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MOLECULAR DOCKING OF SARS-COV-2-NUCLEOCAPSID PROTEIN WITH ANGIOTENSIN-CONVERTING ENZYME II

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SARS-CoV-2 remains life-threatening human pathogen witnessed in the present world. ***Purpose.*** *The key objective of this research was to incorporate a bioinformatics technique to forecast the molecular docking of the ACE2-associated SARS-CoVs nucleocapsid protein.* ***Methods.*** *Different bioinformatics tools were used in this study in order to compare the chemical structures with their biological behaviour at the levels of atoms and the ligand-binding affinity. This research sought to investigate new data analysis.* ***Results.*** *It was computed the basic 2D structure that occurs in all models, requiring ion ligand binding sites to be predicted. The highlights of the analysis and the associated characteristics are largely responsible for nucleocapsid protein and ACE2 receptor that can be further changed for improved binding and selectivity.* ***Conclusions.*** *The precise functional importance of protein-protein docking cannot be established. But the detection of molecular docking can aid in self-association proteins in our summary, serving as a regulatory switch for the protein's localization.*

Keywords: COVID-19, SARS-CoV-2, angiotensin-converting enzyme II (ACE2), nucleocapsid, molecular docking, receptor-binding domain (RBD) protein, RMSD.

During the various stages of the SARS-CoV-2 pandemic, improvements in risk, propaganda and potential interventions have been defined. This is an opportunity to gain insight into the behaviours and the aspirations of the world. In most cases, the bulk of coronaviruses originate from zoonotic dissemination. However, there is still no confirmation that SARS-CoV-2 was born from the marine industry. In the majority of data reports, SARS-CoV-2 could be less virulent as SARS-CoV-2003 and MERS-CoV-2018. SARS-CoV-2 in the Coronaviridae family is related to β-coronavirus and split virus of RNA (sub-family Orthocoronavirinae) [1–3].

Four fundamental structural proteins are encoded by the positive-sense viral RNA genome: spike glycoprotein, envelope protein, membrane protein, and nucleocapsid protein (NP) [4]. Three distinct preserved domains, two structural and independently folded structural regions, make up the NP. The N-terminal domains NTD1 and NTD3 are separated by the central region (RNA-binding domain/2) and the C-terminal domain CTD3 [5]. The NP plays a pivotal role in viral pathogenesis, causes cell cycle deregulation, inhibits type 1 interferon synthesis and improves viral RNA transcription efficiency and viral replication [6]. The synthesis of viral RNA and proteins is also regulated by NP. Moreover, by inducing humoral and cellular immunity, NP serves as a potent immunogen. It was found that in both SARS-CoV and MERS-CoV, NP is considered as a possible vaccine candidate [7].

In the replication cycle, the association between the viral protein and the host cell membrane receptor is a key step. Therefore this process relies on the efficacy of viral infection. The coronavirus binds the human host cell to the angiotensin-converting enzyme II (ACE2) through the binding of the receptor-binding domain (RBD) protein [8, 9]. Currently unclear is the molecular mechanism of this RBD-ACE2 attachment [10]. It exists in the lower respiratory tract cells and governs transmission between animals and between humans. Other cellular receptors, such as CD209L, DC-SIGN, and C-type lectin, play a secondary role in viral attachment to the host cell membrane. Different biochemical variables are correlated with protein-protein relationships. The structure of protein residues and the form of chemical interactions occurring between the ligand and the receptor [11, 12] define these influences. Thus the presence of residues that create an interaction that is energetically preferred can drive binding kinetics

and eventually contribute to the event of fusion.

One research has found that NP has a role in viral pathogenesis as monoclonal anti-N antibodies that sustain fatal infection in mice. Our previous study conducted several immunoinformatics such as CTLPred, NetCTL- NetMHC, BepiPred 2.0, and ABCPred to cytotoxic T-cell (CTL) and B-cell epitopes inside nucleocapsid phosphoprotein peptides [13].

On this basis, the objective of our research was to forecast and analyse the energy profile of the relationship between the SARS-CoV-2 NP and the ACE2 human cell receptor. The mathematical methodology used in this study is to approximate the molecular descriptors and the relationship between descriptors with binding affinity and selectivity using different bioinformatics tools. For viral nucleocapsid protein and ACE2 receptor, research highlights and association characteristics are primarily responsible for further improvement for enhanced binding and selectivity.

Materials and methods

Sequence comparison. In the current study, experimental binding affinity and selectivity data were conducted to determine the critical structural characteristics needed for binding affinity and to explore the structural criteria available for protein docking. SARS-CoV-2 (QJR91601.1), Bat CoV-Cp/Yunnan2011 (AGC74175.1), Bat SARS-CoV HKU3-2 (AAZ41337.1), SARS CoV-TJF (AAT76155.1) and BtRl-Beta-CoV/SC20188, five amino acid sequences of NP linked to the coronavirus family have been selected from the NCBI FASTA format (QDF43818.1). Using the T-COFFEE server, multiple sequence alignment was achieved and checked by the CLUSTA-W tool and confirmed with MAFFT 7 [13].

Protein-protein interaction. Angiotensin-converting enzyme II precursor ACE2 Homo sapiens (NP 001358344.1) was blasted for protein association interaction inside the UniPort alignment server (https:/www.uniprot.org/align/) in addition to five amino acid sequences alignment of NPs and compared to the CLUSTAL-OMEGA tool in EMBL-EBI. Using MAFFT Version 7 (https:/mafft.cbrc.jp/alignment/software/tips.html), the phylogenetic tree was extracted and confirmed using the ViPR server (https://www.viprbrc.org/brc/home.spg?decorator=vipr).

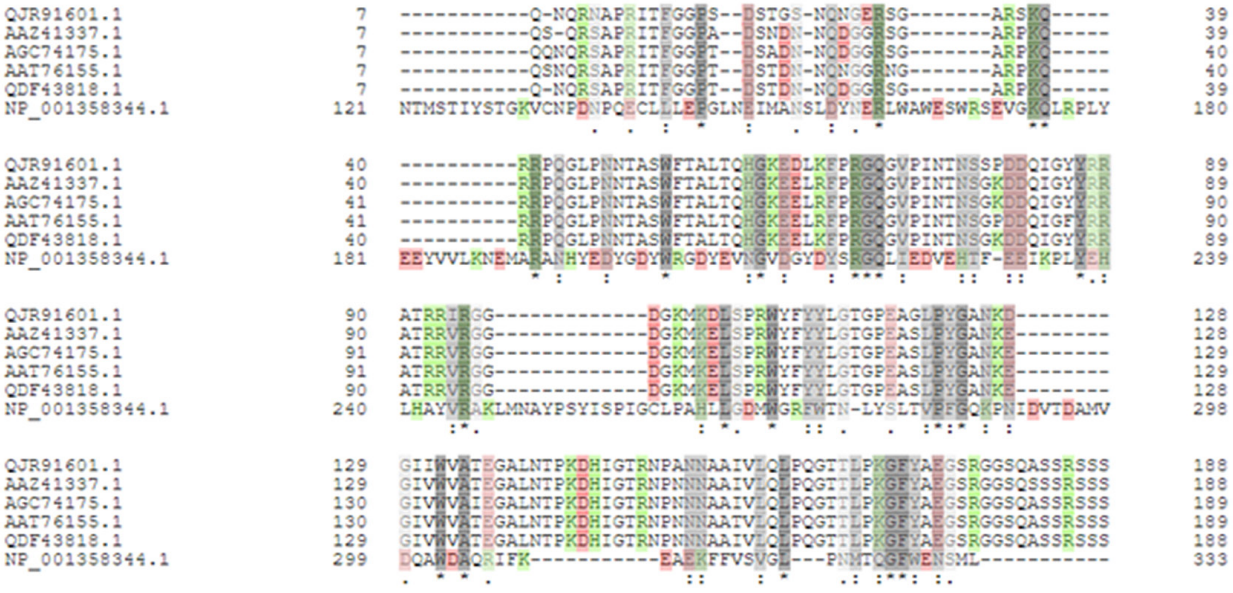
Predication ion ligand binding sites. Ion ligand binding site residues were removed from the IonCom server in Zhang lab (https:/zhanglab.ccmb.med.umich.edu/IonCom/) according to the build-up of the 2D structure of amino acid sequences: complete sequence of SARS-CoV-2 NP (QJR91601.1), RNA binding domain SARS-CoV NP (2OFZ) and ACE22 NP (2OFZ) (1R42).

Protein modelling. The SARS-CoV-2 NP Homology Structural Simulation was built based on the SWISS-MODEL server models and DeepView/Swiss-PdbViewer 4.01 program. Several models were obtained and the higher sequence similarity measured the consistency of each structure. To optimize the protein similarity, we selected the crystal structure of SARS-CoVs NP in protein bank (PDB). The best model was obtained for SARS-CoV-2 NP for predicting the 3D structure. The projected models were subject to further optimization of the protein structure. The described MD simulations were used with NAMD 2.12 and Gasteiger charges. The lowest energy frame of the MD imitation was performed by the obtained structures. With the PROCHECK programs in PDBsum, the consistency of the models was created.

Molecular docking. For coronavirus NPs and ACE2 (1R42), the crystal structure was downloaded from the Protein Data Bank. It checked the homology models for CoV NPs. Then, using molecular docking, binding patterns, and affinity calculations were carried out for the protein-protein interaction between the various domains of NPs and ACE2 receptors. In the present research, molecular docking analysis was applied to better explain the intermolecular interactions that take place between various sequences. Two steps were taken to generate the active docking process; first using Z-dock software, a blind docking between ligand NP and receptor ACE2 was performed. Then using PRODIGY software techniques, the resulting docking data was processed and analysed. (http://www.bonvinlab.org/software/) [14]. Finally, the data findings were clustered and evaluated in each complex, taking into account the binding energies and key interacting residues [15]. For all the receptor-ligand complexes, the ducker interaction energy parameter was tested and the top five scoring models were chosen as favourable for the binding.

Results. There were a high correlation and identification between SARS-CoV-2 NPs, Bat-CoV-HKU3-2, Bat-CoV-Cp/Yunnan, SARS-CoV-TJA, and CoV BtR1-BetaCoV/SC2018 in the multiple sequence alignment (MSA) of the five series from various sources linked to the coronavirus family: 88.76 %, 89.26 %, 89.26 %,

and 89.50 %, respectively. This discovery is not in accordance with our previous research showing that SARS-CoV-2 NP uses the T-COFFEE method to achieve 70 % similarity related to Bat-SARS-CoV due to different statistics on each server, which yield different results [16]. With five NP coronavirus genes, ACE2 was matched. The patterns of contact between the five viral NPs are very comparable. A low share resemblance between ACE2 and the NP sequences was observed as 16.96 %, 16.86 %, 17.11 %, 17.11 %, and 17.16 % (Fig. 1).



F i g. 1. Partial multiple sequence alignment (MSA) of five NP sequences and ACE2: dark grey lines show high match similarity and conserved sits; light grey line shows most conserved in high identity in sequences. Pink line shows positive correlations between sequences. R in green line: exact similarity between sequences.

Arithmetic server research has been used to derive predictive ion ligand binding site residues for both NPs of coronaviruses and ACE2. We had several ion ligands predicted. For the full SARS-CoV-2 NP sequence, 18 residues of Zn (Zinc), 8 residues of Cu (Copper), 7 residues of Ca (Calcium), 5 residues of Na (Sodium), and 2 residues of K (Potassium) were reported in Table 1. The ion binding sites prediction for 2OFZ, were: 9 Zn residues, 3 Fe (iron) residues, 2 Mg (magnesium) residues, 6 Mn (manganese) residues, and 1 Na residue (Table 1). ACE2 has detected 49 residues of ZN, 2 residues of MG, and 6 residues of NA (Table 1). Loci of ions are presented on the prediction with 2D and 3D structure in Fig. 2.

Structural analysis and molecular docking of NP-ACE2 complexes

The SARS-CoV-2 NP crystal structures and Bat SARS-CoV homology models interacting with the putative binding domain site in human ACE2 were studied. According to the realm of engagement, the interaction pattern between them revealed different designs. RNA binding domain X-ray crystal structure of SARS-CoV-2 NP, PDB (6VYO) resolution 1.70 Å showed residues of ligand binding sites (Fig. 3, Table 2).

MSE on (201A, 203A, 202B and 204C), Gol (201B, 203C, 201D, and 202D), Zn ion on (206A, 203B, and 205C), and Cl ion metal are the following ligands: (202A, 205A, 201C, and 202C). The crystal structure of ACE2 in PDB (1R42) in X-ray diffraction 2.2 Å showed residues of ligand binding sites in Fig. 4, Table 2.

NAG (800A, 801A, and 802A), Zn ion metal (804A), and Cl ion metal sites are ligand sites on ACE2 (803C). Figure 5 shows the docking and protein-protein interaction of NP 6VYO-ACE2. To detect probability docking models, we used Zdock server (http://zdock.umassmed.edu). We picked the top five probability models from Zdock that are forecast and evaluated and viewed with Java-Script.

The SARS-CoV NP dimerization domain (2GIB-PDB) crystal structure with 1.75 Å resolution has one SO4 371A (sulphate ion) ligand-binding residue (Fig. 6, Table 2). Figure 6 reveals the top five NP 2GIB-ACE2 docking versions.

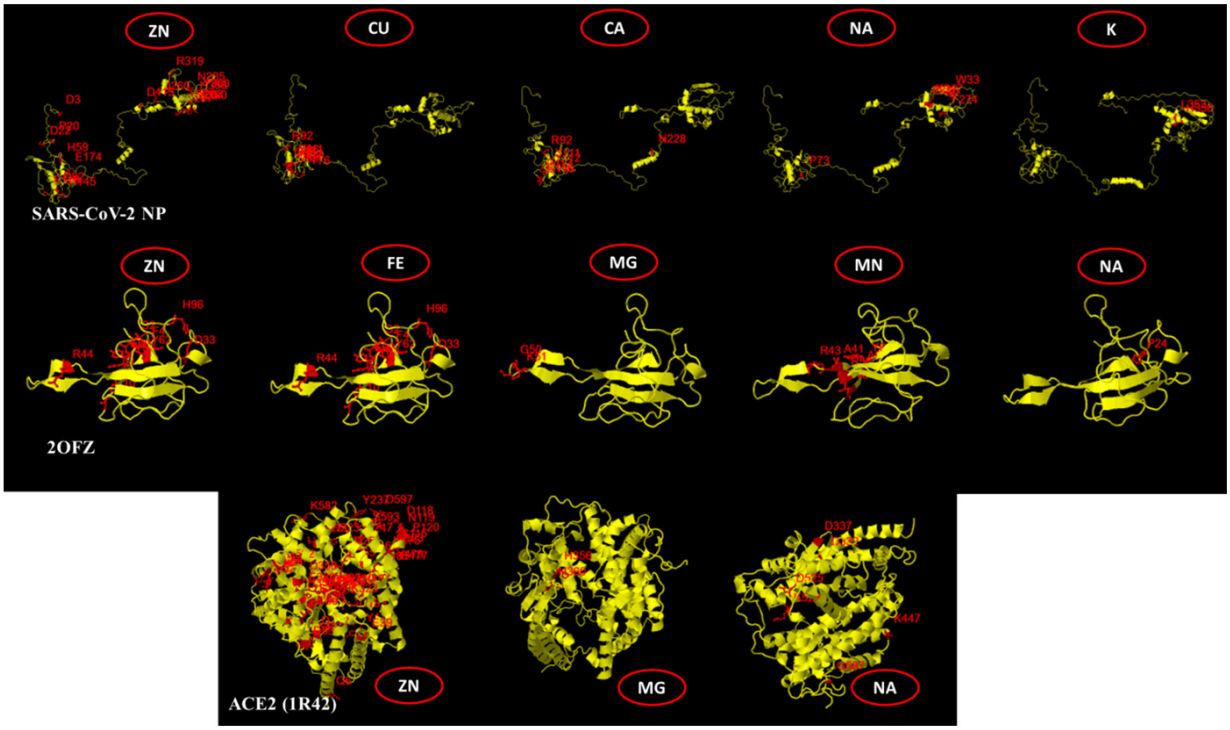
RNA binding domain crystal structure SARS-CoV-2 NP (2OFZ-PDB) with X-diffraction resolution 1.17 Å has one Edo 638 (1, 2-Ethanediol) ligand-binding residue (Fig. 7, Table 2). Figure 8 reveals the top five NP 2OFZ-ACE2 docking versions.

The RMSD is the most common quantitative measure of the correlation between two atomic

Table 1

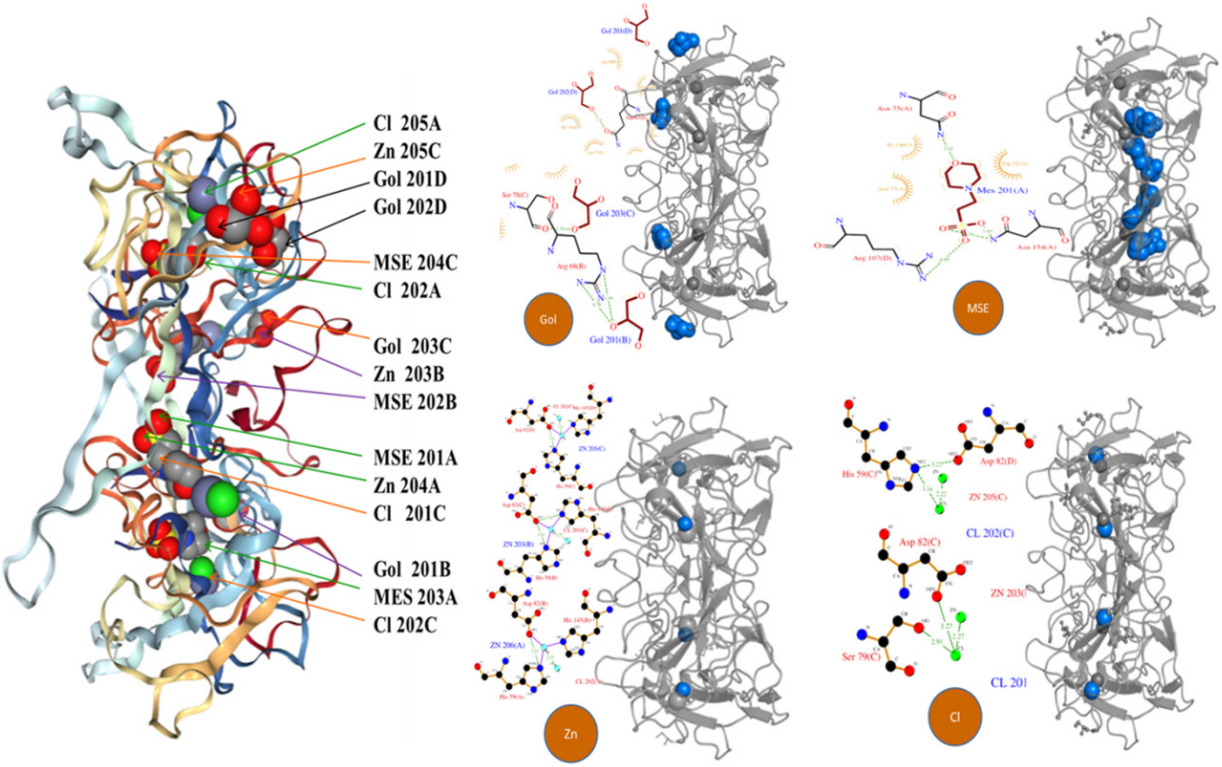
Predication of ion ligand site residues of NP CoVs and ACE2

Source	Ion ligand	Pos.
SARS-CoV-2	**ZN**	D3,P20,D22,H59, D82,E118, H145, E174, Q260, N285, E290, R293, D297, H300, R319, H356, Y360, D415
	CU	T76, D82, Q83, G85, Y86, R92, Y111, Y112
	CA	R92, Y111, Y112, T115, G116, P117, N228
	NA	P73, F274, W330, F346, K347
	K	L353, H356
2OFZ	**ZN**	S2, F4, H10, D33, R44, Y60, Y62, E69, H96
	FE	Y38, Y62, R100
	MG	G50, K51
	MN	A6, T8, A41, R43, R58, Y60
	NA	P24
ACE2 (1R42)	**ZN**	Q6,E39,C11,D118,N119,P120,C123,Y178,D183,H221,H223,Y237,C243,H247,D251,R255,N320,K323, C326,H327,P328,D332,D337,C343,D350,H356,H360,H383,E384,E388,H399,E461,H475,E477,Y479,D481, H487,Y497,H517,L521,H522, C524,D525,E546,E553,N560,K582,S593, D597
	MG	H356, H360
	NA	D332, D337. K447, K523, D525, G587



F i g. 2. Ion binding sites residues. *SARS-CoV-2 NP (QJR91601.1)*: 2D structure and ion ligands (Zn, Cu, Ca, Na, K). *2OFZ*: Crystal structure of NP, RNA binding domain and ion ligands (Zn, Fe, Mg, Mn, and Na), and *ACE2*: Crystal structure of angiotensin-converting enzyme II and ion ligands (Zn, Mg, and Na)

co-ordinates superposed. The RMSD values are displayed and computed in Å. Table 3 shows the docking scores and ligand RMSD for the five patterns. Moreover, without expected ligand binding sites in PDB, we isolated four NP domains of SARS-CoVs. These domains are the N-terminal RNA binding domain NP SARS-CoV (6M3M), the SARS-CoV-2 (6YUN) C-terminal dimerization domain, the SARS-CoV (2CJR) oligomerization domain, and the SARS-CoV (1ssk) N-terminal RNA binding domain.

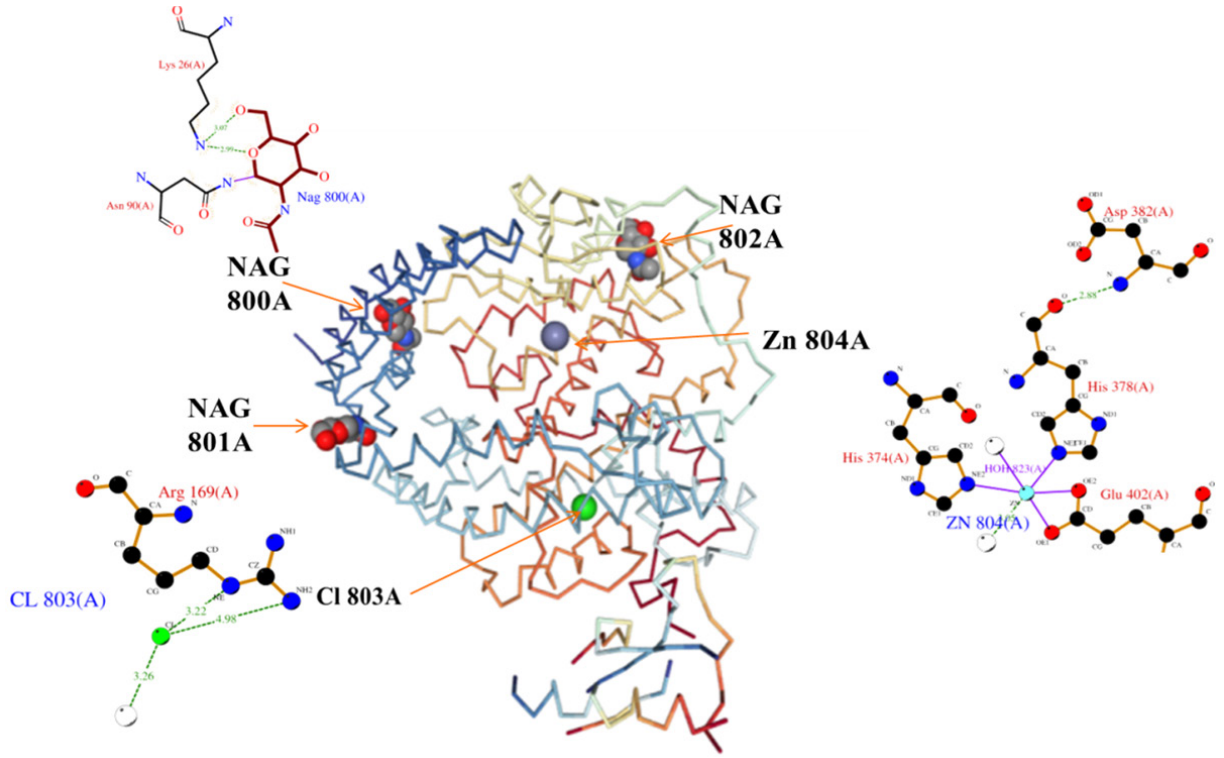


F i g. 3. Crystal structure of NP SARS-CoV-2 RNA binding domain (6VYO). Left figure shows all ligand binding sites. *Gol*: Glycerol binding sites, chemical structures and the loci on NP. *MSE*: 2-(N-Morpholino-Ethanesulfonic acid) binding sites and there loci on NP. *Zn*: Zinc ion metal binding sites and there loci on NP. *Cl*: Chloride ion metal binding sites and there loci on NP.

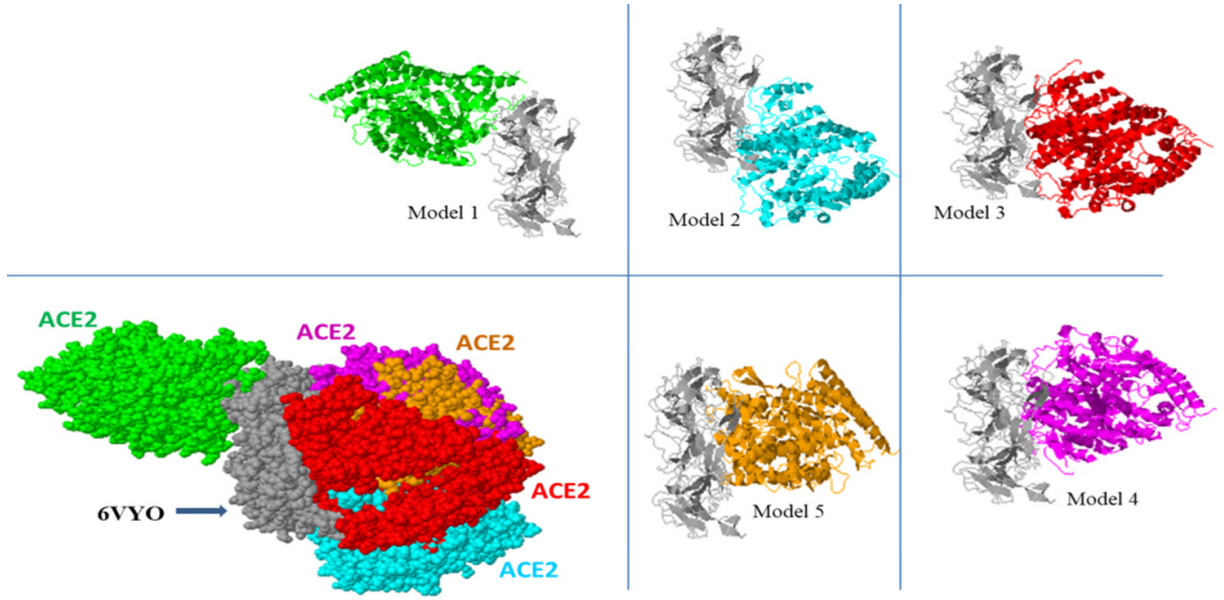
Table 2

Ligand sites residues of NP SARS-CoVs and ACE2. Green highlight: ligands group on 6VYO. Pink highlight: ion metal ligands group of ACE2. Orange highlight unknown ligands group on ACE2

NP SARS-CoV-2 (6VYO)		NP SARS-CoV (2GIB)		NP SARS-CoV (2OFZ)		ACE2 (1R42)	
Lig.	Pos.	Lig.	Pos.	Lig.	Pos.	Lig.	Pos.
MSE 201A	Asn 75	SO4 371A	Arg 277	EDO 638A	Ser 106	NAG 800A	Asn 90
MSE 203A	Asn 154						Lys 26
MSE 202A	Trp 52					NAG 801A	Gln 81
MSE 024C	Arg 107					NAG 802A	Phe 308
Gol 201B	Arg 68					Cl 803A	Arg 169
Gol 203C	Ser 78					Zn 804A	Glu 402
Gol 201D	Trp 132						His 374
Gol 202D	Gln 83						His 378
Zn 206A	His 59					Unk 901B	Asp 615
Zn 203B	Asp 82					Unk 902B	Tyr 613
Zn 205C	His 59					Unk 903B	=
Cl 202A	His 145					Unk 904B	=
Cl 201C	Ser 79					Unk 905B	=
Cl 202C	Zn 59					Unk 906B	=



F i g. 4. Crystal structure of ACE2 shows ligand binding sites residues. *NAG*: N-Acetyl-D-Glucosamine chemical structure and there loci on ACE2. *ZN*: Zinc ion m chemical structure and its locus on ACE2. *Cl*: Chloride ion metal chemical structure and its locus on ACE2.

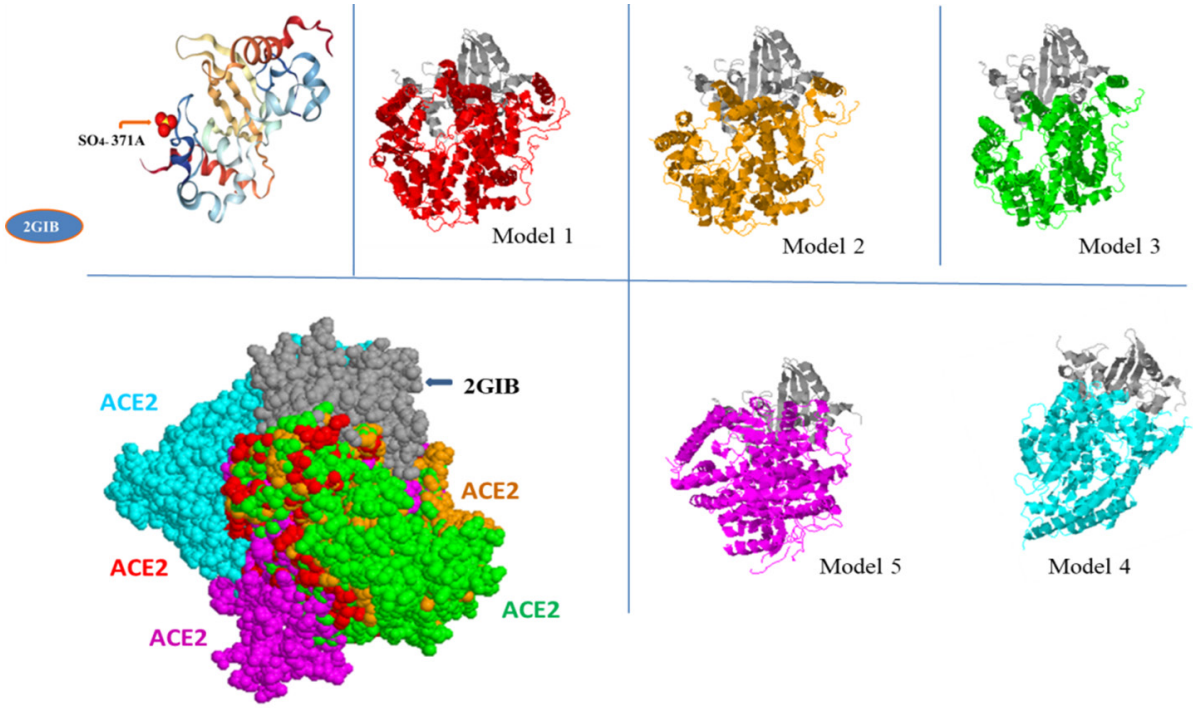


F i g. 5. Five homology models of crystal structure docking NP 6VYO-ACE2. Spacefill architecture of all docking models.

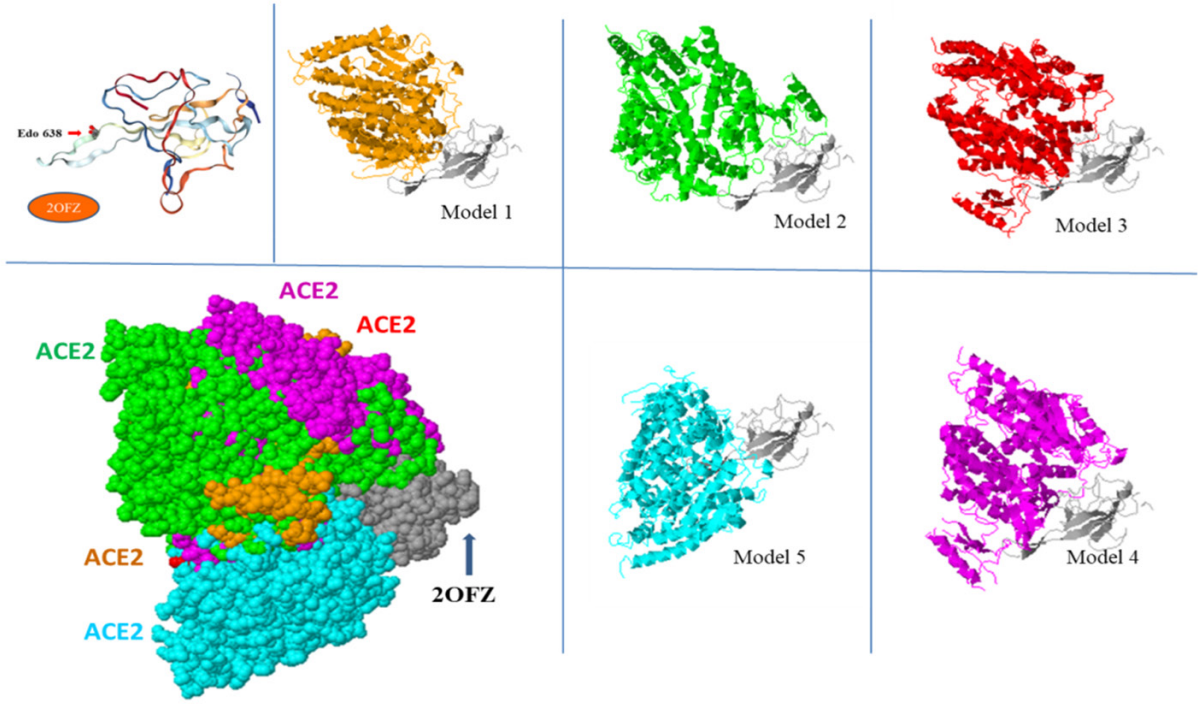
Table 3

Docking scores and RMSD of the top five models of NP-ACE2 interaction

Top	SARS-CoV-2	6VYO-ACE2	SARS-CoV-2	2OFZ-ACE2	SARS-CoV	2GIB-ACE2
Models	Dock score	RMSD (Å)	Dock score	RMSD (Å)	Dock score	RMSD (Å)
1	-268.42	58.23	-258.20	98.61	-223.67	59.28
2	-253.57	54.54	-240.06	94.71	-221.21	82.03
3	-251.23	71.12	-233.58	95.99	-219.93	86.82
4	-242.47	51.09	-225.63	93.11	-211.12	89.87
5	-237.55	64.06	-224.48	93.22	-208.02	62.13



F i g. 6. ***Top left*****: Crystal structure of NP 2GIB with ligand SO4. Top five docking models of NP 2GIB-ACE2.** ***Down left*****: Spacefill architecture of all docking models.**



F i g. 7. ***Top left*****: Crystal structure of NP 2OFZ with ligand Edo. Top five docking models of NP 2OFZ-ACE2.** ***Down left*****: Spacefill architecture of all docking models.**

Discussion. So far it has been confirmed that instead of human SARS-CoV or MERS-CoV, SARS-CoV-2 will quickly transfer and inflict less intense human infection. Different cases have led to SARS-CoV-2 rapid spread to the extent of the outbreak, including high morbidity and mortality, expansion of health facilities in the countries most impacted, absence of vaccine stocks, absence of approved medicines [17, 18].

The NPs of coronaviruses contain a high proportion of serine residues with many sites of phosphorylation. The NP after the infection was

phosphorylated [19]. NP phosphorylation in the infected cells and transfected eukaryote cells was also shown inside the N gene [20].

Interestingly, with >88 percent identity, the sequence comparison between SARS-CoV-2 NP and related SARS-CoVs, the residues present in the receptor-interacting motive is strongly maintained, sharing twenty residues of all coronavirus patterns of NPs.

It is understood now that SARS-CoV-2 uses ACE2 receptors to infect lung alveolar epithelial cells [21]. Roughly 17% of protein-protein cross-sectional tests were of poor retained resemblance between the NP sequences and the ACE2 receptor. During identity declines, 21 strongly retained sites in the grey line between NPs and ACE2 (Fig. 1). This might boost linking locations [22].

We also introduced intelligent consensus simulation methods to forecast the 2D structure of NP CoVs for further refining of the predictions obtained from the individual models. Modelling of consensus aims to enhance the display of the model's evaluation and thereby reduces test errors. In the current analysis we did not only predict the 2D structure of the NPs but also predict the residues in the amino acid sequences under review for ionic binding sites. There are 40 ion residues and 21 residues for 2OFZ in the full sequence of SARS-CoV-2 NP, while ACE2 has 57 ion residues. With the interaction between SARS-CoV-2 NP and ACE2, the most predicted ions were Zn, and this could be significant.

Molecular docking assists in recognizing the optimized conformation between the imaging agent and its receptor of the protein complexes. It provides evidence of the orientation of imaging variables in the receptor-binding area. The key objective is to consider the molecular interactions that take place during binding and compare these results with the study of PROCHECK [23]. In the current work, five NP 6VYO-ACE2 correctly docking models have been observed according to their Figure 5 ligand binding sites. The docking study found that various kinds of bonding interactions and hydrogen-bonding interactions were prevalent.

Locus (Asp 82, His 59 His 145) of 6VYO and (Arg 169, Glu 402, His 374, His 378) of ACE2 are the primary contacting residues. Another high-energy docking was reported in 6VYO and ACE2 loci (Asp 82, His 59 His 145) (Asp 615 Tyr 613, and unknown ligand residues Unk 901B, 902B, 903B, 904B, 905B, and 906B) (Table 2). Previous studies have reported that the two main residues (479 and 487) in the SARS-CoV spike protein are associated with human ACE2 receptor recognition [24], while the residues corresponding to N479, Q493, and T487 are associated with N501 in the SARS-CoV-2 S protein. These residue changes are energetically beneficial changes to the receptor interaction [25, 26]. There has also been shown positive interactions with a Spike glycoprotein-ACE2 complex of -6.8 kcal/mol binding affinity. This association constitutes an essential number of amino acids with which van der Waals associate [27].

The preceding outcome is in accordance with our knowledge. Since it has only one ligand-binding site for both the NP dimerization domain (2GIB) and the binding domain (2OFZ). Five favoured docking models, 2GIB-ACE2 and 2OFZ-ACE2, were registered with the results. In Figures 6 and 7, respectively, the descriptions of the descriptors, their contribution, and frequency of appearance in all five versions are explained in detail. The research on the other hand noted that inhibiting SARS-CoV-2-associated AbI kinase could block the ACE2 receptor [28]. Major structural disruptions in the target proteins can potentially cause changes in thermodynamic stability at earlier docking stages [29]. Analysis showed that phenol derivative and anti-HIV drugs would aid the discovery of COVID-19 drugs by interfering with docking systems [30]. The binding of five molecules to RBD-SARS-CoV-2-ACE2 resulted in binding affinities ranging from (-4.2 to -6.9 kcal/mol) in other tests. ACE2's hydrophobic pocket infiltrates the unique phenylalanine in the loop (F486), thereby playing a significant role in the acknowledgment [31–33].

Ligand binding sites for NP domains of SARS-CoV (6M3M), SARS-CoV-2 (6YUN), SARS-CoV (2CJR), and SARS-CoV (1ssk) were not identified by using *in silico* analysis methods.

It is understood that a docking score lower than -10 typically reflects strong binding interactions that are mainly hydrophobic. The root means a protein's square RMSD deviation in X-ray diffraction resolution is normally 2-3.5 Å. The RMSD within this range is regarded as good, according to the template. Our data scored a lower docking score and RMSD between protein docking interaction of approximately -250 and 50 Å respectively. Our analysis has shown that the results of X-ray diffraction data processing still differ from the use of the methods of bioinformatics and mathematical calculations even though using identical server forms.

Conclusions. Several reports show that blocking the ACE2 receptor in the treatment of SARS-CoV-2 will be an advantageous approach. This research, therefore, aims to investigate new data processing to compare chemical structures with their biological behaviour, as well as ligand-binding affinity, at the level of atoms between the NP and the ACE2 receptor. The research highlights and correlation characteristics are largely responsible for the viral NP and ACE2 receptor that can be further changed for improved binding and selectivity.

The basic two-dimensional (2D) structure appearing in all the models includes the prediction of ion ligand binding sites to be easier to compute. This knowledge will also help to escape the binding of viral proteins to the associated receptors on the host cell in future development.

Data research cannot show the exact practical value of protein-protein docking. However, identification of molecular docks will in our overview lead to autoassociated proteins and serve as a regulatory transition to locate the protein. It may also be a required step for viral entry and assembly.

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Competing Interests. The authors have confirmed that there are no conflicting interests.

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МОЛЕКУЛЯРНИЙ ДОКІНГ БІЛКА НУКЛЕОКАПСИДУ SARS-COV-2 З АНГІОТЕНЗИН-ПЕРЕТВОРЮЮЧИМ ФЕРМЕНТОМ II

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Резюме

Спалахи захворювання COVID-19, викликаного коронавірусом SARS-CoV-2, свідками яких є сучасний світ, залишаються небезпечними для життя людей. **Мета.** Ключовою метою цього дослідження було використання методу біоінформатики для прогнозування молекулярного докінгу, асоційованого з ACE2 нуклеокапсидного білка SARS-Co-V. **Методи.** У цьому дослідженні були використані різні інструменти біоінформатики для порівняння хімічних структур з їх біологічною поведінкою на рівнях атомів та спорідненості до ліганду. Це дослідження було спрямоване на вивчення нового способу аналізу даних. **Результати.** Розрахована базова 2D-структура, яка зустрічається у всіх моделях, що вимагає прогнозування сайтів зв'язування іонних лігандів. Основні моменти аналізу та пов'язані з ним характеристики значною мірою відповідають за білок нуклеокапсиду вірусу та рецептор ACE2, які можуть бути додатково змінені для поліпшення зв'язування та селективності. **Висновки.** Точне функціональне значення білок-білкового докінгу неможливо встановити. Але виявлений молекулярний докінг може мати допоміжну функцію у самозв'язуванні білків, слугуючи регуляторним перемикачем для локалізації білка.

Ключові слова: COVID-19, SARS-CoV-2, ангіотензин-перетворюючий фермент II (ACE2), нуклеокапсид, молекулярний докінг, рецептор-зв'язуючий білок (RBD), RMSD.

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