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Docking Studies of Sars Cov2 Variants in India with Probable Therapeutic Elements

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Abstract

A novel corona virus was first reported in December 2019 in Wuhan, China. Despite intense research there is currently no effective medication available against the new (SARS-CoV-2). This infectious and communicable disease has become one of the major public health challenges in the world. Natural plant based phytochemicals of therapeutic nature are safe and easily available, also some modern medicinal compounds are known to treat corona virus affected patients. The ADAR1 and ZBP1, Z DNA binding protein plays a role in host immune responses and human disease. Hence, are important in recognition of the virus. In this study, we use the docking process, which involves the prediction of ligand conformation and orientation within a targeted binding site for drug design against the spike protein of 3 variants of SARS CoV 2, namely B.1.617, B.1.618 and B.1.1.7 . We selected five phytochemicals with anti-inflammatory property approved by Ayush, namely, Hesperidin CID:10621, Anthraquinone CID:6780, Withaferin CID:265237, Vicenin CID:442664,Tinocardiside CID:177384 and five modern medicinal compounds with anti-viral properties as small molecules (ligands) approved by FAD, namely, Abacavir CID:441300, Ribavirin CID:36791, Zidovudine CID:35370, Viread CID:202138, Lamivudine CID:60825 and Z DNA binding proteins for their role in enhancing immune response. Among all the therapeutic elements, Withaferin A (phytochemical) and Viread (prodrug of tenofovir) were the best candidates found for interfering with the Spike protein-ACE2 site of all three variants. Comparatively, Z DNA binding proteins have shown more binding affinity than the therapeutic elements.

Keywords: COVID-19; *SARS CoV2*; *Therapeutic elements*; *ADAR1*; *ZBP1*

Introduction

A novel coronavirus was reported in December 2019 from genomic screening of clinical samples from patients with viral pneumonia in Wuhan, China. Coronavirus Disease 2019 (COVID-19) was declared as pandemic by the World Health Organization on March 11th, 2020 mainly due to the speed and scale of the transmission of the disease. The current classification of corona viruses recognizes 39 species in 27 subgenera, five genera and two subfamilies that belong to the family Coronaviridae, order Nidovirales. Coronaviridae comprises of 4 genera: Alpha coronavirus, Beta coronavirus, Gamma coronavirus, and Delta coronavirus. The coronavirus (CoV) has a single-stranded, non-segmented RNA genome of positive polarity. Characterized by relatively large spikes that emerge from the virus envelope. Virion contains 4 major structural proteins: the nucleocapsid (N) protein, the transmembrane (M) protein, the envelope (E) protein, and the spike (S) protein. It contains 16 non-structural proteins (nsps), termed nsp1 to nsp16. Genome database (NC_045512.2) ~29.9 Kb in size. The genetic makeup of SARS -CoV -2 is composed of 13-15 open reading frames (ORFs) containing ~30,000 nucleotides with two ORF 1a and 1b. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been mutating since it [1-4] was first sequenced in early January 2020. There is no precise treatment for coronavirus but prevention, management and supporting healthcare may provide relief in the outbreak of COVID -19. These approaches may be categorized in Allopathic, Unani and Homeopathic treatments. Tenofovirdisoproxil fumarate (Viread) is the first nucleotide analog reverse transcriptase inhibitor found to prevent severe symptoms in COVID-19. Abacavir which competitively inhibits HIV reverse transcriptase and terminates provirus DNA chain extension. Abacavir in combination with lamivudine and Zidovudine reduced viral load to below detectable levels in a proportion of patients, and to a similar extent to the protease inhibitor Indinavir in combination with lamivudine and Zidovudine. Several potential therapeutic approaches have been experimented to treat SARS-CoV-2 infection such as protein-based vaccine design, blocking of ACE2 receptor and effect of phytochemicals on spike protein binding with its ACE2 receptor. Dietary intake of phytochemicals basically promotes health benefits and protects the body against diseases. They are not essential nutrients and are not required by the human body for sustaining life, some of the notable ones but not limited to are Withaniasomnifera A (Ashwagandha), it has been reported to have anti-inflammatory, antimicrobial nature other phytochemicals like Vicenin and Tinocardiside which acts as immunomodulatory, antioxidant, Hesperidin and Anthraquinone the binding sites of ACE2 protein for spike protein and hesperidin, are located in different parts of ACE2 protein. Ligand spike protein causes conformational change in three-dimensional structure of protein ACE2, This result indicates that due to presence of hesperidin, the bound structure of ACE2 and spike protein fragment becomes unstable. As a result, this natural product can impart antiviral activity in SARS CoV2 infection. The Z-DNA/RNA binding proteins present from viruses to humans function as important regulators of biological processes. In particular, the proteins ADAR1 and ZBP1 are currently being extensively re-evaluated in the field to understand potential roles of the non-canonical Z-conformation of nucleic acids in host immune responses and human disease. Molecular docking has a wide variety of

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uses and applications in drug discovery. In this study, we will focus on ligand–protein docking, and use the more generic term "target" to refer to the protein, DNA, or RNA macromolecule to which a much smaller molecule (or "ligand") is being docked.

Materials and Methods

The X-ray crystal structure of SARS-CoV-2, Spike RBD bound with hACE2 was retrieved from Protein Data Bank (PDB) with ID: 6LZG (B.1.617), 7LWW (B.1.618), 7LWT (B.1.1.7). DNA binding proteins as ligands are ADAR1 (PDB ID: 3F21), ZBP1 (PDB ID: 2RVC). Data regarding the protein chain length, resolution and surrounding ligands are obtained from PDB, NCBI and Uniprot. The 3D/2D structure of selected ligands and phytochemicals were retrieved from PubChem identifier (Hesperidin CID:10621, Anthraquinone CID:6780, Withaferin CID:265237,Vicenin CID:442664, Tinocardiside CID:177384 and modern medicinal compounds (Abacavir CID:441300, Ribavirin CID:36791, Zidovudine CID:35370, Viread CID:202138, Lamivudine CID:60825) in SDF format drugs described as potential antiviral effect, which were registered simultaneously in the FDA approved drugs and in the Ayush database and, were selected. By [5-11] using Online smile translator we convert the 3D and 2D structure of ligands from SDF format to PDB format, first need to select and upload SDF file, select 3D option in program and choose PDB format and translate option to convert SDF format to PDB format. Molecular docking of spike protein of variants of SARS CoV 2 and ligand using patch dock server: Input the two molecules in PDB format. The molecules are either uploaded to the server or retrieved from the Protein Data Bank. Here, the input consists of two elements: the asymmetric unit (i.e. the monomer), and the symmetry order (2 for dimer, 3 for trimer etc.). The asymmetric unit is uploaded in PDB format of both target protein and ligand also uploaded the E mail ID to receive the results. Output: Just as in Patch Dock, a web page is generated to show the predicted solutions, and a link to that page is sent to the user by email. Here, instead of showing just pair wise interactions involved in the complex, the whole multimer is generated for each solution. The solutions page presents the geometric score, interface area size and desolvation energy of the 20 top scoring solutions. The user can use the 'show next 20' button to view solutions of lower score. The user can download each solution by pressing the solution link in the rightmost column or download an archive file (ZIP format) of the best solutions using the action button at the bottom of the page. Structural analysis: Analysis of structure of docking interactions of protein and ligand by using UCSF Chimera tool (NIH) and iCn3D (NCBI) server.

Results and Discussion

Target proteins: 3D structure of spike protein and its binding site with its host cell receptor ACE2 protein have been highlighted in this study. 6lzg(sequence identity with Angiotensin-converting enzyme 2(ACE 2) 'A' chain with sequence length 596 residues, B chain with sequence length 209 residue and it containing 2 ligands zn2+ and NAG (2-acetamido-2-deoxy-beta-D-glucopyranose) with resolution 2.50 Å. 7LWW (Triple mutant (K417N-E484K-N501Y) SARS-CoV-2 spike protein in the 1-RBDup conformation (S-GSAS-D614G-K417N-E484K-N501Y), sequence identity with Angiotensin-converting enzyme 2(ACE 2), 'A, B, C' with sequence length 1288, containing ligand NAG (N-acetyl derivative of glucosamine) with Resolution 3.00 Å. 7LWT having 3 chains A,B,C with the sequence length 1285, containing NAG ligand.

Ligands: Retrieval of 3D structure of Z- DNA binding proteins of both ADAR1 and ZBP1 from RCSB Protein Data bank the accession number of these two proteins are ADAR1 (PDB ID: 3F21), ZBP1 (PDB ID: 2RVC). ADAR1 Crystal structure of Z-alpha in complex with d(CACGTG). The functions of this is protein-Z-DNA complex, alternative promoter usage, alternative splicing, cytoplasm, disease mutation, DNA-binding, hydrolase, metal-binding, mRNA processing, nucleus, phosphoprotein, polymorphism, RNA-binding, RNA-mediated gene silencing, ubl conjugation, zinc. Resolution is about 2.20 angstrom. A,B,C chains with sequence length is about 81. ZBP1: molecular function of this protein positive regulation of type 1 interferon production, immune system process, innate immune response, DNA binding, double-stranded RNA adenosine deaminase activity. A chain sequence length is 64.

Retrieval of 2D structure of ligand from PubChem data base: Phytochemical: Hesperidin: molecular weight is 610.6 and molecular formula $C_{28}H_{34}O_{15,}$ Anthraquinone: Molecular weight 208.21 and Molecular formula $C_{14}H_8O_{2,}$ Withaferin A: Molecular weight 470.6 and Molecular formula $C_{28}H_{38}O_6$, Tinocardiside: Molecular Weight -396.5 and Molecular formula $C_{21}H_{32}O_{7.}$ Modern medicinal compounds: Abacavir: Molecular weight 286.33 and Molecular formula $C_{14}H_{18}N_6O$ Ribavirin: Molecular weight 244.20 and formula $C_8H_{12}N_4O_4$, Zidovudine: Molecular weight 267.24 and formula $C_{10}H_{13}N_5O_4$, Viread: Molecular weight 635 formula $C_{23}H_{34}N_5O_{14}P$, Lamivudine: molecular weight 229.26 and formula $C_8H_{11}N_3O_3S$. Docking results of spike protein of all the 3 variants B.1.617, B.1.618, B.1.1.7 with ligands: Molecular docking between spike protein of SARS CoV2 B.1.617 variant with phytochemicals (Figure 1); Withaferin A, binding affinity score 7494 which shows highest binding affinity, binding area is 911.40 with atomic contact energy -168.73 and over lapping residues at Tyrosine contains 510 atoms, at first overlapping with water contains 1046 atoms at second overlapping water contains 875 atoms. (Figure 1A). Docking with spike protein and phytochemical Hesperidin, with binding affinity score 6246, binding area is about 807.10 with atomic contact energy -111.27 and over lapping residue, at first overlapping with water contains 875 atoms at second overlapping water contains 830 atoms. (Figure 1B). Docking with spike protein and phytochemical Vicenin, with binding affinity score 5914, binding area is about 706.40 with atomic contact energy -95.31 and over lapping residue, at first overlapping with water contains 921 atoms at second overlapping with glutamine contains 102 atoms, with Leucine contains 95 atoms. (Figure 1C). Docking with spike protein and phytochemical Tinocardiside, with binding affinity score 5236, binding area is about 647.10 with atomic contact energy -106.59 and over lapping residue, at first overlapping with glutamine contains 98 atoms at second overlapping with Alanine contains 102 atoms, another overlapping with the residue water contains 875 atoms. Docking focused region with spike protein and phytochemical Anthraquinone, with binding affinity score 5236, binding area is about 647.10 with atomic contact energy 106.59 and over lapping residue, at first overlapping with glutamine contains 98 atoms at second overlapping with Alanine contains 102 atoms, another overlapping with the residue water contains 875 atomsIn Patch dock binding the higher the value, the smaller the number of the results. The recommended values are 4A for protein- protein docking and 1.5A for

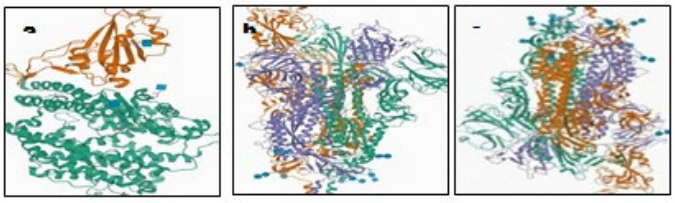

Figure 1: 3D structures of spike protein a; 6LZG of B.1.617 variant, b: 7LWW of B.1.718 variant, c:7LWT of B.1.1.7 variant.

protein-small molecule docking. Patch dock has different sets of parameters, optimized for different types of complexes. Docking results with Withaferin A is showing highest binding affinity with 7494 with lowest atomic contact energy -167.83. Where, Anthraquinone is the least one showing lowest binding affinity with spike protein. Molecular docking between spike proteins of SARS CoV2 B.1.617 variant with modern medicinal compounds (Figure 2). Docking focused region with spike protein and Viread with binding affinity score 6724 which shows highest binding affinity compared to other selected modern medicinal compounds hence was prioritised, binding area is about 797.9 with atomic contact energy -77.9 and over lapping residues with 1046 atoms of water, overlapping with 213 atoms of Aspartic acid another overlapping with 98 atoms of glutamine (Figure 2A). Docking focused region with spike protein and Abacavir, with binding affinity score 4368, binding area is about 515.60 with atomic contact energy -181.66 and over lapping residue, at first overlapping with water contains 921 atoms at second overlapping with Alanine contains 396 atoms and third overlapping with Glutamate contains 98 atoms (Figure 2B). Docking focused region with spike protein and Zidovudine, with binding affinity score 4060, binding area is about 453.60 with atomic contact energy -151.47 and over lapping residue, at first overlapping with water contains 921 atoms at second overlapping with Aspartic acid contains 206 atoms, and with Glutamate contains 208 atoms. Docking focused region with spike protein and Ribavirin, with binding affinity score 3562, binding area is about 400.96 with atomic contact energy -115.16 and over lapping residue, at first overlapping with water contains 921 atoms at second overlapping with leucine contains 95 atoms, another overlapping with the residue Glutamate contains 98 atoms. Docking focused region with spike protein and Lamivudine, with binding affinity score 3534, binding area is about 429.80 with atomic contact energy -226.47 and over lapping residues, at first overlapping with Isoleucine contains 291 atoms at second overlapping with Threonine contains 434 atoms. Patch dock binding the higher the value, the smaller the number of the results you get. The recommended values are 4A for protein- protein docking and 1.5A for protein-small molecule docking. Patch dock has different sets of parameters, optimized for different types of complexes. Docking results with VI read is showing highest binding affinity score 6724 with highest atomic contact energy -77.92. Whereas, Lamivudine is the least one which showing lowest binding affinity 3534 with spike protein and having lowest atomic contact energy-226.47. Molecular docking between spike protein of SARS CoV2 B.1.618 variant with phytochemicals (Figure 3) Docking focused region with spike protein and phytochemical With after in A, with binding affinity score 8128 (it's an algorithm for molecular docking) which shows highest binding affinity compared to other selected phytochemicals hence was prioritized, binding area is about 965.60 with atomic contact energy 87.82 and over lapping residues with Glycine contains 1044 atoms,second overlapping with

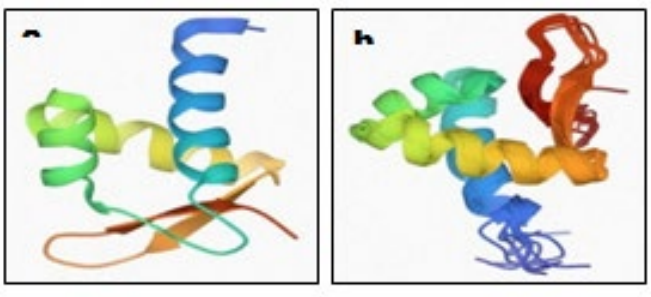

Figure 2: a: 3D structure of Z DNA binding protein of 3F21 of ADAR1, **b:** 3D structure of Z DNA binding protein of 2RCV Of ZBP1.

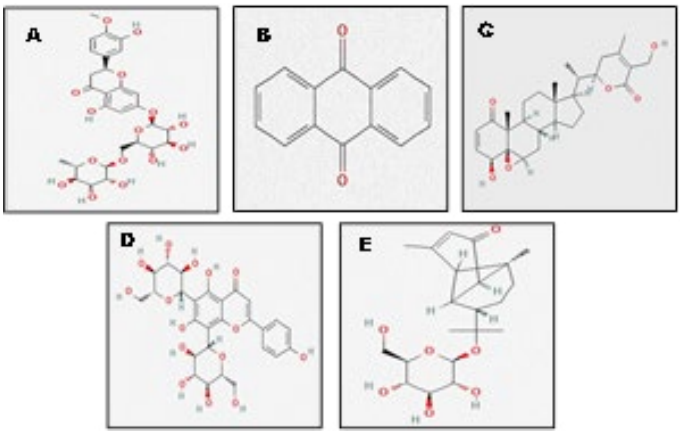

Figure 3: 2D structures of selected phytochemicals, **A**. Hespiridine, **B.** Anthraquinone, **C.** Withaferin A, **D.** Vicenin, **E.** Tinocardiside.

glutamate residue contains 780 atoms, another overlapping with Valine contains 951 atoms (Figure 3A). Docking focused region with spike protein and phytochemical Hesperidin, with binding affinity score 6894, binding area is about 1816 with atomic contact energy 429.43 and over lapping residue, at first overlapping with Leucine contains 977 atoms at second overlapping with Glutamate contains 780 atoms another overlapping with Methionine contains 740 atoms (Figure 3B). Docking focused region with spike protein and phytochemical Vicenin, with binding affinity score 6346, binding area is about 734.90 with atomic contact energy 275 and over lapping residue, at first overlapping with Glycine contains 744 atoms at second overlapping with Threonine contains 549 atoms, with Leucine contains 1012 atoms (Figure 3C). Docking focused region with spike protein and phytochemical Tinocardiside, with binding affinity score 5468, binding area is about 638.40 with atomic contact energy 11.63 and over lapping residue, at first overlapping with glutamine contains 1010 atoms at second overlapping with Arginine contains 1014 atoms, another overlapping with the residue Leucine contains 1012 atoms (Figure 3D). Docking focused region with spike protein and phytochemical Anthraquinone, with binding affinity score 4010, binding area is about 437.60 with atomic contact energy -141.53 and over lapping residue, at first overlapping with Glutamine contains 613 atoms at second overlapping with Proline residue contains 665 atoms, another overlapping with the residue isoleucine contains 666 atoms (Figure 3E). Docking results with Withaferin A is showing highest binding affinity with 8128 with atomic contact energy 87.82. Whereas, Anthraquinone is the least one which showing lowest binding affinity score 4010 with spike protein. And Vicenin is showing the least atomic contact energy -275 compared to other phytochemicals. Molecular docking between spike proteins of SARS CoV2 B.1.618 variant with modern medicinal compounds (Figure 4). Docking focused region with spike protein and Viread, with binding affinity score 5986 (it's an algorithm for molecular docking) which shows highest binding affinity compared to other selected modern medicinal compounds hence we gave first priority, binding area is about 1010.30 with atomic contact energy-12.89 and over lapping residues with Glutamine contains 1010 atoms, overlapping with Arginine residue contains 1014 atoms at another overlapping with glutamic acid contains 1017 atoms (Figure 4A). Docking focused region with spike protein and Abacavir, with binding affinity score 4870, binding area is about 567.90 with atomic contact energy -168.22 and over lapping residue, at first overlapping with valine contains 772 atoms at second overlapping with Serine contains 596 atoms and third overlapping with Threonine contains 768 atoms (Figure 4B). Docking

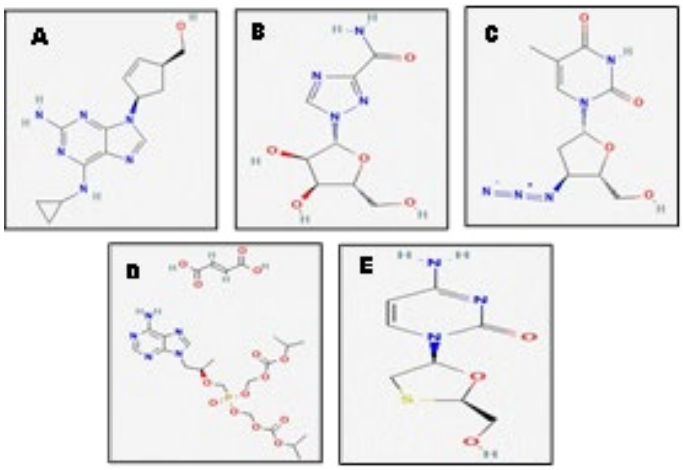

Figure 4: 2D structure selected Modern medicinal compounds A. Abacavir, B. Ribavirin, C. Zidovudine D. Viread, and E. Lamivudine.

focused region with spike protein and Zidovudine, with binding affinity score 4378, binding area is about 494.40 with atomic contact energy -177.06 and over lapping residue, at first overlapping with Alanine contains 647 atoms at second overlapping with Isoleucine residue contains 312 atoms, and with Aspartic acid contains 775 atoms (Figure 4C): Showing docking focused region with spike protein and Lamivudine, with binding affinity score 3826, binding area is about 445.50 with atomic contact energy -131.90 and over lapping residue, at first overlapping with Lysine contains 733 atoms at second overlapping with Proline contains 862 atoms, another overlapping with the residue Isoleucine contains 312 atoms (Figure 4D). Docking focused region with spike protein and Ribavirin, with binding affinity score 3824, binding area is about 426.00 with atomic contact energy -81.76 and over lapping residues, at first overlapping with Glutamine contains 613 atoms at second overlapping with Aspartic acid contains 775 atoms, another overlapping with the residue Leucine contains 816 atoms (Figure 4E). Docking results with Vi read is showing highest binding affinity score 5986 with highest atomic contact energy -12.89. Whereas Ribavirin is the least one which showing lowest binding affinity score 3824 with spike protein And Zidovudine is showing lowest atomic contact energy about -177.60. Molecular docking between spike proteins of SARS CoV2 B.1.1.7 variant with phytochemicals (Figure 5). Docking focused region with spike protein and phytochemical Withaferin A, with binding affinity score 7880 which shows highest binding affinity compared to other selected phytochemicals hence we gave first priority, binding area is about 940.10 with atomic contact energy 43.34 and over lapping residues with Glutamic acid contains 1017 atoms,second overlapping with Leucine residue contains 1012 atoms, another overlapping with Asparagine contains 1023 atoms (Figure 5A). Docking region with spike protein and phytochemical Hesperidin, with binding affinity score 6788, binding area is about 885.80 with atomic contact energy -338.20 and over lapping residue, at first overlapping with Aspartic acid contains 745 atoms at second overlapping with Valine contains 976 atoms another overlapping with Threonine contains 573 atoms (Figure 5B). Docking region with spike protein and phytochemical Vicenin, with binding affinity score 6304, binding area is about 769.20 with atomic contact energy -214.82 and over lapping residues, at first overlapping with Asparginine contains 1023 atoms at second overlapping with Alanine contains 1020 atoms, with Leucine contains 1024 atoms (Figure 5C). Docking region with spike protein and phytochemical Tinocardiside, with binding affinity score 5468, binding area is about 607.30 with atomic contact energy -206.31 and over lapping residue, at first overlapping with Arginine contains 1000 atoms at second overlapping with Serine contains 975 atoms, another overlapping with the residue Threonine contains 572 atoms (Figure 5D). Docking region with spike protein and phytochemical Anthraquinone, with binding affinity score 3902, binding area is about 423.40 with atomic contact energy -209.79 and over lapping residues, at first overlapping with Aspartic acid contains 979 atoms at second overlapping with Cysteine residue contains 391 atoms, another overlapping with the residue Phenylalanine contains 565 atoms (Figure 5E). Docking results with Withaferin A is showing highest binding affinity with 7880 with highest atomic contact energy 43.34. Whereas, Anthraquinone is the least one which showing lowest binding affinity score 3902 with spike protein. And Hesperidin is showing the least atomic contact energy -338.20 compared to other phytochemicals (Table 1). Molecular docking between spike protein of SARS CoV2 B.1.1.7 variant with modern medicinal compounds (Figure 6) showing docking focused region with spike protein and Viread, with binding affinity score 7710 (it's an algorithm for molecular docking) which shows highest binding affinity compared to other selected modern medicinal compounds hence we gave first priority, binding area is about 946.90 with atomic contact energy-185.31 and over lapping residues with Aspartic acid contains 745 atoms, overlapping with Lysine residue contains 986 atoms at another overlapping with Threonine residue contains 572 atoms (Figure 6A). Docking focused region with spike protein and Abacavir, with binding affinity score 4772, binding area is about 527.30 with atomic contact energy -185.01 and over lapping residue, at first overlapping with Threonine contains 1006 atoms at second overlapping with Glutamine contains 1005 atoms and third overlapping with Threonine contains 1009 atoms (Figure 6B). Docking focused region with spike protein and Zidovudine, with binding affinity score 4196, binding area is about 480.20 with atomic contact energy 148.61 and over lapping residue, at first overlapping with Arginine contains 1000 atoms at second overlapping with serine residue contains 975 atoms, and with Threonine contains 572 atoms (Figure 6C). Docking focused region with spike protein and Ribavirin, with binding affinity score 3812, binding area is about 415.20 with atomic contact energy -115.73 and over lapping residue, at first overlapping with Isoleucine contains 666 atoms at second overlapping with Glutamine contains 613 atoms, another overlapping with the residue Glycine contains 667 atoms (Figure 6D).

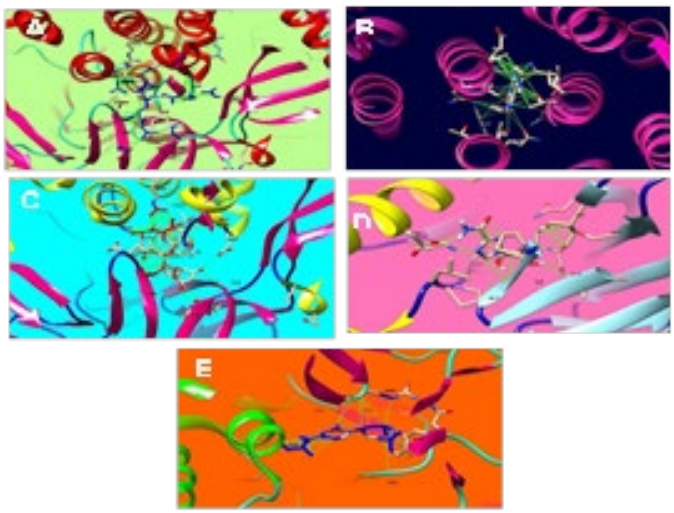

Figure 5: Docking results of spike protein (7LWT ACE 2 receptor) of B.1.1.7 variant with focused regions in binding sites of some modern medicinal compounds, (A: Viread, B: Abacavir, C: Zidovudine, D: Ribavirin , E: Lamivudine).

Table 1: Modern medicinal compound, Binding affinity score, Area, ACE (atomic contact energy), overlapping residues.

Modern medicinal compounds	Binding affinity score	Area	Ace atomic contact energy)	overlapping residues atoms
Viread	**7710**	946.90	-185.31	ASP 745, LYS 986, THR 572
Abacavir	4772	527.30	-185.01	THR 1006, GLN 1005, THR 1009
Zidovudine	4196	480.20	-148.61	ARG 1000, SER 975, THR 572
Ribavirin	3812	415.20	-115.73	ILE 666, GLN 613, GLY 667
Lamivudine	3654	399.70	**-229.56**	ASP 979, PHE 565, LEU 518

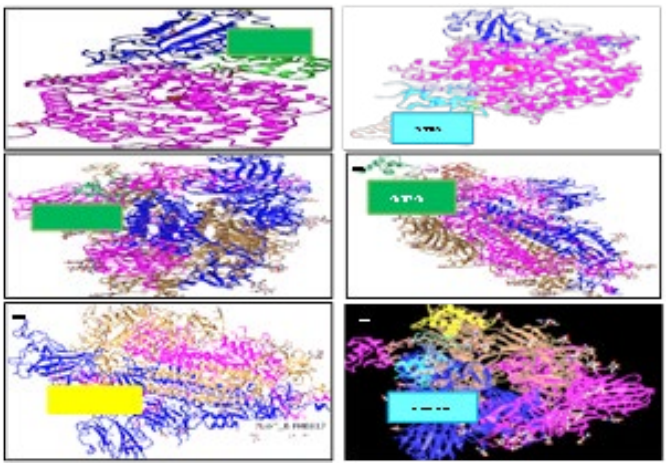

Figure 6A: Docking with 6lzg spike protein(ACE2 receptor) of B.1.617variant and 2RCV (Z DNA binding protein), B: Docking with 6lzg spike protein(ACE 2 receptor) B.1.617 variant and 3F21(Z DNA binding protein), C: Docking with 7lww spike protein(ACE2 receptor) of B.1.618 variant and 2RCV (Z DNA binding protein), D: Docking with 7LWW spike protein(ACE2 receptor) of B.1.618 variant and 3F21 (Z DNA binding protein), E: Docking with 7LWT spike protein(ACE 2 receptor) of B.1.1.7 and 2RCV (Z DNA binding protein),F: Docking with 7LWT spike protein(ACE 2 receptor) of B.1.1.7 and 3F21 (Z DNA binding protein).

Docking focused region with spike protein and Lamivudine, with binding affinity score 3654, binding area is about 399.70 with atomic contact energy -229.56 and over lapping residues, at first overlapping with Aspartic acid contains 979 atoms at second overlapping with phenylalanine contains 565 atoms, another overlapping with the residue Leucine contains 518 atoms (Figure 6E). Docking results with Viread is showing highest binding affinity score 7710 with highest atomic contact energy -185.31. Whereas, Lamivudine is the least one which showing lowest binding affinity score 3654 with lowest atomic contact energy about -177.60. The two proteins were docked using PATCH DOCK SERVER and analysed using iCn3D Structure analysis tool, where the two molecules where docked the sequence annotations gave the complete sequences and their interaction between the other protein. ICn3D gives the every minute details present delineating and extracting elementary structural properties at an level of details (atom, residue, and domain, chain) to reveal the structure underpinning of a given molecular structure and constituent molecular interactions. These are all very simple and very well-known descriptive elements, covalent bonds, Hydrogen bonds, non-bonded interactions (Vander Waals). The interaction between the spike protein of 6lzg of B.1.617 variant with the 2RVC of Z DNA binding proteins (represented in green colour) with docking score 19,560, Area of docking region is about 2755.50, and atomic contact energy 471.30. The interaction between the spike protein of 6lzg of B.1.617 variant with the 3f21 of Z DNA binding proteins(represented in blue color) docking score 13,306, Area of docking region is about 1816.30, and atomic contact energy 429.43. The interaction between the spike protein of 7LWW of B.1.618 variant with the 2RVC of Z DNA binding proteins (represented in green color) With docking score 24,240, Area of docking region is about 3802.40, and atomic contact energy 429.43. The interaction between the spike protein of 7LWW of B.1.618 variant with the 3F21 of Z DNA binding proteins (represented in green color) with docking score 16,972, Area of docking region is about 2451.70, and atomic contact energy 399.20. The interaction between the spike protein of 7LWT of B.1.1.7 variant with the 2RVC of Z DNA binding proteins (represented in yellow color) with docking score 24,504, Area of docking region is about 4104.40, and atomic contact energy 385.62.The interaction between the spike protein of 7LWT of B.1.1.7 variant with the 3F21 of Z DNA binding proteins (represented in blue color) with docking score 16,682, Area of docking region is about 2499.70, and atomic contact energy 492.40 .

Discussion

In line with our study, analysed, Hesperidin, emodin and chrysin as competent natural products from both Indian and Chinese medicinal plants, to treat COVID-19. Among them, the phytochemical Hesperidin can bind with ACE2 protein and bound structure of ACE2 protein and spike protein of SARS-CoV2 non-competitively. Similar to our study, attempted to recognize natural phytochemicals from medicinal plants, in order to neutralize them against COVID-19 by molecular docking. In the present study, we obtained highest binding score among all five phytochemicals with Withaferin A about 7494, reported that Tenofovirdisoproxil fumarate (Viread) is the first nucleotide analog reverse transcriptase inhibitor to be approved by the Food and Drug Administration for the treatment of HIV infection. The results point to a potential effectiveness of Penciclovir, Ribavirin, and Zanamivir, from a set of 48 potential candidates. In our work we got highest binding affinity score with viread about 6724 among all selected modern medicinal compounds. However, docking of S-protein with Z DNA binding proteins has not been reported yet. Hence, it is our novel attempt to explore this possibility.

Conclusion

In the present study of drug repositioning guided by molecular docking, we identified 10 putative candidates for COVID 19 therapy, of both allopathic and plant based therapeutic elements and also Z DNA binding proteins (self-resistance), the therapeutic elements Withaferin A (phytochemical), Viread (modern medicinal compound) are the best candidate found for interfering in the Spike protein-ACE2 interaction of all three variants. Comparatively, Z DNA binding proteins have shown more binding affinity than the therapeutic elements. To confirm the hypotheses raised with this work, further in vitro and in vivo studies are required to verify their potential to inhibit viral replication.

References

1. Haque N (2018) Dietary manipulation : a sustainable way to mitigate methane emissions from ruminants. 1–10.
2. Soltan Y, Morsy A, Sallam S, Hashem N, Abdalla A, et al. (2016) Propolis As a Natural Feed Additive in Ruminant Diets; Can Propolis Affect the Ruminants Performance?: A Review.
3. Morsy AS, Soltan YA, Sallam SMA, Kreuzer M, Alencar SM, et al. (2015) Comparison of the in vitro efficiency of supplementary bee propolis extracts

of different origin in enhancing the ruminal degradability of organic matter and mitigating the formation of methane. Animal Feed Science and Technology 199: 51–60.

4. Soltan YA, Patra AK (2020) Bee propolis as a natural feed additive: Bioactive compounds and effects on ruminal fermentation pattern as well as productivity of ruminants. Indian Journalof Animal Health 59: 50–61.
5. Ristivojevića P, Trifkovićb J, Andrić FB, Milojković-Opsenicab D (2015) Poplartype Propolis: Chemical Composition, Botanical Origin and Biological Activity. Natural Product Communications 10:1869–1876.
6. Machado BAS, Silva RPD, Barreto GDA, Costa SS, Da Silva DF, et al. (2016) Chemical composition and biological activity of extracts obtained by supercritical extraction and ethanolic extraction of brown, green and red propolis derived from different geographic regions in Brazil. PLoS ONE 11:1–26.
7. Papachroni D, Graikou K, Kosalec I, Damianakos H, Ingram V, et al. (2015) Phytochemical analysis and biological evaluation of selected african propolis samples from Cameroon and congo. Natural Product Communications 10: 67–70.
8. Ozdal T, Sari-kaplan G, Mutlu-altundag E, Boyacioglu D (2018) Evaluation of Turkish propolis for its chemical composition, antioxidant capacity, anti-proliferative effect on several human breast cancer cell lines and proliferative effect on fibroblasts and mouse mesenchymal stem cell line. Journal of Apicultural Research 0:1–12.
9. Wozniak M, Mrówczynska L, Agnieszka W, Tomasz R, Izabela R, et al. (2019) The role of seasonality on the chemical composition, antioxidant activity and cytotoxicity of Polish propolis in human erythrocytes. 29:301–308.
10. Tomazzoli MM, Zeggio ARS, Neto RDP, Specht L, Costa C, et al. (2020) Botanical source investigation and evaluation of the effect of seasonality on brazilian propolis from apis mellifera L. Scientia Agricola 77:1-10
11. Mendez-Pfeiffer P, Alday E, Carreño AL, Hernández-Tánori J, Montaño-Leyva B, et al. (2020) Seasonality modulates the cellular antioxidant activity and antiproliferative effect of sonoran desert propolis. Antioxidants 9: 1–15.