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"Molecular Docking Results in SARS COV-2 Drugs" – A Review

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Abstract— *The process of generating vaccine-induced immunity is somewhat challenging in immunology. Currently, informatics paved the way for a better understanding of pathogenesis, diagnosis, immune system response and computational vaccinology. Immuno-informatics techniques were used in the current review to forecast the antigenic epitopes against SARS-CoV-2 for the creation of the coronavirus vaccine. The coronavirus protein encoding SARS-CoV-2 was anticipated to include T-lymphocyte and B-cell epitopes. AutoDock Main Protease, the Protein Data Bank was used to obtain the three-dimensional crystal structure of the MPRO, and MetaPocket 2.0, to predict the active site. The study was focused on Molecular Docking and dynamics simulations, to identify potential targets for novel compounds, the spike protein-ACE-2 interface complex, ACE-2 receptor, Spike protein, and Furin. All target proteins were compared to novel target compounds in clinical development and to presently available medicines that had been repurposed.*

Keywords— *Covid-19; Immunoinformatics; Molecular Docking; Simulation.*

I. INTRODUCTION

The current COVID-19 pandemic has demonstrated the importance of developing effective innovative treatment plans for new viruses. Researchers have recently shown a great deal of interest in studies that concentrate on natural products like bioactive secondary metabolites and antimicrobial peptides from microorganisms and plants in the hope of discovering novel antiviral drugs against emerging viruses that cause epidemics and pandemics. Human immunodeficiency virus, SARS, MERS, hantavirus, dengue, West Nile virus, Ebola, and Zika virus are among recently developing viruses that can cause pandemics. While the creation of vaccines takes time, the advancement of antiviral therapies can be predicted by the creation of broad-spectrum medications that are effective against a variety of viruses [1,2].The infection that leads to COVID-19, a fatal illness, is brought on by SARS-CoV-2. The coronavirus particles have spike proteins around them and are spherical in form. These proteins are in charge of virus replication in the cells of the human host. After interacting with human cells, spike proteins go through structural modifications that cause the membranes of the viral particle and the human host cell to fuse. Angiotensin converting enzyme 2 receptor proteins on the surface of the host cell are what SARS-CoV-2 spike proteins bind to. The SARS-CoV-2 spike protein's receptor binding domain allows it to bind to host human cells at the molecular level. The spike glycoprotein's receptor binding domain interacts with the ACE2 receptor in the protease domain of the host human cell to infect it with the virus[3,4]**.**In the past, various approaches to obtaining data in Q-UEL tag form via the Internet have been investigated. By interacting with the HTML on the webpage for Google searches and the list of results, for instance, a Q-UELCTRACT was produced. Consequently, it was crucial to obtain new information from the Internet [5].Molecular docking has been the method most frequently used for virtual molecular interaction screening. In order to execute molecular docking studies, a range of computer programmes based on different algorithms have been created, as this virtual screening technique has grown to be a vital and crucial instrument in the arena of pharmaceutical research [6].SARS-CoV-2 has recently been discovered to have developed into two main kinds L and S. The L type being more common than the S type. This CoV's spike glycoprotein, or S protein, is thought to be a key inducer of neutralising antibodies. The majority of this CoV's vaccines and medications target the S protein. A genome-wide study of 103 SARS-CoV-2 strains revealed 149 mutation sites dispersed throughout the genome. Based on prior literature, strains representing several subgenus of Beta coronaviruses, such as SARS-CoV and MERS-CoV, were included[7]**.**

A. ORIGIN OF COV-2

Although the Wuhan, South China Seafood Market has been linked to the earliest cases, the origin of the SARS-CoV-2 virus is still unknown. Although other sources, such as potential animal vectors, have challenged the claim, the researchers are still looking for the origins of COV 2. Through codon studies, it has been hypothesized that snakes may be the potential source of the viral infection. Since humans and bats are more closely tied to the Coronavirus lifecycle, it was believed that people and bats were more efficiently infected by the virus. According to studies from human serology, the connection of bat CoV proteins results in zoonotic transmission of deadly outbreaks of the SARS-like bat coronavirus. These lessons from SARS and MERS emphasizes how critical it is to discover the source of SARS-CoV-2 as soon as possible in order to stop the ongoing outbreak [8, 9, 10}

B. ORPHOLOGY:

The SARS-CoV-2 is a member of the coronavirus beta family. A lipid membrane, spike-like protein S, membrane

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protein M, nucleo-capsid N protein, and envelope protein surround the single-stranded RNA virus. The endogenous viral RNA genetic material is released into the host cell as a result of the spike protein's attachment to the Angiotensin-Converting Enzyme 2 receptor of mammalian lung cells [11][12]. SARS-CoV-2's spike glycoprotein (COVID-19) is a trimeric viral fusion protein with S1 and S2 subunits that are present in a non-covalently bound state[13]. Spike protein undergoes conformational rearrangements that result in the S1 subunit being shed, the S2 subunit being cleaved by host cell proteases, and the exposure of a fusion peptide next to the S2 proteolysis site[14]. In addition, it has been crucial in controlling blood pressure and anti-arteriosclerosis mechanisms, and it is thought to be a primary target for SARS-Cov-2. The 380 amino acid difference between SARS-CoV-2 and SARS-CoV results in five of the six essential amino acids in the receptor-binding domain that is part of the S1 subunit connecting the viral spike (S) protein with cell membrane human ACE-2 being altered. For the S-protein that enhances and facilitates cell entry after ACE-2 binding through the S2 subunit, which reported as a membrane fusion unit, SARS-CoV-2 had found to use a wide variety of hostproteases, including cathepsin L, cathepsin B, trypsin, factor X, elastase, Furin, and transmembrane protease serine 2[15]. One person can infect more than two healthy subjects with SARS-CoV-2, making it more contagious than other flu viruses[16].

C. Spike Protein Fragment And Human ACE2 Receptor:

When a spike protein fragment is molecularly docked with its receptor in a human host, the human ACE receptor is taken into consideration as the receptor protein. The docking structure of the human ACE2 receptor's A chain binds to the SARS CoV2 spike protein fragment with a binding energy of approximately 779.8 kcal/mole using the ClusPro27 web server. A conformational shift takes place when the S protein fragment interacts to the ACE2 receptor protein. The ASP136, ASN 137, PRO 138, and GLN 139 amino acids are located in the distorted site of ACE2, and the GLN 403, LYS 451, and ASP 416 amino acids interact with the spike protein fragment The ACE2 receptor protein-bound structure of the SARS CoV2 spike protein fragment is thought to be a potential therapeutic target for SARS-CoV2 treatment.

II. Materials And Methods

There are already more than 30 docking programmes available, with AutoDock being the most popular. The goal of molecular docking is to identify the binding mode, which calls for a search technique to run simulations of native protein-ligand interactions[17]. These computational tools make it possible to visualise the ligand-target interaction and identify the substances that bind the target more effectively [18].Based on lowest-binding energies, this approach aids us in the thorough analysis of protein-ligand conformations [19]. The chosen library contains 1615 FDA-approved compounds that were all minimised using UCSF Chimaera and Chemdraw to produce stable configurations. All of these medications were originally sourced from the ZINC database. Molecular Operating Environment, AutoDock tools, and AutoDockVina were used to conduct the molecular docking analyses. Based on S-score and root-mean-square deviation values, the top hits were chosen. The chemical and physical characteristics of hits that resembled drugs were calculated using the admet SAR server, Molinspiration, and Osirisexplorer. The UCSF Chimaera and Ligplotprogramme was used to analyse and display the interacting residues [20,21,22].By molecular docking MPRO with viral protease inhibitors that were approved by the FDA, the study was compared. The protease was shown to be very efficiently inhibited by medications such atazanavir, saquinavir, and darunavir, and the interactions were compared with natural substances[22].All drugs were docked using the Triangle Matcher placement method and the London dG score tool in accordance with the recommended methodology. The best stance was visually examined. The last docking simulation steps were then performed using the GlideSP module in Schrodinger [23, 24].Then, using MOE's Protonate 3D Protocol with the default settings, the protein structures were constructed. In order to analyse the IONPs-receptor interactions in the active site and forecast their binding affinities and modes, the docking methodology was first verified[25, 26]. Small compounds are docked into the protein binding site using molecular docking techniques. The receptor preparation wizard in FlexX is used to define the binding cavity in the receptor. The pool of ligand conformations was used to construct a set of poses using an alpha triangle, which produces a variety of potential conformations depending on how many rotatable bonds are present in the structure. The docking energy and binding interaction dictate the optimal postures for a specific molecule[27, 28, 29, 30]. Using the dock score, a final energy assessment was performed. Maestro interface was used to visualise docked ligands [31, 32, 33]. Using the fully automated protein-ligand interaction profiler system, the binding sites of the finished construct and TLR3 were investigated. The outputs of PLIP were visualisation files, flat text files, PYMOL and XML format files[34, 35,36].

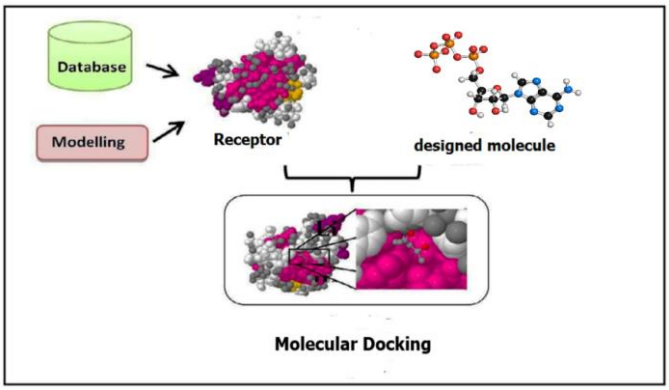

Fig. 1. Process flow of molecular docking

III. Results and Discussion

AMBER18 was used to parameterize MD simulations with ANTECHAMBER. Then, using Amber18 tools, the 200 ns trajectories were submitted to MM-GBSA analysis on all 5000

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frames. Using UniProt KB, the following proteins were found: replicase protein, NSP1, spikes, membrane, nucleocapsid, and envelope. The NETCTL server and ABC pred server were used to predict HTL and CTL epitopes from the selecteproteins. Using the ProtParam, Vaxijen, Toxinpred, and IEDB servers, respectively, their physiochemical characteristics, antigenicity, toxicity, and immunogenicity were predicted. The epitopes that were chosen were used to manually design an adjuvant-based MEV construct, and RaptorX was used to predict the 3D structures. The SAVES server validated the structures, and the HADDOCK server docked the revised structures with TLR3 and TLR8. The two top-scoring complexes were put through an MD simulation after completing protein-protein molecular docking to determine the optimal angles for the vaccine candidate and the receptor proteins to connect. The GROMACS 2018 package was used to do each and every MD simulation. Both the TLR4 and HLA, RMSD values in NOM protein-TLR4 complexes are quite stable, and the average values do not rise to very high levels.

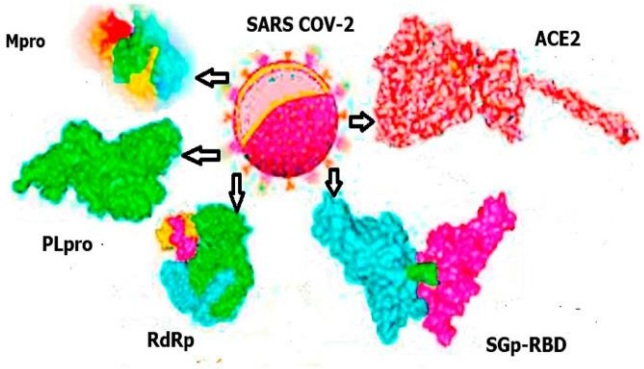

Fig. 1. Molecular docking simulation for SARSCOV-2

A. *Molecular Docking Trajectory Analysis And Prime Mm/Gbsa Calculations:*

The ligand binding free energies and ligand strain energies for docked lead compounds with SARS-CoV-2 Mpro were calculated using the MM/GBSA. The polar solvation energies, non-polar solvation energies, and potential energy make up the binding free energy. The binding free energy in this method is obtained by subtracting the complex's free energy from the sum of the free energies of the ligand and protein. The enhanced OPLS-2005 force field, the SGB solvation model for polar and non-polar solvation, and the Molecular Mechanics Energies that assembled various nonpolar solvent accessible surface areas and van der Waals interactions make up the core of the Prime MM-GBSA. The following equations were used to determine the changes in free energy caused by ligand binding. DGbind 14 Gcomplex—Gprotein—Gligand—G14 EMM—GSGB—GNP: Gligand is the unbound ligand energy, Gprotein is the energy of the receptor, and the Gcomplex is the energy of the complex. Molecular mechanics energies are represented by EMM, polar solvation is represented by GSGB, and nonpolar solvation is represented by GNP[37,38,39,40].

TABLE I. Molecules developed using molecular docking method.

DRUGS	AFFINITY (kcal/mol)	H BOND FORMATION	PROTEIN RECEPTOR
Favipiravir	-4.5	Gly 143,ser 144, cys 145	**6Y2F** [41,42,43,44,45,46,47, 48,49,50,51]
Ganciclovir	-5.1	Gly 143,ser 144, cys 145, phe 140, glu 166, leu 141	
Raltegravir	-7.4	Gly 143,ser 144, cys 145, glu 166, gln 192 leu 141	
remdesivir	-6.9	Gly 143, ser 144, cys 145, gln 189, cys 44	
Alacepril	−5.10	Asn90/H-acceptor, Asp30/H-acceptor	**hACE2** [52,53,54,55]
Captopril	−3.40	Asp30/H-acceptor	
Zofenopril	−4.6	Pro389/arene-H	
Enalapril	−4.8	Asp30/H-donor	
Ramipril	−4.6	Lys26/H-acceptor	
Quinapril	−4.60	Pro389/arene-H, Gln96/H- acceptor	
Perindopril	−4.2	Asp30/H-donor, Asp30/H- acceptor	
Lisinopril	−4.70	Asn90/H-acceptor, Thr92/H-acceptor	
Benazepril	−4.70	Lys25/H-donor	
Imidapril	−4.4	Asp30/H-donor	
Trandolapril	−5.60	Asp30/H-donor, Gln95/H-acceptor	
Cilazapril	−4.5	Pro389/arene-H, Asp30/H- donor	
Fosinopril	−5.04	Gln96/H-acceptor	
Moexipril	−5.10	Asp30/H- donor	
NAG	−4.4	Asp30/H- donor	

IV. Conclusion

Bioinformatics and computational biology advancements have produced a number of new characteristics that have helped to solve problems like the determination of inhibitory constants for docked conformations that existed in the past. In the long term, we advise FDA-approved IONPs to enter COVID-19 clinical studies. These applications are suggested as a cutting-edge strategy for preventing nosocomial and viral infections in hospitals. Additionally, lead compounds form a stable complex with SARS-CoV-2 Mpro, according to calculations using the MM/GBSA free energy calculation method and hydrogen bond monitoring. In overall AutoDock were used in most of the studies for docking process. In recent studies computational aided drug design plays major role in the development of novel drugs. Hence molecular docking is significant in bioinformatics and computational biology.

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References

[1] Dassanayake MK, Khoo TJ, Chong CH, Di Martino P. Molecular Docking and In-Silico Analysis of Natural Biomolecules against Dengue, Ebola, Zika, SARS-CoV-2 Variants of Concern and Monkeypox Virus. Int J Mol Sci. vol.23, 2022.

[2] Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh C-L, Abiona O, et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science. vol. 367, pp.1260–3, 2020.

[3] Basu A, Sarkar A, Maulik U. Molecular docking study of potential phytochemicals and their effects on the complex of SARS-CoV2 spike protein and human ACE2. Sci Rep. vol.10, pp.17699. 2020.
[4] Tai W, He L, Zhang X, Pu J, Voronin D, Jiang S, et al. Characterization of the receptor-binding domain (RBD) of 2019 novel coronavirus: implication for development of RBD protein as a viral attachment inhibitor and vaccine. Cell Mol Immunol. vol.17, pp. 613-20, 2020.
[5] Robson B. Computers and viral diseases. Preliminary bioinformatics studies on the design of a synthetic vaccine and a preventative peptidomimetic antagonist against the SARS-CoV-2 (2019-nCoV, COVID-19) coronavirus. Comput Biol Med. vol. 119, pp.103670, 2020
[6] Schrödinger, L.; De Lano, W. Incentive PyMOL Software Package. 2020. Available online: https://pymol.org/2/ (accessed on 8 August 2021).
[7] Khan S, Tiwari R, Patel S, Karthik K, Yatoo DM, Malik Y, et al. Coronavirus disease 2019 (COVID-19) in domestic animals and wildlife: advances and prospects in the development of animal models for vaccine and therapeutic research. Hum Vaccines Immunother. vol. 16, pp. 3043-54, 2020.
[8] Waqas M, Haider A, Rehman A, Qasim M, Umar A, Sufyan M, et al. Immunoinformatics and Molecular Docking Studies Predicted Potential Multiepitope-Based Peptide Vaccine and Novel Compounds against Novel SARS-CoV-2 through Virtual Screening. Biomed Res Int. pp. 1596834, 2021.
[9] Kam Y-W, Okumura Y, Kido H, Ng LFP, Bruzzone R, Altmeyer R. Cleavage of the SARS coronavirus spike glycoprotein by airway proteases enhances virus entry into human bronchial epithelial cells in vitro. PLoS One. vol.4, pp.e7870, 2009
[10] Chu DKW, Pan Y, Cheng SMS, Hui KPY, Krishnan P, Liu Y, et al. Molecular Diagnosis of a Novel Coronavirus (2019-nCoV) Causing an Outbreak of Pneumonia. Clin Chem. vol.66, pp.549-55, 2020.
[11] Bosch BJ, van der Zee R, de Haan CAM, Rottier PJM. The coronavirus spike protein is a class I virus fusion protein: structural and functional characterization of the fusion core complex. J Virol. vol.77, pp.8801-11, 2003.
[12] Ge X-Y, Li J-L, Yang X-L, Chmura AA, Zhu G, Epstein JH, et al. Isolation and characterization of a bat SARS-like coronavirus that uses the ACE2 receptor. Nature. vol.503, pp.535-8, 2013.
[13] Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell. vol.181, pp.271-280, 202..
[14] Tortorici MA, Veesler D. Structural insights into coronavirus entry. Adv Virus Res. vol.105, pp. 93-116, 2019.
[15] Wysocki J, Ye M, Soler MJ, Gurley SB, Xiao HD, Bernstein KE, et al. ACE and ACE2 activity in diabetic mice. Diabetes vol. 55, pp. 2132-9, 2006
[16] Shah B, Modi P, Sagar SR. In silico studies on therapeutic agents for COVID-19: Drug repurposing approach. Life Sci. vol. 252, pp. 117652, 2020.
[17] Sousa SF, Fernandes PA, Ramos MJ. Protein-ligand docking: current status and future challenges.Proteins.vol.65, pp.15-26, 2006.
[18] Zoete V, Grosdidier A, Michielin O. Docking, virtual high throughput screening and in silico fragment-based drug design. J Cell Mol Med. vol.13, pp.238-48, 2009.
[19] Srikanth Kumar K, Lakshmana Rao A, Basaveswara Rao M V. Design, synthesis, biological evaluation and molecular docking studies of novel 3-substituted-5-[(indol-3-yl)methylene]-thiazolidine -2,4-dione derivatives. Heliyon. vol. 4, pp. e00807, 2018.
[20] Feroz Khan, QSAR, Molecular Docking and MD Simulation guided Lead Identification and Exploration of Binding mode of Action on Potential Targets, Current topics in medicinal chemistry, vol.8, pp.1555–72, 2023
[21] Wallace AC, Laskowski RA, Thornton JM. LIGPLOT: a program to generate schematic diagrams of protein-ligand interactions. Protein Eng .vol. 8, pp. 127*34, 1995.
[22] C S, S DK, Ragunathan V, Tiwari P, A S, P BD. Molecular docking, validation, dynamics simulations, and pharmacokinetic prediction of natural compounds against the SARS-CoV-2 main-protease. J Biomol Struct Dyn. vol.40, pp. 585-611, 2022.
[23] Sinha SK, Prasad SK, Islam MA, Gurav SS, Patil RB, AlFaris NA, et al. Identification of bioactive compounds from Glycyrrhiza glabra as possible inhibitor of SARS-CoV-2 spike glycoprotein and non-structural protein-15: a pharmacoinformatics study. J Biomol Struct Dyn. vol.39, pp.4686-700, 2021.
[24] Khattab ESAEH, Ragab A, Abol-Ftouh MA, Elhenawy AA. Therapeutic strategies for Covid-19 based on molecular docking and dynamic studies to the ACE-2 receptors, Furin, and viral spike proteins. J Biomol Struct Dyn. vol.40, pp.13291-309, 2022.
[25] Abo-Zeid Y, Ismail NSM, McLean GR, Hamdy NM. A molecular docking study repurposes FDA approved iron oxide nanoparticles to treat and control COVID-19 infection. Eur J Pharm Sci Off J Eur Fed Pharm Sci. vol.153, pp.105465, 2020.
[26] Annamalai A, Karuppaiya V, Ezhumalai D, Cheruparambath P, Balakrishnan K, Venkatesan A. Nano-based techniques: A revolutionary approach to prevent covid-19 and enhancing human awareness. J Drug Deliv Sci Technol. vol.86, pp.104567, 2023.
[27] Lokhande KB, Doiphode S, Vyas R, Swamy KV. Molecular docking and simulation studies on SARS-CoV-2 M(pro) reveals Mitoxantrone, Leucovorin, Birinapant, and Dynasore as potent drugs against COVID-19. J Biomol Struct Dyn. vol.39, pp. 7294-305, 2021.
[28] Bhardwaj VK, Singh R, Sharma J, Rajendran V, Purohit R, Kumar S. Identification of bioactive molecules from tea plant as SARS-CoV-2 main protease inhibitors. J Biomol Struct Dyn. vol. 39, pp.3449–58. 2021.
[29] Bursulaya BD, Totrov M, Abagyan R, Brooks CL 3rd. Comparative study of several algorithms for flexible ligand docking. J Comput Aided Mol Des. vol.17, pp.755-763, 2003.
[30] De Vivo M, Masetti M, Bottegoni G, Cavalli A. Role of Molecular Dynamics and Related Methods in Drug Discovery. J Med Chem. vol.59, pp.4035-61, 2016.
[31] Bhuvaneshwari S, Sankaranarayanan K. Identification of potential CRAC channel inhibitors: Pharmacophore mapping, 3D-QSAR modelling, and molecular docking approach. SAR QSAR Environ Res. vol.30, pp.81-108, 2019.
[32] Beniac DR, Andonov A, Grudeski E, Booth TF. Architecture of the SARS coronavirus prefusion spike. Nat Struct Mol Biol. vol. 13, pp.751-2, 2006.
[33] Berman HM, Westbrook J, Feng Z, Gilliland G, Bhat TN, Weissig H, et al. The Protein Data Bank. Nucleic Acids Res. vol.28, pp.235-42, 2000.
[34] Behbahani M, Moradi M, Mohabatkar H. In silico design of a multi-epitope peptide construct as a potential vaccine candidate for Influenza A based on neuraminidase protein. Silico Pharmacol. vol. 9, pp.36, 2021.
[35] Brielle ES, Schneidman-Duhovny D, Linial M. The SARS-CoV-2 Exerts a Distinctive Strategy for Interacting with the ACE2 Human Receptor. Viruses. vol.12, 2020.
[36] Wu F, Zhao S, Yu B, Chen Y-M, Wang W, Song Z-G, et al. A new coronavirus associated with human respiratory disease in China. Nature. vol.579, pp.265-9, 2020.
[37] Enayatkhani M, Hasaniazad M, Faezi S, Gouklani H, Davoodian P, Ahmadi N, et al. Reverse vaccinology approach to design a novel multi-epitope vaccine candidate against COVID-19: an in silico study. J Biomol Struct Dyn. vol.39, pp. 2857-72, 2021.
[38] Şahin S, Dege N. Synthesis, characterization, computational analyses, in silico ADMET studies, and inhibitory action against SARS-CoV-2 main protease (Mpro) of a Schiff base. Turkish J Chem. vol.46, pp. 1548-64, 2022.
[39] Kumar A, Singh R, Kaur J, Pandey S, Sharma V, Thakur L, et al. Wuhan to World: The COVID-19 Pandemic. Front Cell Infect Microbiol. vol.11, pp.596201, 2021.
[40] Afzal A. Molecular diagnostic technologies for COVID-19: Limitations and challenges. J Adv Res. vol.26, pp. 149-59, 2020.
[41] Das S, Khan M, Bakhtiar M, Shahriar M. In silico Molecular Docking and ADMET Study of Some Potential Antiviral Drug Candidates as Potential Inhibitors of SARS-CoV-2 Protease Mpro (6Y2F). Dhaka Univ J Pharm Sci. vol.20, pp.177-83, 2021.
[42] Agostini ML, Andres EL, Sims AC, Graham RL, Sheahan TP, Lu X, et al. Coronavirus Susceptibility to the Antiviral Remdesivir (GS-5734) Is Mediated by the Viral Polymerase and the Proofreading Exoribonuclease. MBio. vol.9, 2018.
[43] Ksiazek TG, Erdman D, Goldsmith CS, Zaki SR, Peret T, Emery S, et al. A novel coronavirus associated with severe acute respiratory syndrome. N Engl J Med. vol.348, pp.1953-66, 2003.
[44] Guest PC, Kesharwani P, Butler AE, Sahebkar A. The COVID-19 Pandemic: SARS-CoV-2 Structure, Infection, Transmission,

Symptomology, and Variants of Concern. Adv Exp Med Biol. vol.1412, pp. 3-26, 2023.
[45] Dhingra N, Bhardwaj R, Bhardwaj U, Kapoor K. Design of hACE2-based small peptide inhibitors against spike protein of SARS-CoV-2: a computational approach. Struct Chem. pp.1-14, 2023.
[46] Egieyeh S, Egieyeh E, Malan S, Christofells A, Fielding B. Computational drug repurposing strategy predicted peptide-based drugs that can potentially inhibit the interaction of SARS-CoV-2 spike protein with its target (humanACE2). PLoS One. vol.16, pp. e0245258, 2021.
[47] Wang C, Horby PW, Hayden FG, Gao GF. A novel coronavirus outbreak of global health concern. Lancet. vol.395, pp.470-3, 2020.
[48] Shi L, Wen Z, Song Y, Wang J, Yu D. Computational investigation of potent inhibitors against SARS-CoV-2 2'-O-methyltransferase (nsp16): Structure-based pharmacophore modeling, molecular docking, molecular dynamics simulations and binding free energy calculations. J Mol Graph Model. vol.117, pp.108306, 2022.
[49] Shang J, Ye G, Shi K, Wan Y, Luo C, Aihara H, et al. Structural basis of receptor recognition by SARS-CoV-2. Nature. vol. 581, pp. 221-4, 2020.
[50] Mulgaonkar N, Wang H, Zhang J, Roundy CM, Tang W, Chaki SP, et al. Montelukast and Telmisartan as Inhibitors of SARS-CoV-2 Omicron Variant. Pharmaceutics. vol.15, 2023.
[51] Devaux CA, Fantini J. ACE2 receptor polymorphism in humans and animals increases the risk of the emergence of SARS-CoV-2 variants during repeated intra- and inter-species host-switching of the virus. Front Microbiol. vol.14, pp. 1199561, 2023.
[52] Al-Karmalawy AA, Dahab MA, Metwaly AM, Elhady SS, Elkaeed EB, Eissa IH, et al. Molecular Docking and Dynamics Simulation Revealed the Potential Inhibitory Activity of ACEIs Against SARS-CoV-2 Targeting the hACE2 Receptor. Front Chem. vol.9, pp.661230, 2021.
[53] Rahman A, Sarkar A. Risk Factors for Fatal Middle East Respiratory Syndrome Coronavirus Infections in Saudi Arabia: Analysis of the WHO Line List, 2013-2018. Am J Public Health. vol.109, pp.1288-93, 2019.
[54] Bao L, Deng W, Huang B, Gao H, Liu J, Ren L, et al. The pathogenicity of SARS-CoV-2 in hACE2 transgenic mice. Nature. vol.583, pp.830-3, 2020.
[55] Humeniuk R, Mathias A, Cao H, Osinusi A, Shen G, Chng E, et al. Safety, Tolerability, and Pharmacokinetics of Remdesivir, An Antiviral for Treatment of COVID-19, in Healthy Subjects. Clin Transl Sci. vol.13, pp.896-906, 2020