameters were calculated for the RBD site only (RBD), the whole spike glycoprotein only (SPIKE) and the spike RBD-hACE-2 (RBD-ACE-2) complex.

The measurement of the systems convergence and stability is referred to as RMSD [43]. Figs. 4–6 showed the result of the RMSD plot that measures the complexes’ convergence and stability for the RBD, SPIKE and RBD-hACE-2 complex, respectively. Table 4 showed the average values of each parameter used to interpret structural stability of each system. For the RBD (Fig. 4a), the RMSD plot, after maintaining convergence at approximately 8 ns, all the complexes exhibited favorable stability throughout the MD simulations, except for the RBDOM with raised RMSD plot at 28 ns. The average RMSD value for RBDOM (2.95 Å) is higher that the estimated values for RBDWT and RBDDT with average values of 2.54 Å and 2.47 Å, respectively (Table 4). The mutations on the OM variant increase the RMSD plot, thereby altering its stability. However, for the whole spike systems, after all the systems maintained convergence at approximately 5 ns, SPIKEOM and SPIKEDT systems exhibited unfavorable stability throughout the MD simulations (Fig. 5a). With the DT variant showing the highest average RMSD value of 8.95 Å, and SPIKEOM exhibited the lowest value of 7.28 Å. A similar trend was observed in the RBD-ACE-2 complexes, where the RBD-ACE-2DT exhibited the highest instability as evidenced by its high average RMSD value of 10.58 Å compared to the RBD-ACE-2WT and SPIKE-ACE-2OM complexes with average RMSD of values of 9.23 Å and 7.81 Å, respectively (Fig. 6a). The RMSD plots of the RBD, SPIKE and RBD-DT showed that both OM and DT mutations affect the stability of the protein but, with the DT variant exhibiting pronounced instability in its protein complexes.

To understand the compactness of the alpha carbon backbones of the protein complexes, the RoG values for each complex were examined. The RoG value is a measure of the extent of compactness of the alpha carbon backbones of the proteins. An increase in RoG values implies a decrease in protein structure compactness, thereby suggesting decreased stability [44]. Figs. 4b, 5b and 6b showed the RoG plots for all the RBD, SPIKE and RBD-ACE-2 systems, respectively and Table 4, showed the average RoG values for all the systems. RoG is a measure of the impacts of the binding of molecule on the behavior of the active residue [45]. And high RoG values indicated increase flexible movements, and in contrast, lower values meant restricted fluctuations. For the RBD systems (Fig. 4c), RBDWT and RBDOM showed higher flexible movements as evidenced by higher overall average values of 18.75 Å and 18.57 Å, compared to the RBDDT. Nevertheless, at amino acid residues 1060–1070 (the residues on RBD involved in interaction with hACE-2), all the RBD systems showed a noticeable increase in fluctuation, with the RBDOM exhibiting more flexibility than others. This finding is suggestive of how much activity and flexibility required of the interacting amino acid residues in interacting with hACE-2. A look at the whole spike structure, we observed the SPIKEWT exhibited higher fluctuation (7.49 Å) than both the SPIKEWT and SPIKEOM. This finding further corroborates our previous findings that showed that the DT mutations mostly disturbed the protein stability than the SPIKEOM mutations. Similarly, the both the RBD-hACE-2DT (9.66 Å) and RBD-hACE-2OM (7.05 Å) induces more flexible movements on the amino acid residues, with both variants showing higher flexibility than the RBD-hACE-2WT (6.11 Å).

To measures the proteins exposure to solvent molecules, the SASA plots for all the systems were examined (Figs. 4–6). A high SASA value suggesting high mobility and less stability as evidenced by the higher average RoG values of 18.75 Å and 18.57 Å for RBDWT and RBDOM, respectively when compared to the RBDWT (18.43 Å). For the whole spike (SPIKE) systems, a similar trend was observed. The RoG plots of SPIKEWT and SPIKEOM demonstrated decline in structural compactness suggestive of high mobility and less stability as supported by the higher average RoG values of 47.69 Å and 45.16 Å for SPIKEWT and SPIKEOM respectively when compared to the SPIKEWT (44.93 Å). Likewise, just as observed in both RBD and SPIKE systems, the estimated RoG plots of RBD-ACE-2WT and RBD-ACE-2OM also demonstrated decline in structural compactness indicative of high mobility and less stability as evidenced by the higher average RoG values of 60.94 Å and 60.58 Å for RBD-ACE-2WT and RBD-ACE-2OM, respectively when compared to the RBD-ACE-2WT (58.41 Å). The results of the RoG plots of the RBD, SPIKE and RBD-ACE-2 showed that both OM and DT mutations disturb the stability of the interaction between hACE-2 and RBD, however, the DT mutations exhibit more obvious instability in its protein complexes than the OM mutations.

Figs. 4c, 5c and 6c showed the RMSF plots for all the RBD, SPIKE and RBD-ACE-2 systems, respectively and Table 4, showed the average RMSF values for all the systems. RMSF is a measure of the impacts of the binding of molecule on the behavior of the active residue [45]. And high RMSF values indicated increase flexible movements, and in contrast, lower values meant restricted fluctuations. For the RBD systems (Fig. 4d), RBDWT and RBDOM showed higher flexible movements as evidenced by higher overall average values of 18.75 Å and 18.57 Å, compared to the RBDWT. Nevertheless, at amino acid residues 1060–1070 (the residues on RBD involved in interaction with hACE-2), all the RBD systems showed a noticeable increase in fluctuation, with the RBDOM exhibiting more flexibility than others. This finding is suggestive of how much activity and flexibility required of the interacting amino acid residues in interacting with hACE-2. A look at the whole spike structure, we observed the SPIKEWT exhibited higher fluctuation (7.49 Å) than both the SPIKEWT and SPIKEOM. This finding further corroborates our previous findings that showed that the DT mutations mostly disturbed the protein stability than the SPIKEOM mutations. Similarly, the both the RBD-hACE-2WT (9.66 Å) and RBD-hACE-2OM (7.05 Å) induces more flexible movements on the amino acid residues, with both variants showing higher flexibility than the RBD-hACE-2WT (6.11 Å).

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**Fig. 4.** Comparative a). RMSD b). RoG c). RMSF, and d). SASA profile plots of C-a atoms of RBD calculated throughout 50 ns molecular dynamics simulation.
has been reported to be an indication of decrease in the exposure of buried hydrophobic residues which suggest decrease in systems stability [46,47]. The result of average SASA values for the systems (Table 4), showed both RBD\textsubscript{OM} and RBD\textsubscript{DT} increase the SASA plots and average values far higher than the RBD\textsubscript{WT}. This finding indicates that both RBD\textsubscript{OM} and RBD\textsubscript{DT} decreased the exposure of buried hydrophobic residues which means decrease in the RBD stability. Likewise, in the whole spike complexes, the two variants decreased the SPIKE stability as proven by high SASA values of 59078 Å\textsuperscript{2} (SPIKE\textsubscript{DT}) and 58152 Å\textsuperscript{2} (SPIKE\textsubscript{OM}) compared to the SPIKE\textsubscript{WT} (56596 Å\textsuperscript{2}). Equally, as reported in both the RBD and SPIKE systems, in the RBD-hACE-2 systems the RBD-hACE-2\textsubscript{OM} (82051 Å\textsuperscript{2}) and RBD-hACE-2\textsubscript{DT} (82721 Å\textsuperscript{2}) increase the SASA average values far higher than the RBD\textsubscript{WT}, which indicates that both RBD\textsubscript{OM} and RBD\textsubscript{DT} decreased the exposure of buried hydrophobic residues which mean decrease in the RBD-hACE-2 complex stability.

The findings of this study from all the structural stability parameters uniformly showed that mutations from both DT and OM variants disturbed the stability of either the spike protein or the RBD-hACE-2 complex. From the examination of the mutations present on the RDBs of the two variants; OM (G339D, S371L, S373P, S375F, K417 N, N440K,
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4. Conclusion
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Evaluation of a monomer of Spike protein instead of trimers over a
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Declaration of competing interest
The authors declare that they have no known competing financial
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References
[1] Ganeshpurkar A, Gatti G, Singh SK. RNA-dependent RNA polymerases and their
emerging roles in antiviral therapy. In: Viral polymerases: structures, functions and
roles as antiviral drug targets. Elsevier; 2018. p. 1–42. https://doi.org/10.1016/
B978-0-12-815422-9.00001-2.[2] World Health Organization. easy-to-say labels for SARS-CoV-2 variants of interest
and concern. Retrieved from, https://www.who.int/news/item/31-05-2021-wh o-announces-simple-easy-to-saylabels-for-sars-cov-2-variants-of-interest-and-con-
cern-2021.[3] Micchonova P, Kemp S, Dhar MS, Papa G, Meng B, Ferreira IATM, Gupta RK. SARS-CoV-
2 B.1.617.2 Delta variant replication and immune evasion. Nature 2021.
https://doi.org/10.1038/s41586-021-03949-y.[4] World Health Organizations. Classification of omicron (B.1.1.529): world health
organizations (2021). SARS-CoV-2 variant of concern. 2021. Retrieved from,
https://www.who.int/news/item/26-11-2021-classification-of-omicron-(b.1.1.52
9)sars-cov-2-variant-of-concern.[5] World Health Organizations. Tracking SARS-CoV-2 variants. 2022. Retrieved from,
https://www.who.int/activities/tracking-SARS-CoV-2-variants/.[6] Public Health England. SARS-CoV-2 variants of concern and variants under
investigation in England. Sagar; 2021. p. 1–50. April.[7] World Health Organization. Classification of omicron (B.1.1.529). T. A. G. on S.C-
V. E. (TAG-V. 2021. SARS-CoV-2 Variant of Concern. Retrieved from, https://www.who.int/news/item/26-11-2021-classification-of-omicron-(b.1.1.52
9)sars-cov-2-variant-of-concern.[8] Kumar S, Thivyta BT, Kalimuthu K, Gunasekaran S. Omicron and Delta variant of SARS-CoV-2: a comparative computational study of spike protein. J Med Virol 2021;94(2022):1641–9. https://doi.org/10.1002/jmv.27526.[9] Gouwissanark A, Priyanka T, Banerjee S. Omicron: a mysterious variant of concern.
Euro. phy. j. plus 2022;137(1):100. https://doi.org/10.1140/epjp/s13360-021-
02251-y.[10] Pulliam J, van Schalkwyk C, Govender T, Groome MJ, Dushoff J, Milanes K, Moellette H. Increased risk of SARS-CoV-2 reinfec-
tion associated with emergence of Omicron in South Africa. Science 2022. https://doi.
oi/10.1126/science.abc4947. Advance online publication.[11] Brandal LT, MacDonald E, Veneti L, Ravot L, Lange H, Naseer U, Feruglio S, Bragstad K, Hungnes O, Odeskaug LE, Hagen F, Hanch-Hansen KE, Lind A, Watle SV, Taxt AM, Johansen M, Vold L, Aavitsland P, Nygård Y, Kaldsetsen EH.
Outbreak caused by the SARS-CoV-2 omicron variant in Norway, november to
december 2021. Euro Surveill: bullet. Europ. sur les malad. transmis – transmis. commun. dis. bul.
test 2021;26(50):2101147. https://doi.org/10.2807/1560-7917.ES.2021.26.50.2101147.[12] Espenhain L, Funk T, Overvad M, Edslev SM, Fønager J, Igham AC, Rasmussen M,
Madsen SL, Espersen CH, Sieber RN, Stegger M, Gunalan V, Wilkikowski B,
Larsen NR, Legarth R, Cohen AS, Nielsen F, Lam J, Levy W, Næs K, Karaskis M, Müllerrer.
Epidemiological characterisation of the first 785 SARS-CoV-2 Omicron variant
cases in Denmark, December 2021. Euro Surveill: bullet. Europ. sur les malad.
transmis – Europ. commun. dis. bul. 2022;26(50):2101146. https://doi.org/10.2807/1560-7917.
ES.2021.26.50.2101146.[13] Lupala CS, Ye Y, Chen H, Su XD, Li H. Mutations on RBD of SARS-CoV-2 Omicron
variant result in stronger binding to human ACE2 receptor. Biochem Biophys Res
Commun 2022;590:34–41. https://doi.org/10.1016/j.bbrc.2021.12.079.[14] Elle S, Buckland-Merrett G. Data, disease, and diplomacy: GISAID’s innovative
ctribution to global health. Glob. challenge. (Hoboken, NJ, 2017;1(1):33–46. https://doi.org/10.1002/gch.2018.[15] Cerutti G, Guo Y, Liu L, Liu Z, Zhang L, Luo Y, Huang Y, Wang HH, Bo DD, Sheng Z,
Shapiro L, Czysz-EM structure apo of the SARS-CoV-2 Spike protein. Cell Rep 2022;38
(9):110428. https://doi.org/10.1016/j.celrep.2021.110428.[16] Cui Z, Liu P, Wang N, Wang L, Fan K, Zhu Q, Wang K, Chen R, Feng R, Jia Z,
Yang M, Xu G, Zhu B, Fu W, Chu T, Feng L, Wang Y, Pei X, Yang P, Xie XS, Wang X.
Structural and functional characterizations of infectivity and immune evasion of
SARS-CoV-2 Omicron. Cell 2022;185(5):860–71. https://doi.org/10.1016/j.
cell.2022.01.019, e13.[17] Sabhi Saeheb, Idowu K. An insight on the nature of biochemical interactions
between glycyrrhizin, myricetin and CYP3A4 isoform. J Food Biochem 2021;2(3):
43. https://doi.org/10.1111/jfbc.13831.[18] Uhomoibhi JO, Shode FO, Kehinde Ademola I, Sabhi S. Molecular modelling
identification of phytochemicals from selected African botanicals as promising
therapeutics against drugable human host cell targets of SARS-CoV-2. J Mol Graph
Model 2022. https://doi.org/10.1016/j.jmgm.2022.108185.[19] Idowu AK, Egbajumi A, Kaur M, Onyenaka C, Adebusuyi T, Olayeye OA. Inhibitory
mechanisms of ambrutile and bromilene hydrochlorides as potent blockers of
molecular interaction between SARS-CoV-2 spike protein and human angiotensin-
converting enzyme-2. J Mol Graph and Dyn 2022.
Obakachi, V. A., Idowu, K, Narva Deshwar Kushwaha, Olayinka I. Akinpelu, Babita Kushwaha, Srinivas Reddy Merugu, Rajeshkhar Karpoomath. “Structural based investigation of novel pyrazole-thiazole hybrids as dual CDK-1 and CDK-2 inhibitors for cancer chemotherapy” molecular chemistry. DOI: 10.1080/08927022.2022.2045016.

Xu C, Wang Y, Liu C, Zhang C, Han W, Hong X, Wang Y, Hong Q, Wang S, Zhao Q, Wang Y, Yang Y, Chen K, Zheng W, Kong L, Wang F, Zuo Q, Huang Z, Cong Y. Conformational dynamics of SARS-CoV-2 trimeric spike glycoprotein in complex with receptor ACE2 revealed by cryo-EM. Sci Adv 2021;7:eabe5765.

Shapovalov MV, Danbrak Jr RL. A smoothed backbone-dependent rotamer library for proteins derived from adaptive kernel density estimates and regressions. 1993 Structure (London, England 1991;3(6):844–84. https://doi.org/10.1016/j.

Yang Z, Lasker K, Schneidman-Duhovny D, Webb B, Huang CC, Pettersen EF, MacKerell AD Jr, Case DA, Simmerling C, Eastwood JD, Darden TA, Gohlke H, Grozovsky R, Honigs B, Koepsell KD, Kollman PA, Levitt M, Matsumura N, Merz KM Jr, Olson AJ, Reedijk J, Simmerling C, Sippl MJ, Sternberg M, Stowers R, Szabo K, Thompson JR, Voelz G, Wang Y, Woods NC, Dzubiella U, Moreland L, Wang P, Honig B. Amber 2021. San Francisco: University of California; 2021.

Nair PC, Miners JO. Molecular dynamics simulations: from structure function relationships to drug discovery. Silico Pharm 2014;2(1):1–4. https://doi.org/10.1186/s40303-014-0004-8.

Jorgensen WL, Chandrasekhar J, Madura JD, Impey RW, Klein ML. Comparison of simple potential functions for simulating liquid water. J Chem Phys 1983;79(2):926–35.

Bonn et P. SHAKE: a quadratically convergent SHAKE in O(n2). J Comput Phys 2007;220(2):740–50. https://doi.org/10.1006/jcph.2006.05.032.

Basoni JE, Shir OE. Effects of temperature control algorithms on transport properties and kinetics in molecular dynamics simulations. J Chem Theor Comput 2015;11(7):2887–99. https://doi.org/10.1021/acs.jctc.5b00109.

Ryckaert JP, Cicotti G, Berendsen HJ. Numerical integration of the Cartesian equations of motion of a system with constraints: molecular dynamics of n-alkanes. J Comput Phys 1977;23(3):327–41. https://doi.org/10.1016/0021-9991(77)90098-5.

Izaguirre JA, Catarello DP, Wozniak JM, Sreed RD. Langevin stabilization of molecular dynamics. J Chem Phys 2001;114(5):2900–8. https://doi.org/10.1063/1.1329996.

Vilari M, Pentikainen OT. MMGBSA as a tool to understand the binding affinities of fentanyl-peptide interactions. J Chem Inf Model 2011;51(10):2626–33.

Idowu K, Ramharack P, Nlooto M, Gordon M. Molecular dynamic mechanism(s) of inhibition of bioactive antiviral phytochemical compounds targeting cytochrome P450 3A4 and P-glycoprotein. J Biomol Struct Dyn 2020:1–11. https://doi.org/10.1080/07391102.2020.1821780.

Abdullahi M, Oluot FA, Soliman ME. Allosteric inhibition abrogates dysregulated LFA-1 activation: structural insight into mechanisms of diminished immunologic disease. Comput Biol Chem 2018;73:49–56. https://doi.org/10.1016/j.

Hwang S, Baek S, Park D. Interaction analysis of the spike protein of delta and omicron variants of SARS-CoV-2 with hACE2 and eight monoclonal antibodies using the fragment molecular orbital method. J Chem Inf Model 2022 2022;62: 1771–82.

Lan J, He X, Ren Y, Wang Z, Zhou H, Fan S, Zhu C, Liu D, Shao B, Liu T-Y, Wang Q, Zhang L, Ge J, Wang T, Wang X. Structural and computational insights into the SARS-CoV-2 omicron RBD-ACE2 interaction. bioRxiv 2022. https://doi.org/10.1101/2022.01.03.674655.

Costa CH, Freitas CA, Alves CN. Assessment of mutations on RBD in the spike protein of SARS-CoV-2 alpha, delta and omicron variants. Research Square 2022. https://doi.org/10.21203/rs.3.rs.4101853/v1.

Kehinde I, Ramharack P, Nlooto M, Gordon M. The pharmacokinetics of HIV-1 protease inhibitors: a computational perspective on herbal phytochemicals. Helv 2019;5(10):e02656. 10.1016/j.

Vincent OA, Kushwaha ND, Kushwaha B, Mavela CM, Srinivas RM, Idowu KA, Rajeshkhar K. Design and synthesis of pyrazolone-based compounds as potent blockers of SARS-CoV-2 viral entry into the host cells. J Mol Struct 2021;1241: 130665. https://doi.org/10.1016/j.molstruc.2021.130665.

Sindhu T, Srinivasan P. Exploring the binding properties of agonists interacting with human TGR5 using structural modelling, molecular docking and dynamics simulations. RSC Adv 2015;5(19):14202–13. https://doi.org/10.1039/C4RA16617E.

Aribisala JO, Nkosi Sonto, Kehinde Idowu, Nurain Ismailia, Shohe FO, Saheed Sabiu. Astaxanthin-mediated bacterial lethality: evidence from oxidative stress contribution and molecular dynamics simulation. Oxid Med Cell Longev 2021. https://doi.org/10.1155/2021/7159652.

John OU, Kehinde Al, Shohe OF, Saheed S. Molecular modelling identification of potential drug candidates from selected African plants against SARS-CoV-2 key druggable proteins. Scientific African 2022.

Hess B. Convergence of sampling in protein simulations. Phys Rev 2002 653(5): 31910.

Idowu AK, Egbeymori Anu, Kaur Manvir, Onyenaka Collins, Adesbusiya Tolulope, Olaleye Omonike A. Inhibitory mechanism of clioquinol and its derivatives at the exopeptidase site of human angiotensin-converting enzyme-2 and receptor binding domain of SARS-CoV-2 viral spike protein. J Biomol Struct Dyn 2022. https://doi.

Kumar CV, Swetha RG, Anbarasu A, Ramaiah S. Computational analysis reveals the association of threonine 118 methionine mutation in PMP22 resulting in CMT-1A’. Advan. Bioinformatics 2014:2014110.

Ogidijo JO, Emmanuel Al, Ibeji CU, Okpaleke O, Soliman MES. Natural phyto, compounds as possible noncovalent inhibitors against SARS-CoV2 protease: computational approach. https://doi.org/10.1080/07391102.2020.1873681; 2020.

Sinyani A, Idowu K, Shunnumag K, Kumalo HM, Khan Rene. A molecular dynamics perspective into estrogen receptor inhibition by selective flavonoids as alternative therapeutic options. J Biomol Struct Dyn 2022. https://doi.org/10.1080/

Joseph A Lewnard, Hong Vennis X, Patel Manish, Kahn Rebecca, Lipsitch Marc, Sara YT. Clinical outcomes among patients infected with Omicron (B.1.1.529) patients before and after the emergence of Omicron. https://doi.org/10.1101/2022.01.03.474855.

Lindsay W, Berger Nathan A, David C, Kaelber, Pamela B, Davis, Nora D, Volkow, Xu Rong. Comparison of outcomes from COVID infection in pediatric and adult patients before and after the emergence of Omicron. https://doi.org/10.1101/2021.12.30.21268495; 2022.