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Molecular Basis of Host-Virus Interactions to Explain Relative Transmission and Severity Caused by Omicron and Delta variants of SARS-CoV-2

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Abstract

In India and other affected countries, Omicron variant of SARS-CoV-2 has shown faster transmission but less clinical severities when compared to Delta strain. Present study was aimed to investigate how molecular changes in the spike proteins of Omicron variant has increased its transmission but reduced the disease severity. We report molecular interactions of Spike proteins of Delta and Omicron variants with ACE-2 receptor to explain how change in chemical and physical nature of mutated amino acids of Omicron variant has affected the internalization competence of virus into host cell. The Research Collaboratory Structural Bioinformatics (RCSB) and Protein Data Bank (PDB) were used to construct ACE2-Spike Protein interaction. The binding affinity of both omicron and delta variant spike proteins with human ACE2 receptor was observed. Spike protein of Omicron variants has revealed total number of 93 dissimilarities of amino acids from Delta strain,15 of which are in its Receptor Binding Domain (RBD). Our study showed that RBD of Delta variant contained only one hydrophobic amino acid whereas there were 6 hydrophobic amino acids in the RBD of Omicron variant. We report that increased number of Hydrophobic Amino Acids in RBD of Omicron variant affects its binding with ACE2 receptor to enter into the cell. The failure of internalization of virus has increased concentration of extracellular virions at nasopharyngeal region leading to faster expulsion of infective droplets during coughing or sneezing to increase transmission but has reduced the severity of infection. The reported observations could prove to be of public health and therapeutic significance.

Keywords: COVID-19, SARS-CoV-2, Hydrophobicity, Omicron, Transmission

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INTRODUCTION

The pandemic situation caused by SARS-SARS-CoV-2 all around the world became the highest cause of severity and mortality amidst any of the existing respiratory viruses as of date[1]. India was also among the countries hit by the pandemic in the beginning of the year 2020[2]. The disease was manifested to be 'severe' in patients with co-morbidities of Hypertension, Diabetes and Cardiovascular disease etc.[3-10] With time, a number of "Variants Of Concerns" started to appear in the form of Alpha, Beta, Gamma, Delta and Omicron and some "Variants Under Monitoring" also appeared.[11] In India, the 3rd wave of COVID-19 caused by Omicron variant 8.1.1 had experienced a sudden increase in emergence of daily new cases from 2,837 on 29th December, 2021 to as many as 52,697 cases on 13th January, 2022. However, mortality of the patients during this period has not increased with reported deaths of only 302 patients on 29th December, 2021 and 380 deaths on 13th January, 2022.[12,13] The SARS-CoV-2 enters the nasal epithelial cells through aerosols received from an infected person via host receptor ACE-2.[14,15] Recent studies have reported that Omicron variant of SARS-CoV-2 replicates slowly in human lung cells and Vero E6 cells[16,17]. Based on the study of interactive proteomics of Receptor Binding Domains of both variants of SARS-CoV-2 and ACE-2 host receptor, we present first report on the chemical and physical properties of amino acids as the basis of high transmission and low mortality due to Omicron variant when compared to the Delta variant.

MATERIALS AND METHODS

Analysis of Epidemiological data

Analysis of cumulative data of total confirmed cases reported per day, daily increase in cases as compared to preceding day and percentage of daily change in cases, was taken from the data available in the W.H.O. website.[1,2] The peak of COVID-19 cases in terms of new cases as observed during the months of April to December 2021 was taken as escalation of transmission of Delta variant. Similarly, number of maximum cases caused by Omicron variant as reported during December to January 2022 was studied as peak transmission level of Omicron variant.

Analysis of cumulative data of deaths due to COVID-19 reported per day, daily increase in mortality cases as compared to preceding day and percentage of daily changes in mortality due to Delta as well as Omicron variants were recorded from the W.H.O. website.[4] Hazard ratios have been calculated for the relative morbidity and mortality caused by the variants.

Study of mutations of Spike proteins of variants in Receptor Binding Domain with ACE-2 Receptor

The databases from Research Collaboratory for Structural Bioinformatics (RCSB) and Protein Data Bank (PDB) were used to construct Protein (ACE-2)-Protein (Spike Protein) structural interaction through the amino acid sequences of the spike glycoprotein of SARS-CoV-2 variants i.e. Omicron (PDB ID: 7T9J) and Delta (PDB ID: 7V7Q). Using the Clustal Omega similarity multiple sequence alignment tool, the mutations in the amino acids of two variants of the spike proteins were studied.

Protein-Protein Docking

Clus Pro versatile protein-protein docking online sever[18] was used to derive the binding affinity of both omicron and delta variant spike proteins with the human ACE-2 receptor. A visualizing tool was used to assess the results.

RESULTS

Epidemiological transition of Delta and Omicron variants in India

In the month of April 2021, when the country faced peak of Delta variant, the cases rose from 50,000 on 30th March to as many as 3,86,452 cases on 30th April, 2021(33 Days). There was more than 7 times increase in cases within a period of 33 days (Figure 1). The Hazard Ratio of increase in cases was 7.7.

The analysis of mortality data during above period showed an increasing trend of death during April 2021, a wave caused by the Delta variant. Death cases rose from 500 to 3645 deaths (Figure 2). The increase in death also rose to 8 times of death cases in period of 32 days. The Hazard Ratio calculated for death cases was 7.9.

During the current 3rd wave of COVID-19 in India which started from December 31st and rose till 16th January, 2022 (16 days), the cases increased from 6,058 on 28th December to as many as 2,71,202 cases in just 16 days (Figure 3). There was an immense increase of 44 times cases in just 16 days with Hazzard Ratio of 44.7.

The death cases in the same period during 3rd wave as caused by Omicron variant rose only from 400 cases to 534 deaths on 5th January, 2022 and then reduced to 355 deaths on 17th January, 2022. There was only one time increase in death cases in 16 days and a clear trend of no increase in death with only 1.3 as the Hazard Ratio was observed (Figure 4).

Comparative study of difference of amino acids of RBD of spike proteins of Delta and Omicron variants

Study of alignment of amino acid sequences of Spike proteins of Delta and Omicron variants revealed 93 dissimilarities of amino acids between spike proteins of two variants. However, the difference of amino acids observed between Receptor Binding Domain of Spike protein and ACE-2 receptor, showed 15 changes in Delta and Omicron variant (Table). The amino acid Glycine of Delta variant which is a non-polar compound has been replaced by Aspartic Acid, whereas three molecules of Serine amino acids in Delta variant have been replaced by three other amino acids, two of which are hydrophobic in nature. A complete comparison of amino acids in RBD of spike proteins of Delta and Omicron variants showed that Delta variant RBD contained only one hydrophobic amino acid whereas there are 6 hydrophobic amino acids in the RBD of Omicron variant.

Macro molecular interactive structures of RBD of Spike proteins of Delta and Omicron variants with ACE-2 receptor

The interactive structure of macro molecules of protein of RBD of spike proteins of Delta and Omicron variants with ACE-2 receptor is shown in Figure 5 & 6. The Delta variant Spike

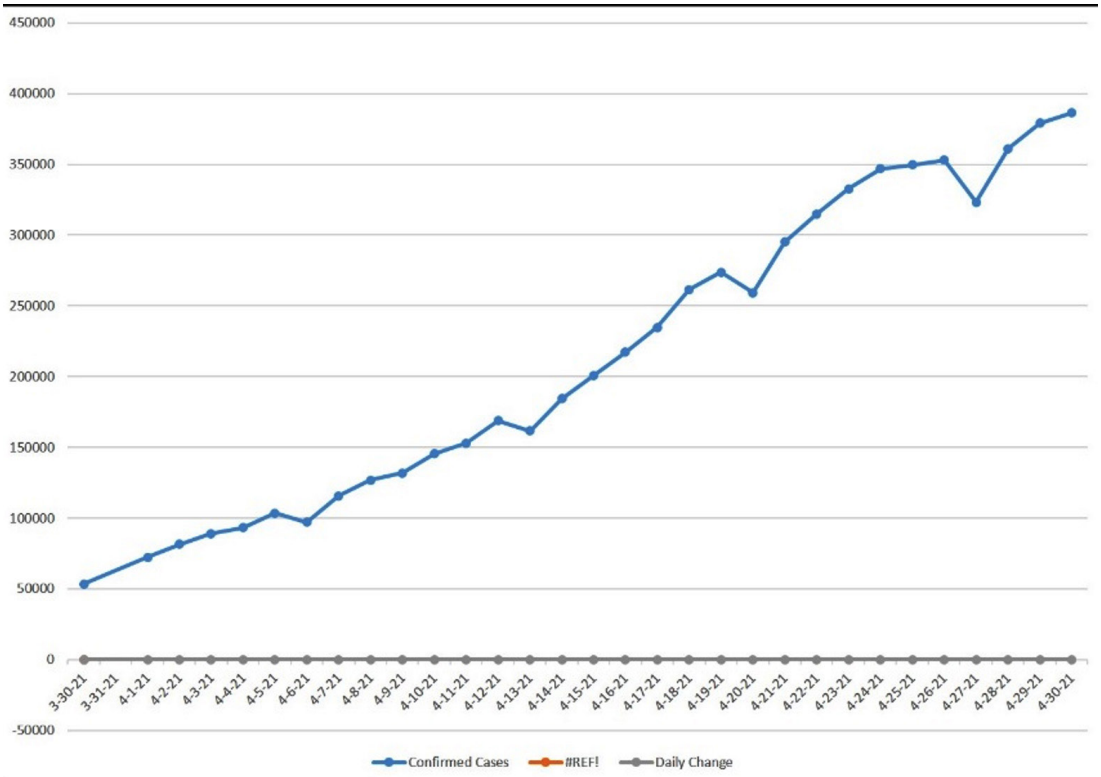

Figure 1. Increasing trend of confirmed cases (Delta variant) from lower to highest peak in April 2021

protein in RBD with ACE-2 receptor showed deep anchoring of viral spike protein (Figure 5a & 5b). The viral spike protein involved the Beta sheet of ACE-2 receptor than Alpha helix (Figure 5c).

Our docking studies showed that RBD of the Spike protein of Omicron variant could not penetrate the ACE-2 receptor of the host cells (Figure 6a & 6b). Rather, the viral spike protein involved the Alpha helix of ACE-2 receptor only, than the Beta sheet (Figure 6c).

The Omicron variant showed a binding score of -969.9, whereas the Delta variant had

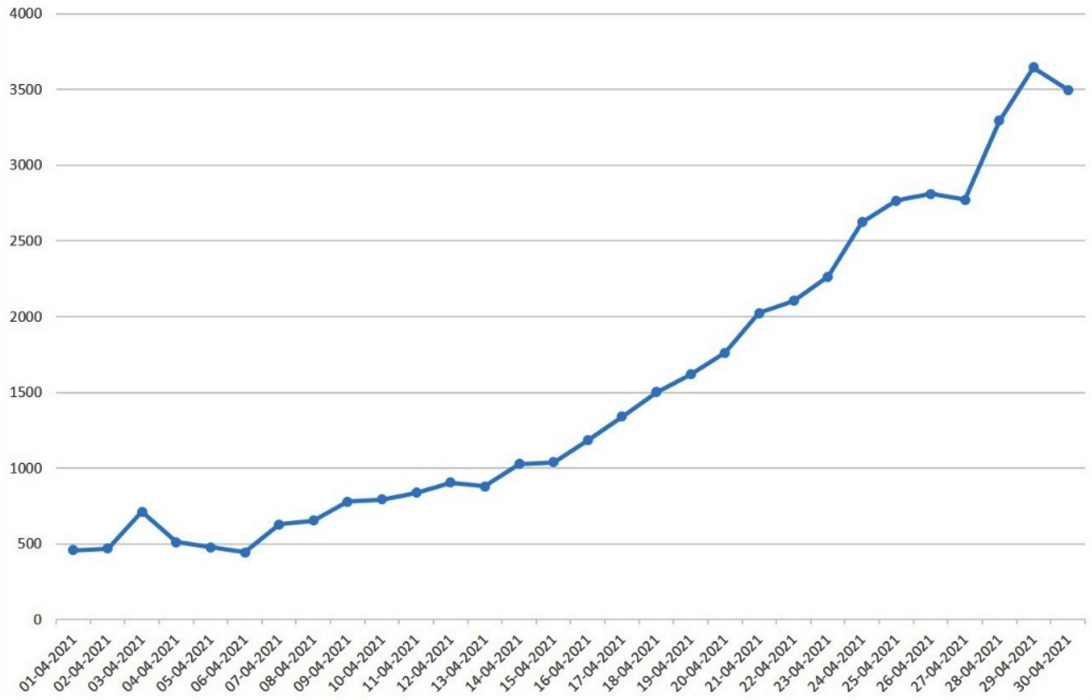

Figure 2. Trend of death cases (Delta variant) in April 2021

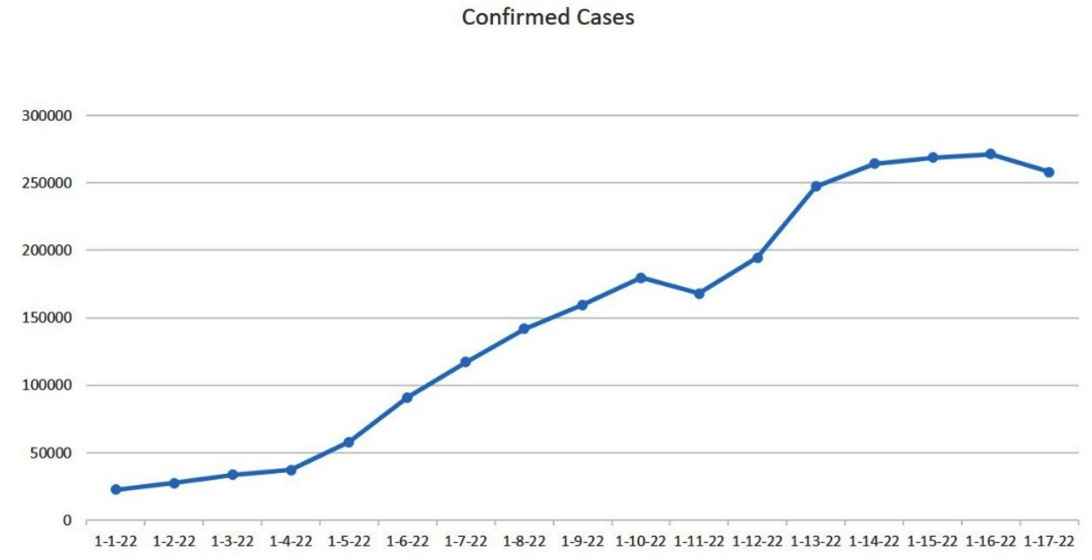

Figure 3. Increasing trend of confirmed cases (Omicron variant) from lower to highest peak in January 2022

a binding score of -1046.3 when analysed by Proprietary Molecular Visualization System (PyMOL). Our docking results showed 6 residues viz; Y449, N487, R493, S494, R498, and Y501 of Omicron Spike glycoprotein in the receptor binding region with ACE-2 receptor. The residues of ACE-2 interacting region were K156, A251, Y255, S611, P612, and D615. Similarly, for Delta variant spike protein, 8 residues were observed in the receptor binding interacting region with ACE-2 receptor. Amino acid residues of spike protein observed were R344, V349, V443, G445, Y447, N448, R450, and E469, whereas those of ACE-2 were N121, S128, K131, Q139, E140, C141, and Y510.

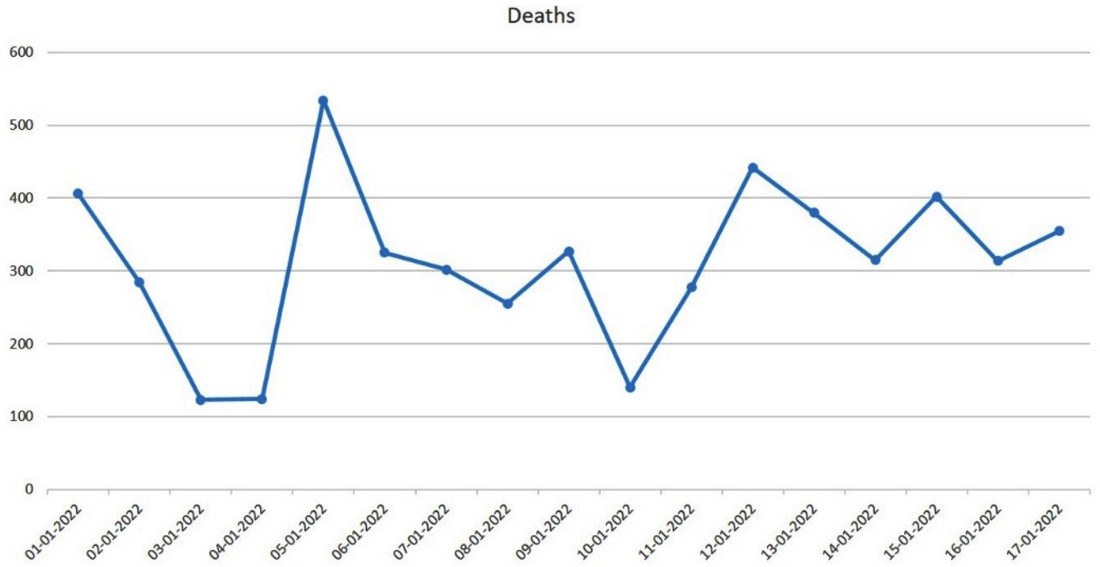

Figure 4. Trend of death cases (Omicron variant) in January 2022

Table. Comparison of amino acid changes in Receptor Binding Domains of Delta and Omicron variants of SARS-CoV-2

No.	Amino acid number in Spike protein sequence	Delta variant amino acid	Omicron variant amino acid
1.	336	G (GLYCINE)	D (ASPARTIC ACID)
2.	368	S (SERINE)	L (LEUSINE)*
3.	370	S (SERINE)	P (PROLINE)*
4.	372	S (SERINE)	F (PHENYLALANINE)*
5.	414	K (LYSINE)	N (ASPARAGINE)
6.	437	N (ASPARAGINE)	K (LYSINE)
7.	443	G (GLYCINE)	S (SERINE)
8.	449	R (ARGININE)	L (LEUSINE)*
9.	474	S (SERINE)	N (ASPARAGINE)
10.	481	E (GLUTAMIC ACID)	A (ALANINE)*
11.	490	Q(GLUTAMINE)	R (ARGININE)
12.	493	G (GLYCINE)	S (SERINE)
13.	495	Q(GLUTAMINE)	R (ARGININE)
14.	498	N (ASPARAGINE)	Y (TYROSINE)*
15.	502	Y (TYROSINE)*	H (HISTIDINE)

*Hydrophobic Amino acid

DISCUSSION

A comparative analysis of epidemiological transition of Delta variant as compared to Omicron variant in terms of their relative transmissibility showed a clear trend that Omicron transmission was six times faster than that of Delta variant. Realizing the fact that as per the National Data of vaccination, during 2nd wave of COVID-19 (10th February 2021) when Delta variant was infective agent, only 0.5% (70,17,114) of population in India were vaccinated (single dose) whereas during 3rd wave (2nd December 2021) caused by Omicron variant, 56.2% of population (79,45,28,313; single dose vaccination) and 33.4% (46,13,38,098; fully vaccinated) in India were vaccinated; how then faster transmission has taken place? The other fact is that though transmission of Omicron was much higher but mortality was much lower as compared to Delta variant how? Our detailed analysis of chemical differences between amino acids constituting RBD of Delta and Omicron variant showed that in Omicron variant out 15 amino acids present in interacting receptor binding domain, only 6 amino acids were hydrophobic. This has been established that spike protein of SARS-CoV-2 need to be cleaved by hydrolyzing enzyme ACE-2 to ensure the entry of virus into the human cell.[16,17] We report here that due to increase in the hydrophobic amino acids in the RBD of Spike protein of Omicron, its cleavage is not taking place, because hydrophobic amino acids in Omicron will be inert for reacting with hydrolyzing enzyme ACE-2. We thus infer that lack of clinical severity among Omicron patients is due to the fact that virus is unable to enter into human epithelial cells in the nasopharyngeal region and has failed to carry out its intracellular replication and further progression

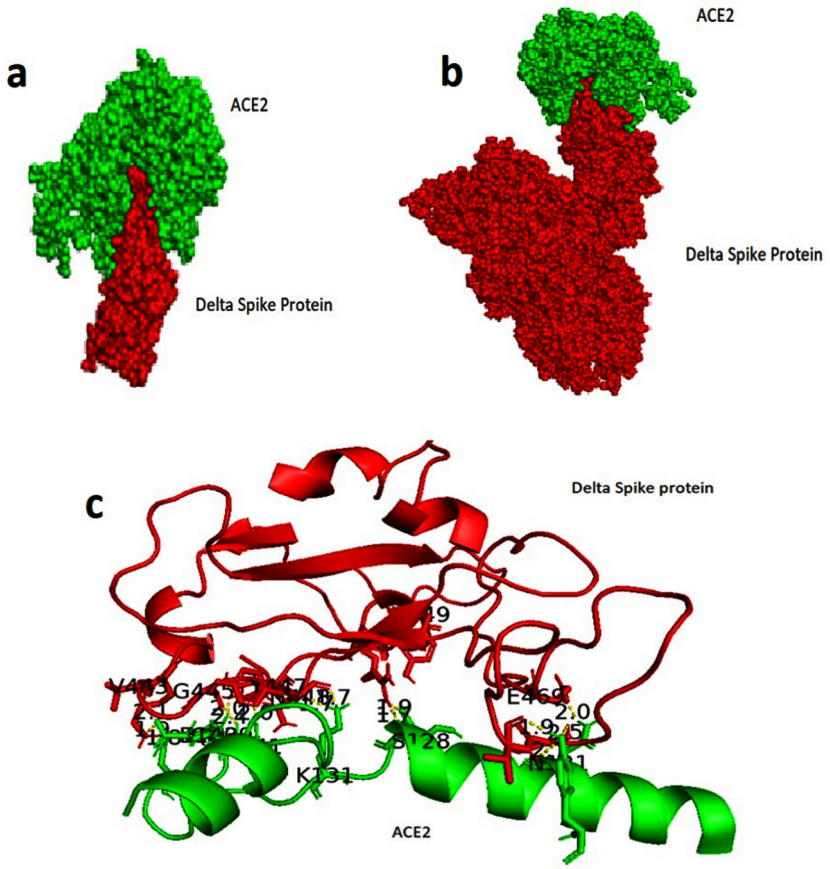

Figure 5. Macromolecular interaction of ACE-2 receptor with Binding Domain of Delta variant (PDB ID: 7V7Q)

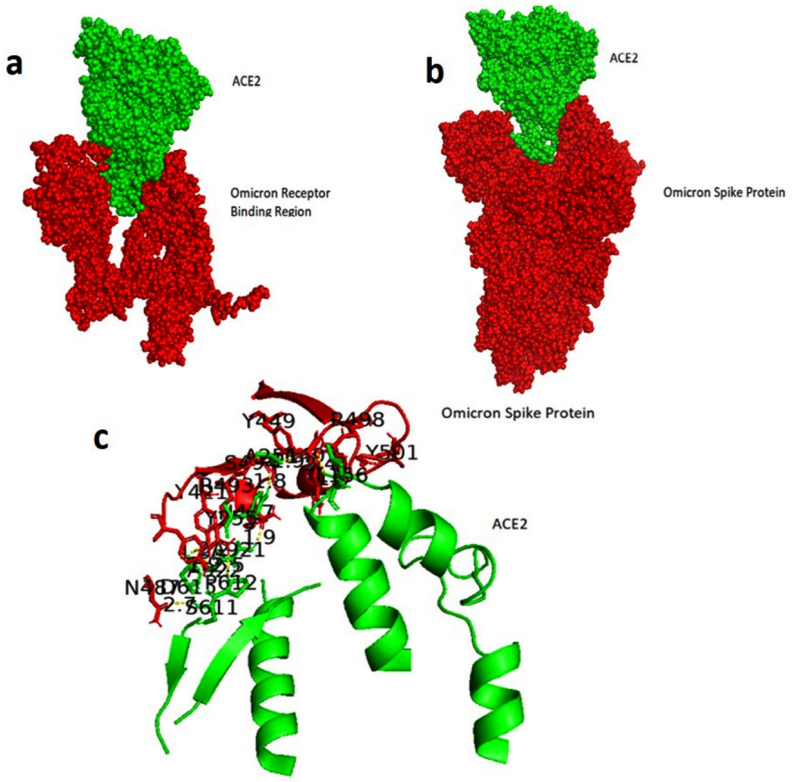

Figure 6. Macromolecular interaction of ACE-2 receptor with Binding Domain of Omicron variant (PDB ID: 7T9J)

up to the pulmonary region. Slow replication rate of Omicron variant in In-Vitro studies as reported by other studies[19,20] also support the fact that Omicron has poor competence of intracellular replication. In the present paper we report to implicate hydrophobic tendency of amino acids of RBD zone as the possible cause of failure of virus internalization. The study is first of its type to interpretate chemical basis of proteomic interaction of virus and host which can be of therapeutic value in neutralizing internalization of virus particles into human cells.

The docking interactions of Spike protein of Delta variant with ACE-2 receptor has shown the further evidence in support of our contention as we observed a deep anchoring of viral spike into ACE-2 whereas in cases of Omicron variant, figures clearly show that Spike Protein of virus has not anchored into ACE-2, rather ACE-2 has penetrated into spike protein.

The clinical symptoms shown by Omicron involves a very mild fever that is around 37.2°C to less than 37.7°C, no breathlessness and no oxygen saturation depletion. All these symptoms indicate that virus for its inability to infect the cells, could not even sensitize the innate immune response in terms of increase in body temperature and has simply caused allergic reactions due to surface agglutination of virus around human epithelial cells in the nasopharyngeal region.

Through present study based on increase in hydrophobic amino acids in the Omicron variant, we report that virions or infected cells in the patients are simply surrounding the human epithelial cells and because they are not able to enter into epithelial cells due to more hydrophobic amino acids, the oral concentrations of loosely bound virions to human cells has increased and hence chances of transmission of virus from person to person while spitting, coughing or sneezing is increasing but without much severity.

CONCLUSION

The observations reported in the present study carries the therapeutic significance, that

application of the dehydrating drug molecules could prevent entry of respiratory viruses into human epithelial cells. We conclude that increase in hydrophobic amino acids in RBD zone of Spike protein of Omicron variant has made it less penetrating into human epithelial cells leading to less severity caused by this variant.

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None.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS' CONTRIBUTION

All the authors listed have made a substantial, direct, and intellectual contribution to the work, and approved it for publication.

FUNDING

None.

DATA AVAILABILITY

All datasets generated or analyzed during this study are included in the manuscript.

ETHICS STATEMENT

Not applicable.

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