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Validation of the binding affinities and stabilities of ivermectin and moxidectin against Sars-CoV-2 receptors using molecular docking and molecular dynamics simulation

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Abstract

Corona-viruses (CoVs), a large family of single-stranded RNA viruses, can infect animals and also humans, causing respiratory, gastrointestinal, hepatic, and neurologic disease. As the largest known RNA viruses, they are further divided into four genera: alpha-coronavirus, beta- corona- virus, gamma-corona virus and delta-coronavirus. SARS-CoV-2 belong to genus betacoronavirus. The viral genome of SARS-CoV-2 codes 4 major structural proteins: the nucleocapsid (N) protein, the transmembrane (M) protein, the envelope (E) protein, and the spike (S) protein. It also encodes 16 nonstructural proteins (NSPs) and 9 accessory proteins required for replication and pathogenesis. The Molecular docking simulations was used to determine the binding affinities of Ivermectin, Moxidectin and Molnupiravir against NSP13 receptor of SARS-CoV-2. The experimental crystal structures of the receptor was obtained from the protein data bank (PDB). The receptor was prepared using Chimera-1.10.1 and AutoDock tools-1.5.6. The 3D structure of the selected approved drugs and the reference ligand was obtained from PDB and Drugbank and prepared using AutoDock tools-1.5.6. Validation of docking protocol was done by reproducing the PDB crystal structures *insilico*. Molecular docking simulations were performed using AutoDockVina-4.2.6 on the Linux operating system (ubuntu) 20.04. Then the docking results were analysed and visualized using Pymol-2.3.0. Molecular dynamics of the frontrunners with the reference ligand and protein was done in 10000 ps. Moxidectin, molnupiravir and Ivermectin showed high binding affinities to the receptors. Moxidectin and Ivermectin showed stability after molecular dynamics simulation to further validate the claim. These drugs are predicted as possible antivirals in the treatment of Covid-19.

Keywords: Sars-CoV-2; Ivermectin; Moxidectin; Molecular docking; Molecular Dynamics; Corona Virus

1. Introduction

Corona virus is an enclosed, single-stranded, positive sense RNA virus with a helical-symmetric nucleocapsid [3]. A new virus that was first identified as the 2019 novel coronavirus (2019-nCoV) appeared in the Chinese city of Wuhan in December 2019 [1]. The symptoms were observed to include; Fever, a dry cough, dyspnea, headaches, pneumonia with a possible risk of developing respiratory failure due to alveolar injury, and perhaps death were some of the clinical symptoms it generated [2][4]. It spread greatly across the world with majorly respiratory symptoms along with severe acute respiratory syndrome in some victims [6][3]. Previously existing drugs have been tested on this virus with various methods and while some proved to have activity against the virus others displayed however no response [5].

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The concept of drug repurposing entails the use of already existing drugs with known pharmacologic effects and testing them for new pharmacological action and effects [7]. This has been performed in the search for therapeutic agents for SARS-CoV-2 after it became a world pandemic. The field of Computer -Aided Drug Design (CADD) is expanding quickly with a lot success recently. Along with academics a lot of pharmaceutical corporations use CADD to find medication leads [8].

The rapid development in structural informatics, genomics and proteomics has greatly aided in the search for new drugs in the modern day [16]. Molecular dynamics uses computer simulation to study the actual movement of atoms and molecules, molecular docking is utilized in CADD to anticipate the optimum interaction between molecules [9]. With the benefit of reducing time and money of medication development, CADD is a crucial tool in drug repurposing, it provides a target approach to drug repurposing that enables quick screening of chemical libraries[17].

The endeavor of finding a new medicine is quite challenging. A major component of modern drug discovery is an *Insilico*, chemical, and biological approach [18][19]. The acceptance use and popularity of computer-aided techniques (CAT) in the drug research and development process are growing quickly [20].

2. Material and methods

2.1. Materials

The materials used were, Pymol, Chimera, autodock tools, autodock vina, gromacs Linux Operating System (Ubuntu), Open Babel, Visual Molecular Dynamics (Vmd), Grace, Gromacs PubChem Database, Bioinformatic and Chemical Databases, ChemSpider Database, A windows 10 Laptop

2.2. Methodology

2.2.1. Preparation of receptors

Bioinformatics mining of the protein data bank (PDB) was done to identify the necessary Sars-CoV-2 targets suitable for the study. The 3D atomic crystal structures of the proteins were obtained from PDB. The proteins were prepared for molecular docking simulations using Chimera 1.10.1 and Auto dock tools 1.5.6. Polar hydrogen and charges were added. The grid spaces were assigned.

2.2.2. Preparation of ligands

The electronic structure of the reference ligand, selected approved drugs (ivermectin, moxidectin and molnupiravir) were obtained from DrugBank and PubChem database. Molnupiravir was only used for the docking process and was not used during the molecular dynamics as the focus was not on it. The ligands were prepared for molecular docking simulations using Autodocktools 1.5.6. Rotatable bonds were assigned, Gesteiger charges were added and then saved as pdbqt files. The prepared proteins and ligands were used for molecular docking simulations.

2.3. Molecular docking

AutodockVina1.1.2 was used for molecular docking simulations. The ligands were docked into the receptor to predict their free binding energies using AutodockVina with the aid of a virtual screening script. Four replicate simulations were done for each of the ligand and the binding affinities reported as mean and standard deviation. The ligands were ranked based on binding energies and frontrunners selected for molecular dynamics simulations.

2.4. Molecular dynamics

Molecular dynamics simulations were done using GROMACS on Linux platform. The molecular dynamics simulations for three drug-complexes and for the receptor were implemented for three different receptors of Sars-CoV-2.

2.4.1. Molecular dynamics simulation of protein

The protein was inspected for missing residues, after which GROMACS topology file for the protein was generated. A simulation box for the system was generated after which *in vacuo* energy minimization was done. The system was neutralized appropriately. Energy minimization of the solvated and ionized system was done. Position restrain dynamics was done for 30 ps so as to restrain the molecules in a reference position after which molecular dynamics was done for 10000 ps and the results analysed.

2.4.2. Molecular dynamics simulation of protein – ligand complex

In this process a directory was first made for the molecular dynamics simulation and the receptor was examined for missing residues. A .itp file was generated for the protein and ligand from PRODRG server which was used for the simulations. Molecular dynamics simulations were implemented as described above and the results analysed.

3. Results and discussion

3.1. Molecular Docking results

The following are the results from the molecular docking and molecular dynamics of ivermectin, molnupiravir and moxidectin on SARS-CoV-2 receptors with the pdb codes in table I

Table 1 Names of SARS-CoV-2 Target and Associated Human Drug Targets Used and Their Protein Database (Pdb) Codes

NAME	**PDB CODE**
SARS-COV-2 TARGET	
Mainprotease (Mpro)	7jkv
NSP14 (Exonuclease)	5c8t
RNA dependent RNA polymerase (RdRp)	7d4f
Papain-like protease (PLpro)	7jit
Spike protein	7lm9
NSP13 (Helicase)	5rlj
ASSOCIATED HUMAN DRUG TARGETS	
Transmembrane serine protease 2 (TMPRSS 2)	7meq
Angiotensin converting enzyme 2 (ACE 2)	6vw1

Table 2 The binding affinities of the various ligands against the receptors of Sars-CoV-2. D1 is the first binding score, D2 is the second binding score, D3 is the third binding score, D4 is the fourth binding score, AV is the average score and S.D is the standard deviation

S/N	**7jkv**	**D1**	**D2**	**D3**	**D4**	**AV**	**S.D**
1	V7G	-8.4	-11.5	-11.5	-11.4	-10.7	1.5
2	Moxidectin	-7	-7	-7	-7.1	-7.0	0.0
3	Molnupiravir	-7.0	-7.0	-7.0	-7.0	-7.0	0.0
4	Ivermectin	-7.1	-6.9	-6	-7	-6.8	0.5
S/N	**5c8t**	**D1**	**D2**	**D3**	**D4**	**AV**	**S.D**
1	Molnupiravir	-7.9	-7.9	-7.9	-7.9	-7.9	0.0
2	SAM	-7	-7	-7	-7.1	-7.0	0.0
3	Moxidectin	-1.4	-1.4	-1.6	-1.4	-1.5	0.1
4	Ivermectin	7.6	7.6	4.3	7.5	6.8	1.6
S/N	**7d4f**	**D1**	**D2**	**D3**	**D4**	**AV**	**S.D**
1	H3U	-11	-11	-11	-11	-11	0
2	Ivermectin	-8.8	-9.1	-9.2	-9.2	-9.1	0.2

3	Moxidectin	-8.6	-8.8	-8.7	-8.7	-8.7	0
4	Molnupiravir	-6.8	-6.7	-6.8	-6.8	-6.8	0
S/N	**7jit**	**D1**	**D2**	**D3**	**D4**	**AV**	**S.D**
1	Y95	-12.8	-12.8	-12.8	-12.8	-12.8	0.0
2	Molnupiravir	-6.6	-6.6	-6.7	-6.7	-6.7	0.1
3	Moxidectin	-4.4	-4.4	-5.1	-4.5	-4.6	0.3
4	Ivermectin	-5.1	-2.2	-3.4	-3	-3.4	1.2
S/N	**7lm9**	**D1**	**D2**	**D3**	**D4**	**AV**	**S.D**
1	Ivermectin	-9	-8.5	-9	-9.1	-8.9	0.3
2	Moxidectin	-8.5	-8.5	-8.5	-8.5	-8.5	0.0
3	Molnupiravir	-6.9	-6.8	-6.9	-6.8	-6.9	0.1
4	EDO	-3.2	-3.2	-3.3	-3.2	-3.2	0.0
S/N	**5rlj**	**D1**	**D2**	**D3**	**D4**	**AV**	**S.D**
1	Molnupiravir	-6.3	-6.4	-6.3	-6.3	-6.3	0.4
2	VM4	-5.3	-5.4	-5.4	-5.3	-5.4	0.1
3	Ivermectin	6.1	10.4	4.2	4.4	6.3	2.9
4	Moxidectin	14.5	14.4	14.5	25.3	17.2	5.4
S/N	**7meq**	**D1**	**D2**	**D3**	**D4**	**AV**	**S.D**
1	Molnupiravir	-7.1	-7.1	-7.1	-7.1	-7.1	0.0
2	GBS	-6.5	-6.5	-6.5	-6.5	-6.5	0.0
3	Moxidectin	33.1	35.5	21.1	35	31.2	6.8
4	Ivermectin	35.1	38.6	26.8	35.5	34.0	5.0
S/N	**6vw1**	**D1**	**D2**	**D3**	**D4**	**AV**	**S.D**
1	Moxidectin	-6.7	-6.7	-6.7	-6.7	-6.7	0
2	Ivermectin	-6.2	-6.3	-6.3	-6.3	-6.3	0
3	Molnupiravir	-5.5	-5.5	-5.5	-5.5	-5.5	0
4	EDO	-2.7	-2.7	-2.7	-2.7	-2.7	0

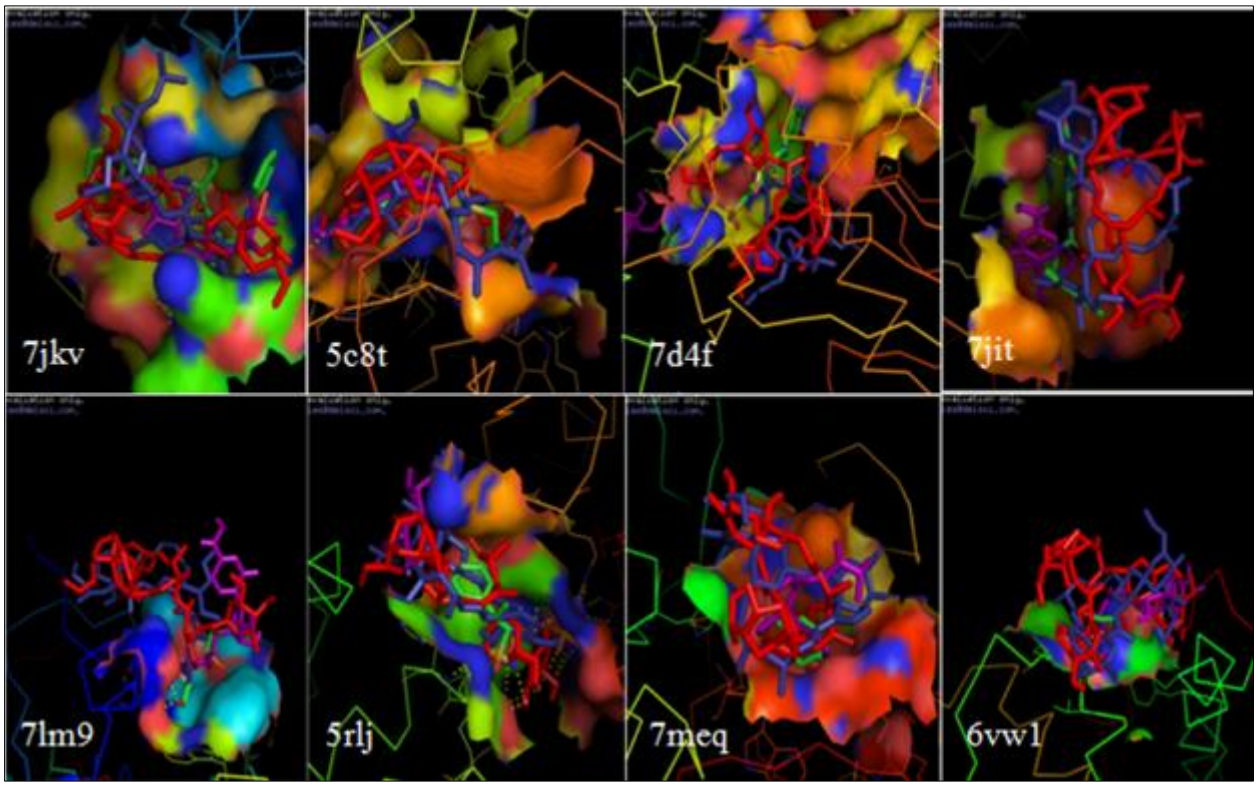

Figure 1 The snapshots of the drugs within the binding pocket for the molecular docking of the drugs against their receptors as seen in table 2

Table 3 Keys for the drugs on figure 1

Drug	Colour
Ivermectin	
Moxidectin	
Molnupiravir	
Reference ligand	

In Table 2; the various receptors of Sars-CoV-2 with their PDB codes were displayed showing the binding affinities of ivermectin, moxidectin and molnupiravir. From the table ivermectin and moxidection has good affinity against all targets except for the 5rlj and 7meq targets. The Mpro of SARS-CoV-2 with the PDB code of 7jkv it can be deduced that the reference ligand V7G has a higher binding affinity of -10.7 kcal/mol followed by Moxidectin (-7.0 kcal/mol), Molnupiravir (-7.0 kcal/mol) then Ivermectin (-6.8 kcal/mol). Therefore, it can be predicted that Moxidectin, Molnupiravir and Ivermectin have the ability to inhibit the cleaving of the viral polyprotein during replication and transcription.

In Figure 1; it can also be seen that ivermectin, moxidectin and molnupiravir are all in the binding pockets of the protein. It can then be predicted to elicit an action against SARS-CoV-2.

The associated human drug targets (7meq and 6vw1) that were used did not show good results especially for 7meq when compared with other targets used in the study.

3.2. Molecular Dynamics results

For the Molecular dynamics result, three of the receptors 7JIT, 7JKV and 5RLJ that were docked was selected. Following the list of command lines and after simulation runs for protein receptors, 7JIT, 7JKV and 5RLJ along with protein-ligand

complex for Ivermectin, Moxidectin and reference ligands of the receptors. The results gotten from the dynamics simulations are as follows;

3.3. Energy minimization results

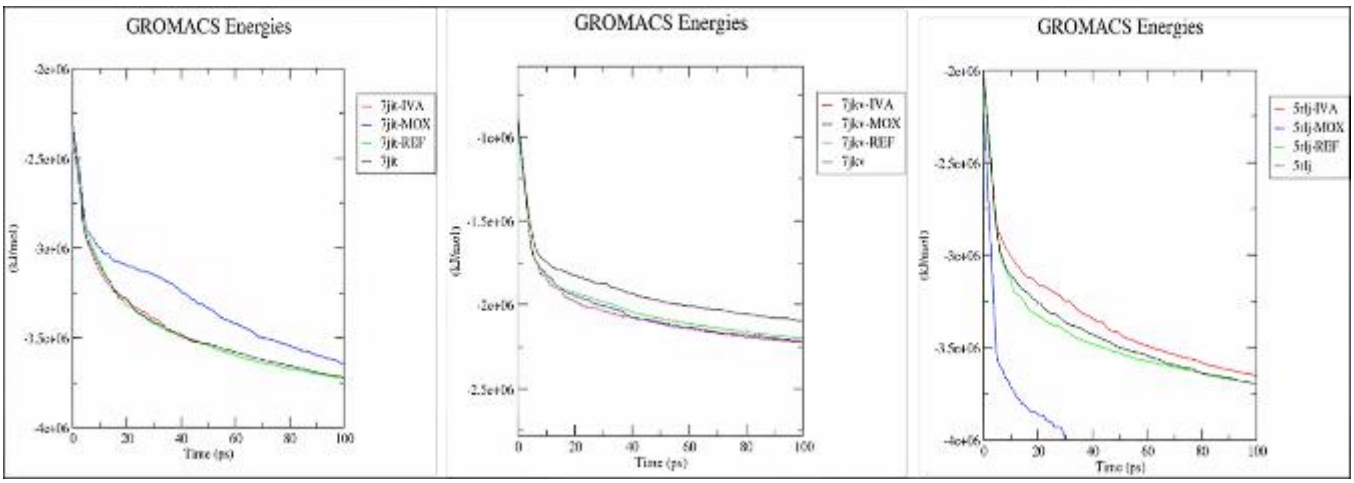

Figure 2 The energy minimization results of the Papain-like protease (7jit), Main protease (7jkv) and Helicase NSP13 (5rlj)

Energy minimization was done to bring the protein and Ligands to zero energy level so that there won't be excitation within the system. It is essential to determining the proper molecular arrangement in space since the drawn chemical structure is not energetically favorable [10], it ensures that the system has no steric clashes or inappropriate geometry

The figure above shows the energy minimization of solvated and neutralized molecular system. This indicates the successful removal of restraining forces in the molecular coordinates and systems at global energy minimum. To reduce the excited energy level to a more stable state. From the graphs, it can be seen that all systems were properly minimized. The more minimized the systems are the smaller the forces that will pull them apart or together and this enhances the simulation.

3.4. Position restraint dynamics simulation results

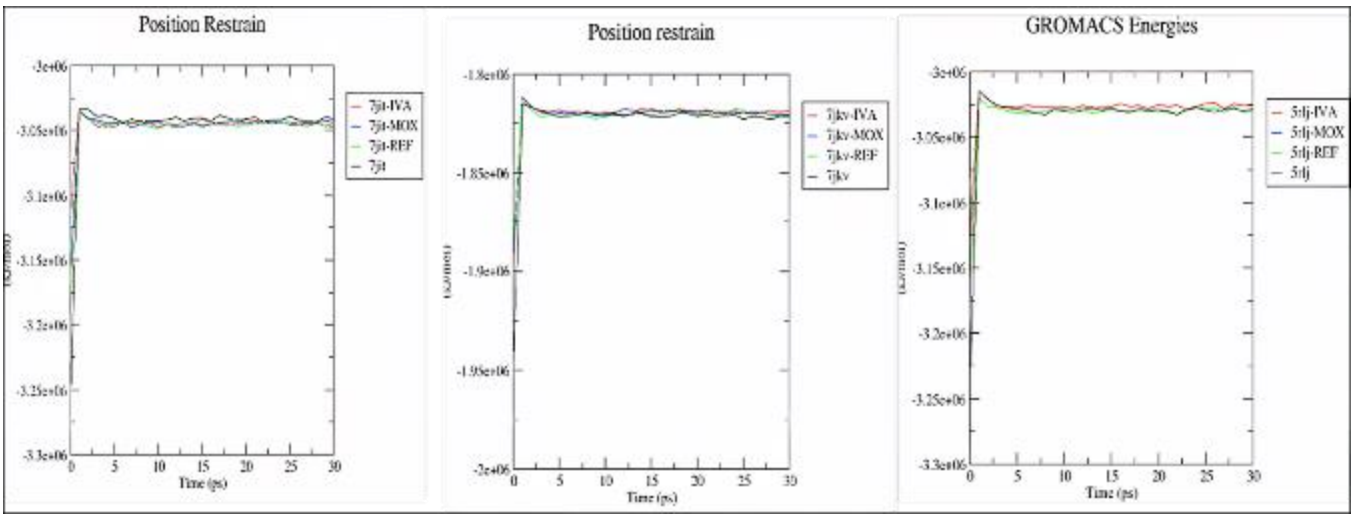

Figure 3 Position restrain dynamics simulation results of the drug target and ligands for the three receptors Papain-like protease (7jit), Main protease (7jkv) and Helicase NSP13 (5rlj)

A short molecular dynamics simulation is performed with harmonic position restraints on the heavy protein atoms. This allows solvents to equilibrate around the protein without disturbing the protein structure [11] it also aids to avoid drastic rearrangement of critical parts according to Gromacs 2023 documentation this in turns reduces fluctuations within the system.

Position restraints are used to restrain particles to fixed reference positions. They can be used during equilibration in order to avoid drastic rearrangements of critical parts (e.g. to restrain motion in a protein that is subjected to large solvent forces when the solvent is not yet equilibrated)

From figure 3, the proteins and ligands were restrained in one position, this occurred from 2 pico seconds.

3.4.1. Production run

Different results from the production run trajectories were computed from the production run. The results include: Stability Profile analysis, flexibility studies, radius of gyration and interaction.

3.4.2. Stability Profile analysis

Fig illustrates protein-ligand complex stability in terms of RMSD. The C-alpha RMSD of the stimulated protein over time is a reliable parameter to analyse the stability of the system.

Root Mean Square Deviation (RMSD) is used for measuring the difference between the backbones of a protein from its initial structural conformation to its final position [12] the lesser observed deviation, the more the stability of the system. From figure 3 above, as compared to the reference ligand Y95, Ivermectin and Moxidectin showed considerable stability in the binding pocket of 7JIT protein receptor with Ivermectin exhibiting more stability which ranged from 3800 picoseconds and throughout the simulation process, Moxidectin however exhibited stability 2000 picoseconds to 7500 picoseconds after which it returned to stability at 8200 picoseconds and throughout the rest of the simulation process.

From 7jkv results it is evident that the first 1900ps and 2100ps were considered as equilibration phase where slight structural re-organisation occurs for the simulations. The RMSD of the reference ligand in black colour showed varying degrees of fluctuation between 1ps to 4500ps of the simulation hence showing point of little instability. The RMSD of the reference ligand was more stable than that of the protein; from times 4500ps to 10,000ps the ligands exhibited high stability. Moxidectin in blue showed higher stability than Ivermectin in red.

From 5rlj,having the protein in complex with the ligand, the RMSD of the reference ligand represented in black colour, showed varying degrees of fluctuations at 2500 pico seconds to around 5500 picoseconds hence, showed points of instability. The RMSD of the protein showed more stability than that of the reference ligand. However, the RMSD of ivermectin was more stable than that of the reference ligand followed by the protein and then moxidectin and the reference ligand respectively. This is seen at point 4000 pico seconds to 7000 pico seconds in ivermectin. Certain degrees of instabilities occurred but notwithstanding, all simulations exhibited stable total energy trajectories.

It can be deduced that from the graph that ivermectin in red and moxidectin in blue is more stable than the reference ligand.

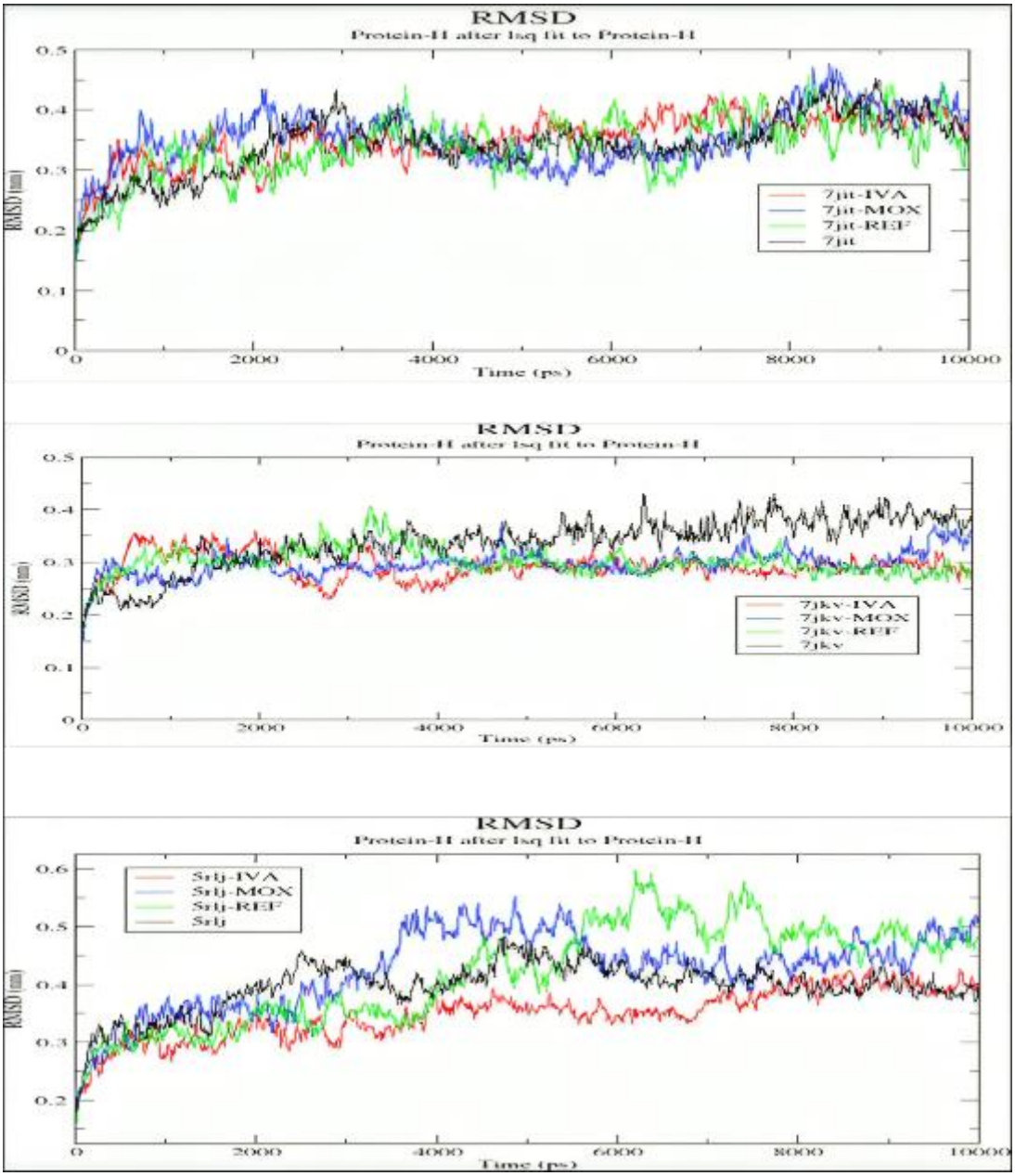

Figure 4 RMSD plot of the molecular dynamics simulation of the drug target and ligands

3.4.3. Radius of gyration

Protein Compactness is the ratio of the accessible surface area of a protein to that of the ideal sphere of the same volume [13]. The Compactness of the system is measured in Radius of gyration (Rg) and indicates the ligand's ability to remain stable in the binding pocket of the protein receptor during the simulation process [15]. Gyration implies the act of turning or whirling around a fixed center.

From the gyration plot in figure 4 above, in 7JIT, the referenced ligand exhibited highest compactness being the most compact from 5000 picoseconds and throughout the system which instigates its ability to remain stable within the system, among the drug targets, Moxidectin exhibited higher compactness than Ivermectin with high compactness from 7000 picosceonds and throughout the system which implies that even with being the less stable among the ligands, Moxidectin has the highest probability of remaining stable with longer time.

Ivermectin on the other hand exhibited high compactness from 800 picoseconds to 3400 picoseconds after which it spiraled until 5000 picoseconds to 6700 picoseconds and it spiraled once again until 7500 picoseconds to which it remained compact until the end of the simulation process.

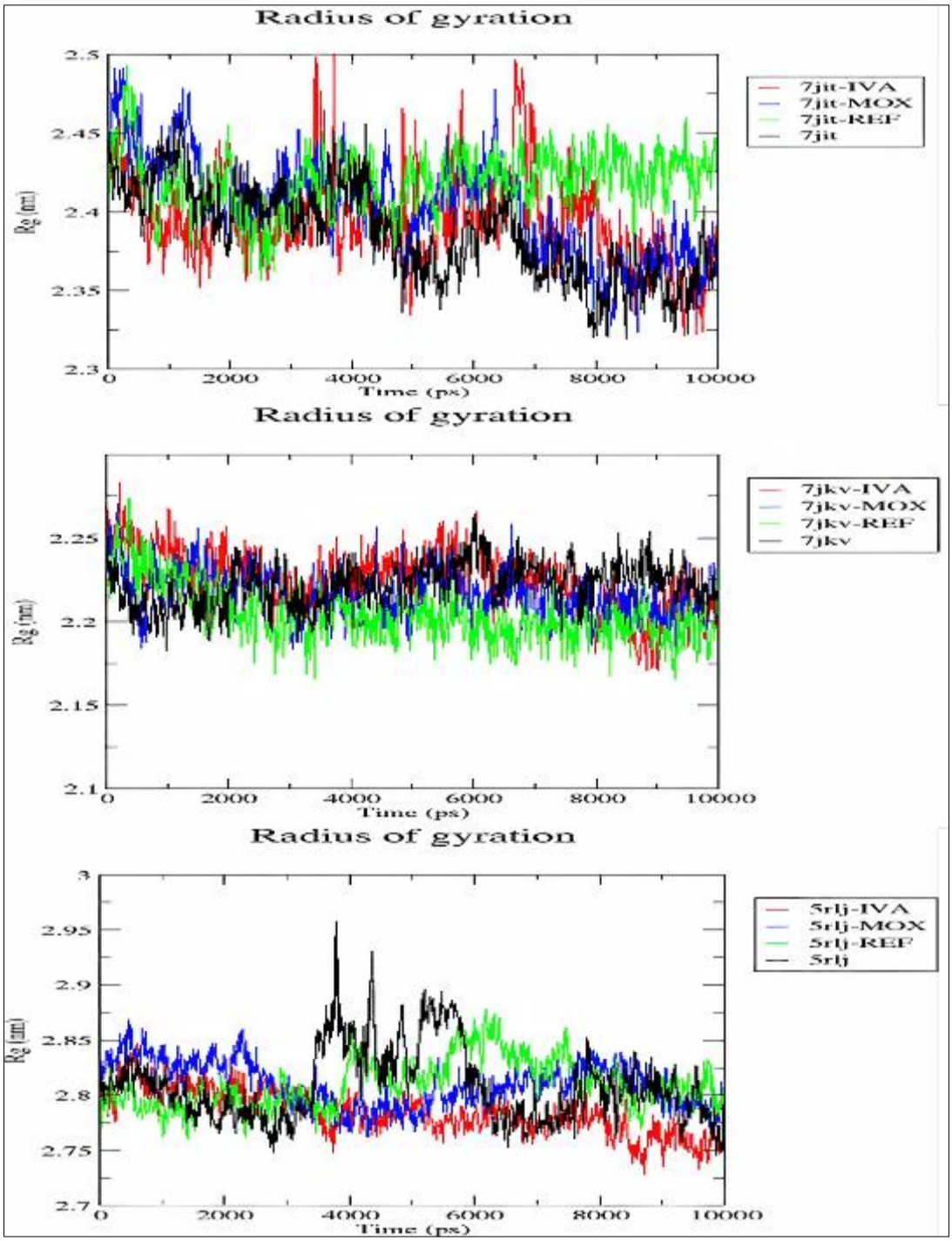

Figure 5 Radius of gyration plot

From the results in 7JKV above the protein and the ligand exhibited high compactness which predicts high stability.

From the results in 5RLJ above, the unstable structure of the protein and the reference ligand simulations between 3400 pico seconds to 6000 pico seconds for the protein and between 4000 pico seconds to 6700 pico seconds for the reference ligand showed lesser compactness.

However, Moxidectin showed more compactness followed by ivermectin, reference ligand and protein respectively.

3.4.4. Flexibility Profile analysis

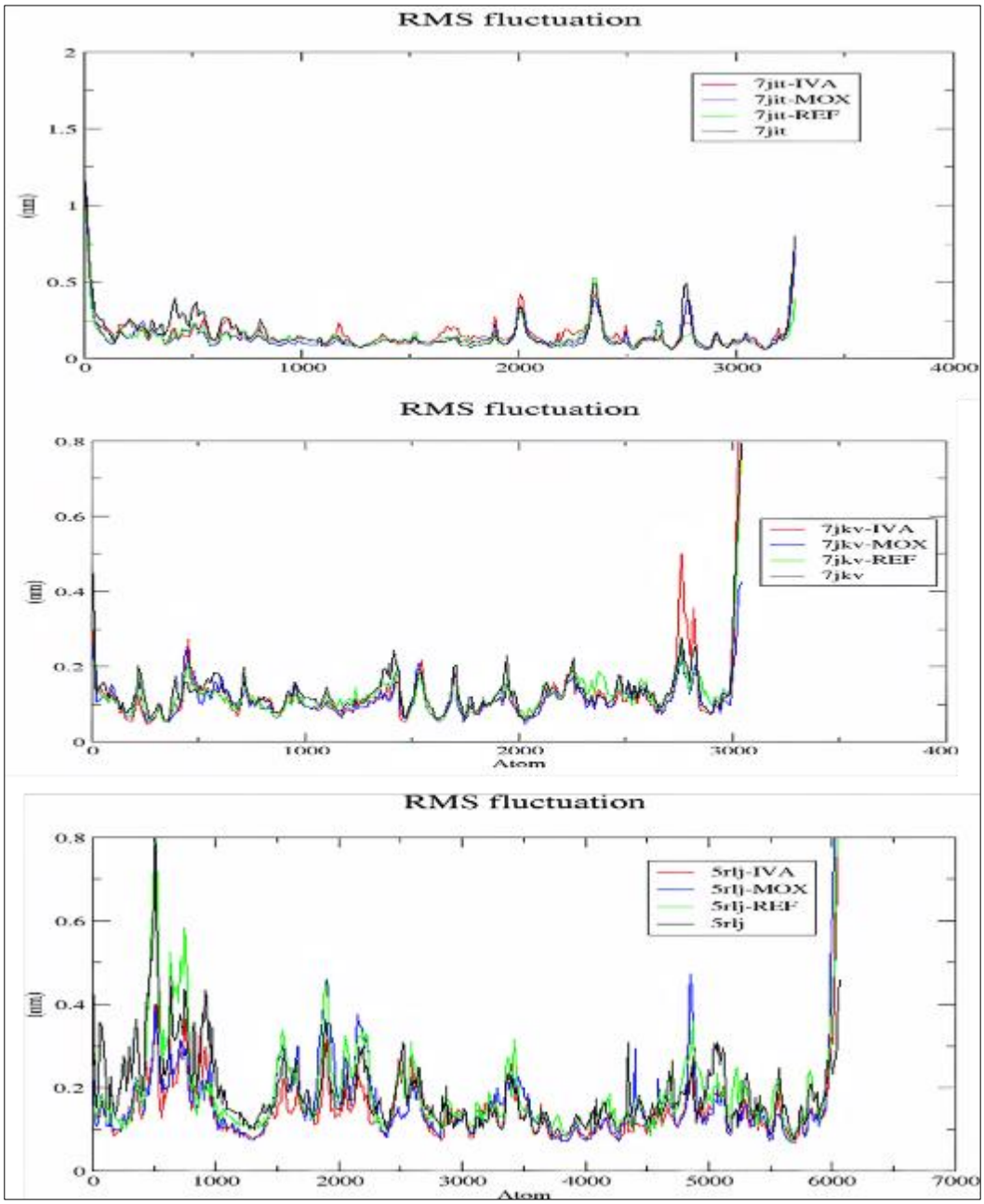

Figure 6 RMSF Plot of the molecular dynamics simulation of the drug target and ligands

Root Mean Square Fluctuation is a measure of the displacement of a particular atom or group of atoms, relative to the reference structure, averaged over the number of atoms. It is used for the analysis of time-dependent motions of the structures [14]. From the results in 7JIT, In the RMS fluctuation plot, the system was reasonably stable between 1500 atoms and 2000 atoms which indicates that above 2000 atoms, some amino acid residues caused fluctuation within the system with the least fluctuations between 800 atoms and 1800 atoms

From the results in 7JKV,from point 1 atom to 2700 atoms the system was more stable than from point 2800 atoms to 3100 atoms. It can also be seen that Moxidectin exhibited better stability than Ivermectin.

From the results in 5rlj,in the graph above, it can be deduced that there were a lot of fluctuations which might be due to the presence of amino acid residues in the system. However, there was still stability at points 3600 pico seconds to 4600 pico seconds.

It can be commented that ivermectin and moxidectin showed certain levels of stability and can be predicted to be possible antivirals for the treatment of COVID-19 although further studies should be done to ascertain this.

4. Conclusion

From the study, Ivermectin and moxidectin is predicted to have activity against SARS-CoV-2 replication due to the ability to bind with Papain-like protease (7jit), Main protease (7jkv) and Helicase NSP13 (5rlj)and maintain stability in its binding pocket, with Ivermectin exhibiting higher stability

Moxidectin may have been less stable than ivermectin as seen in the RMSD plot, but it exhibited an higher compactness in the gyration plot radius thus it is predicted to be able to maintain stability for longer and its higher binding affinity gotten from the binding score is also a factor to its activity

It can then be concluded that Ivermectin and Moxidectin, has good activity against SARS-CoV-2 especially the Main Protease receptor which is responsible for viral transcription and replication. Sotherefore, in the treatment of SARS-CoV-2 infection it is worthy to note when using ivermectin or moxidectin that it will inhibit viral transcription and replication of the virus making it a good agent for the treatment of SARS-CoV-2 infection.

Recommendation

Clinical trials should be done to ascertain the appropriate dose at which activity of Ivermectin and Moxidectin will be effective and the extent of its activity or duration, possible side effects and adverse effects.

Compliance with ethical standards

Disclosure of conflict of interest

The authors have no conflicts of interest to declare. All co-authors have seen and agree with the contents of the manuscript. We certify that the submission is original work and is not under review at any other publication.

References

[1] Shyr, Z. A., Gorshkov, K., Chen, C. Z., & Zheng, W. (2020). Minireview Drug Discovery Strategies for SARS-COV-2. October, 127–138. https://doi.org/10.1124/jpet.120.000123

[2] Emmanuel Chuks Oranu, Adanna Ijeawele, Roselyn Nneka Egbuna, Ebere Ifejirika Ezeonyi, Chukwubuikem C Okolo and Ikemefuna C Uzochukwu (2023). Previous and potential mutations of Sars-cov-2 receptors and their interaction with known inhibitors. GSC Biological and Pharmaceutical Sciences, 2023, 24(03), 234–246

[3] Gierer S, Bertram S, Kaup F, Wrensch F, Heurich A, Krämer-Kühl A, Welsch K, Winkler M, Meyer B, Drosten C, (2013). The spike protein of the emerging betacoronavirus EMC uses a novel coronavirus receptor for entry, can be activated by TMPRSS2, and is targeted by neutralizing antibodies. JVirol 87:5502–5511.

[4] Hofmann, H., Pyrc, K., Hoek, L. Van Der, Geier, M., Berkhout, B., & Po, S. (2005). Human coronavirus NL63 employs the severe acute respiratory syndrome coronavirus receptor. 102(22). https://doi.org/10.1073/pnas.0409465102

[5] Satarker, S., & Nampoothiri, M. (2020). Structural Proteins in Severe Acute Respiratory Syndrome Coronavirus-2. Archives of Medical Research, 51(6), 482–491. https://doi.org/10.1016/j.arcmed.2020.05.012

[6] Yoshimoto, F. K. (2020). The Proteins of Severe Acute Respiratory Syndrome Coronavirus - 2 (SARS CoV - 2 or n - COV19), the Cause of COVID - 19. The Protein Journal, 39(3), 198–216. https://doi.org/10.1007/s10930-020-09901-4

[7] Alok, D., Ramakant, Y., & S, A. V. (2020). Ivermectin : Potential Role as Repurposed Drug for COVID-19. 27(May), 154–158.

[8] Awad, H., Hassan, B., Dweek, S., Aboelata, Y., Rawas-qalaji, M., & Ahmed, I. S. (2022). Repurposing Potential of the Antiparasitic Agent Ivermectin for the Treatment and/or Prophylaxis of COVID-19. Pharmaceuticals, MDPI, 1–18.

[9] Eweas, A.F.; Alhossary, A.A.; Abdel-Moneim, A.S. Molecular Docking Reveals Ivermectin and Remdesivir as Potential Repurposed Drugs AgainstSARS-CoV-2. Front. Microbiol. 2020, 11, 592908.

[10] Kunal Roy, Rudra Narayan Das, Supratik Kar (2015) understanding the basics of QSAR for application in Pharmaceutical sciences and risk assessment. Computational chemistry chapter 5. https://doi.org/10.1016/B978-0-12-801505-6.00005-3

[11] Oliver Beckstein (2013). Position restraints MD. Practical 13:ADK Tutorial 1.0 documentation topic 4

[12] Aier, I. et al. Structural insights into conformational stability of both wild-type and mutant EZH2 receptor. Sci. Rep. 6, 34984; doi:10.1038/srep34984 (2016)

[13] Tuckerman, M. E., & Martyna, G. J. (2000). Understanding Modern Molecular Dynamics : Techniques and Applications. 159–178.

[14] Leandro Martinez (2015) Mar; 27(3): e0119264. Doi: 10.1371/journal.pone.0119264. PMCID: PMC4376797. PMID: 25816325

[15] Galzitskaya OV, Bogatyreva NS, Ivankov DN. Compactness determines protein folding type. J Bioinform Comput Biol. 2008 Aug; 6(4):667-80. Doi: 10.1142/s0219720008003618. PMID: 18763735

[16] Hwa, M., Chaudhary, K. K., & Mishra, N. (n.d.). A Review on Molecular Docking : Novel Tool for Drug Discovery Related papers A Review on Molecular Docking : Novel Tool for Drug Discovery.

[17] LG Ferreira, RN dos Santos, G Oliva, AD Andricopulo. Molecular docking and structure-based drug design strategies. Molecules. 2015; 20: 13384-13421

[18] López-Vallejo, F.; Caulfield, T.; Martínez-Mayorga, K.; Giulianotti, M.A.; Houghten, R.A.; Nefzi, A.; Medina-Franco, J.L. Integrating virtual screening and combinatorial chemistry for accelerated drug discovery. Comb. Chem. High Throughput Screen. 2011, 14, 475–487.

[19] Marak, B. N. (n.d.). Step toward repurposing drug discovery for COVID-19 therapeutics through in silico approach. https://doi.org/10.1002/ddr.21757

[20] Masoudi-sobhanzadeh, Y. (2020). Computational-based drug repurposing methods in COVID-19. 10(3), 205–206. https://doi.org/10.15171/bi.2014.008