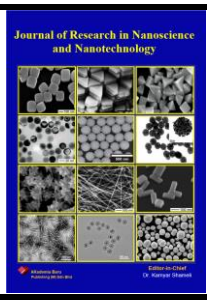
Penerbit Akademia Baru

Journal of Research in Nanoscience and Nanotechnology

Journal homepage:
http://akademiabaru.com/submit/index.php/jrnn/index
ISSN: 2773-6180



Molecular Docking Studies of Potential Drugs for Covid-19 Targeting on the Coronavirus Hemagglutinin Esterase

Farhana Abu Samah[1], Siti Zalita Talib[2], Nur Ainun Mokhtar[1], Nurulbahiyah Ahmad Khairudin[1,*]

[1]Malaysia-Japan International Institute of Technology, Universiti Teknologi Malaysia, Jalan Sultan Yahya Petra, 54100, Kuala Lumpur, Malaysia
[2]Pusat Pengurusan Makmal Universiti Universiti Teknologi Malaysia, Jalan Sultan Yahya Petra, 54100, Kuala Lumpur, Malaysia
* Correspondence: r-bahiah@utm.my
https://doi.org/10.37934/jrnn.4.1.1318

ABSTRACT

The goal of this project is to contribute to the search for potential drug candidates for Covid-19 using molecular docking simulation. The Covid-19 receptor used in this study was coronavirus hemagglutinin esterase and the drugs were spirosolane, oridonin and silymarin. The protein and the ligands were downloaded from the protein data bank (PDB) and PubChem website, respectively. Using Autodock Tools, all downloaded proteins and ligands were then prepared. AutoDock Vina was used to perform molecular docking. The best binding sites were selected based on the ranking of binding energy or binding affinity given in kcal/mol. It was found that all three ligands produced low binding energies between -8 to -10 Kcal/mol. The analysis on molecular interactions were carried out to investigate the formation of hydrogen bonds and hydrophobic interactions in all docked conformations and silymarin was found to be the best ligand out of the three in terms of binding to the coronavirus hemagglutinin esterase.

Keywords:
Covid-19, Hemagglutinin Esterase, Molecular Docking, PDB, Autodock

Received: 23 August 2021 **Revised: 21 September 2021** **Accepted: 26 September 2021** **Published: 17 October 2021**

1. Introduction

Around 2019, China reported an outbreak of pneumonia in Wuhan known as severe acute respiratory syndrome coronavirus 2 or SARS-CoV-2 (Covid-19) [1-3]. This pandemic is by far the most serious, but not the first human-related SARS outbreak [4]. The Covid-19 virus has high transmissibility and has the ability to cause societal and also economic disruption [5]. SARS-CoV-2 is a single stranded RNA-enveloped virus [6]. This virus is composed of crown-shaped peplomers with a diameter of 80-160 nm, with only single-strand, and is around 30 kilo meters in length [7]. It has a positive polarity RNA molecule with a 5' cap and a 3' Poly-A tail. The SARS-CoV-2 spike protein

interacts on its surface with the cellular receptor ACE2 (angiotensin-converting enzyme 2), which is extensively expressed in a variety of cell types in human tissues as described by [8]. The problem faced is that there is still no promising treatment to fight this epidemic that have been faced by the world since 2019. Many researches have been conducted either experimentally or computationally to better understand the behavior of this virus and its mechanism of actions. Previous molecular docking studies have revealed a few potential ligands or commercial drugs that could act as potentials anti-Sars-Cov-2 agents [9-13]

Thus, the purpose of this study is to investigate the effectiveness of the binding of three different drugs (spirosolane, oridonin, silymarin) with the coronavirus hemagglutinin esterase using molecular docking simulations by looking at the binding energy and the molecular interactions between the ligand and the receptor. It is hoped that the outcome of this research could contribute in the search of potential drug candidates for Covid-19 using molecular docking simulation approach.

2. Materials and Methods

Figure 1 shows the summary of the molecular docking simulation carried out in this study. The structures of the protein receptor, hemagglutinin esterase coronavirus was downloaded from The Protein Databank (PDB id: HKU1) and Kollman charges were added to the protein [12]. Biovia software was used to identify the binding site of the protein. The ligands used in this study are spirosolane, oridonin and silymarin in which the structures were obtained from PubChem and saved in PDBQT format [13]. The most critical step in molecular docking is to assign the grid parameters because it navigates the ligand to the protein's binding site. Centre grid box for all three ligands were set to x = 128.793, y = 128.798 and z =129.182. Autodock Vina was used to run the docking simulation [14]. The molecular interactions analyses were carried out using the software LigPlot [15].

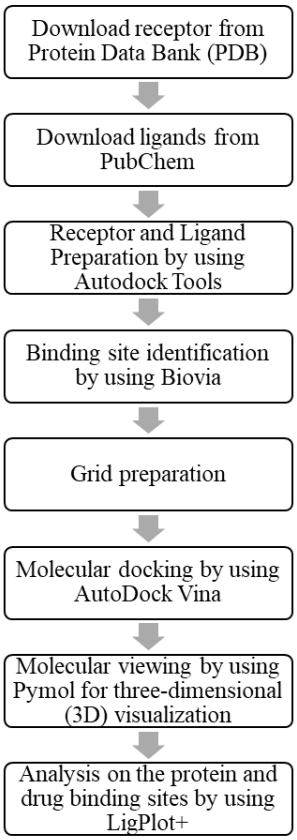


Figure 1. Molecular Docking Procedure.

3. Results and Discussion

3.1 Binding Energy of Docked Conformation

Table 1 shows the top 10 docked conformation between hemagglutinin esterase-spirosolane (Glut-Spiro, hemagglutinin esterase-oridonin (Glut-ori), hemagglutinin esterase-silymarin (Glut-marin). It was shown that Glut-Spiro complex had the lowest energy compared to Glut-ori and Glut-marin with the docked energy values of -10.3 Kcal/mol compared to -8.1 and -9.6 Kcal/mol, respectively. The more negative the energy, the better the ligand is for the receptor and the more stable the complex is. The difference in binding energy between Glut-spiro and Glut-marin is only 0.7 Kcal/mol. Both drugs can be considered as the best ligands for this current receptor. Figure 2, Figure 3 and Figure 4 show the surface presentation of Glut-spiro for the former and Glut-marin, for the latter, in which it can be seen that the ligand was docked in the vicinity of the active site of hemagglutinin esterase.

Table 1. Binding Energy of the Docked Conformations.

No.	Glut-spiro Kcal/mol	Glut-ori Kcal/mol	Glut-marin Kcal/mol
1	-10.3	-8.1	-9.6
2	-10.3	-8.1	-9.6
3	-9.5	-7.5	-9.4
4	-9.5	-7.5	-9.4
5	-9.4	-7.5	-9.1
6	-9.3	-7.5	-9.1
7	-9.3	-7.4	-8.9
8	-8.9	-7.3	-8.9
9	-8.8	-7.3	-8.7
10	-8.7	-7.3	-8.5

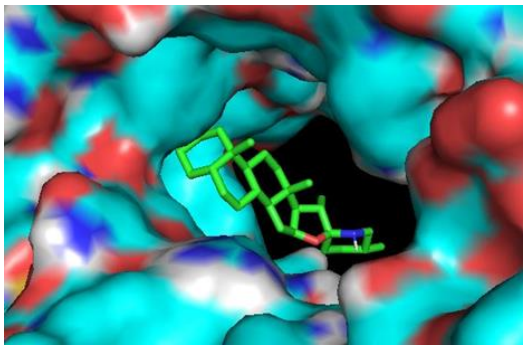


Figure 2. Surface presentation of the docked glut-spiro complex. The drug spirosolane is shown as stick model.

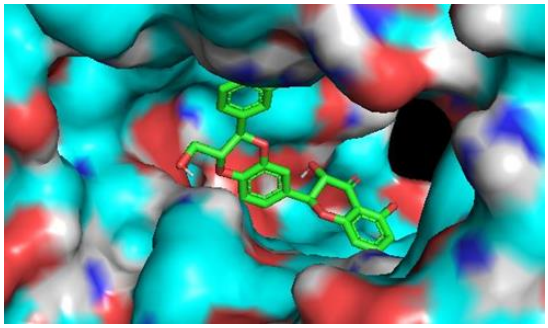


Figure 3. Surface presentation of the docked glut-marin complex. The drug silymarin is shown as stick model.

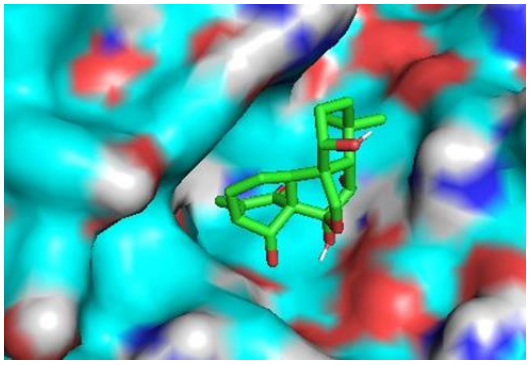


Figure 4. Surface presentation of the docked glut-ori complex. The drug oridonin is shown as stick model.

3.2 Binding Interactions of Protein and Drug Candidates

Table 2 shows the summary of the formations of hydrogen bonds and hydrophobic interactions for the three docked complexes. The simulation produced 20 docked complexes but only the first five were chosen as they showed the lowest binding energy compared to the rest. It was shown that the complex Glut-spiro had no hydrogen bonds compared to Glut-Ori and Glut-marin. This is in accordance with the previous finding by Patel and friends [9]. They also conducted molecular docking of similar protein with spirosolane and found that there was zero formation of hydrogen bonds. The presence of hydrogen bonds and hydrophobic interactions are the indicators of the presence of binding activities between the receptor and the ligand. The complex with the highest number of both hydrogen bonds and hydrophobic interactions was Glut-marin in which the values are 8 and 10, respectively which signifies the strongest binding among the three docked complexes.

Table 2. Hydrogen bonds and hydrophobic interactions for the docked complexes.

Drugs	Complex	Hydrogen Bonding	Hydrophobic Interactions
Spirosolane	1	0	8
	2	0	8
	3	0	6
	4	0	6
	5	0	6
Oridonin	1	2	7
	2	2	7
	3	2	8
	4	2	8
	5	1	7
Silymarin	1	3	10
	2	4	10
	3	8	7
	4	5	8
	5	5	7

Figure 5 shows the hydrogen bond interactions and hydrophobic interactions for the complex Glut-marin. The hydrogen bonds are shown as green dotted lines while the hydrophobic interactions are represented by the "eyelid". The residues Ser205(A), Gly208(B), Val206(A), Val206(B), Ser205(B) and Tyr221(A) of hemagglutinin esterase were found to form hydrogen bonds with the ligand, silymarin as shown in the figure. The residues that formed hydrophobic interactions with the ligand were Ile220(B),Tyr207(A), Gly208(A), Tyr207(B),Ile220(A), Tyr221(B), Ile222(B).

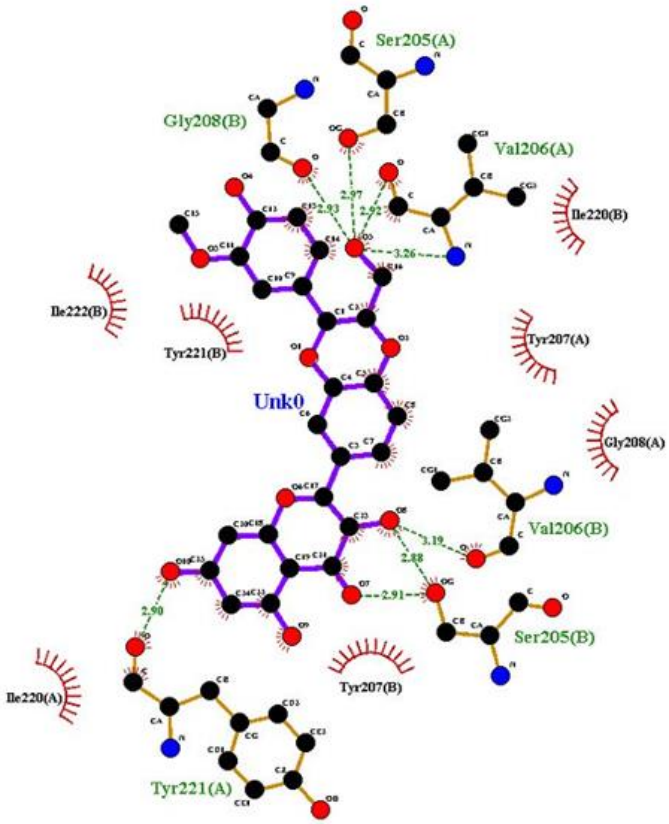


Figure 5. Hydrogen bonding (as green dotted lines) and hydrophobic interactions (eyelid shape) between hemagglutinin esterase and silymarin.

4. Conclusions

From the analyses, it can be concluded that out of the three drugs, spirosolane formed the most stable complex with hemagglutinin esterase followed by silymarin and oridonin. However, the hydrogen bond analyses indicated that silymarin formed better hydrogen bonding network with hemagglutinin esterase compared to the other two drugs. It is recommended to conduct a real experimental study to investigate the effectiveness of spirosolane towards the coronavirus hemagglutinin esterase as one of the future work.

Acknowledgement

A big thank you to the laboratory of Chemical Engineering Conversion and Application (CheCA) from MJIIT, UTMKL for providing support and space for the student to do her work.

References

1. Pascarella, G., A., Strumia., A., Piliego., C., E. "COVID-19 diagnosis and management: a comprehensive review." *J. Intern. Med.* 2(282) (2020): 192- 206. DOI: https://doi.org/10.1111/joim.13091

2. Horby, P., W., Marfham., M., Bell., J., J. "Lopinavir-ritonavir in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial." *Lancet* 10259 (396)(2020): 1345-1352. DOI: https://doi.org/10.1016/S0140-6736(20)32013-4
3. Tang, B., Bragazzi., N., L., Q., Tang., J. "An updated estimation of the risk of transmission of the novel (2019-nCOV)." *Infect. Dis. Model.* 5 (2020): 248-255. DOI: http://dx.doi.org/10.1016/j.idm.2020.02.001
4. Hui, David S., Esam I. A, Tariq A. M, Francine N, Richard K, Osman D, Giuseppe I et al. "The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health—The latest 2019 novel coronavirus outbreak in Wuhan, China." *Int. J. Infect. Dis.* 91 (2020): 264-266. DOI: https://doi.org/10.1016/j.ijid.2020.01.009
5. Huang, C, Yeming W, Xingwang L, Lili R, Jianping Z, Yi, Li Z et al. "Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China." *Lancet* 395, no. 10223 (2020): 497-506. DOI: https://doi.org/10.1016/S0140-6736(20)30183-5
6. Lu, R., Zhao, X., Li, J., Niu, P., Yang, B., Wu, H.,Tan, W. "Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding." *Lancet* 395(10224) (2020): 565-574. DOI: https://doi.org/10.1016/s0140-6736(20)30251-8
7. Klasse, P. J., and John P. Moore. "Antibodies to SARS-CoV-2 and their potential for therapeutic passive immunization." *eLife* 9 (2020): e57877. DOI: https://doi.org/10.7554/eLife.57877
8. Zhou, Y, Binqing F, Xiaohu Z, Dongsheng W, Changcheng Z, Yingjie Q, Rui S, Zhigang T, Xiaoling X, and Haiming W. "Pathogenic T-cells and inflammatory monocytes incite inflammatory storms in severe COVID-19 patients." *Nat. Sci. Rev.* 7 no. 6 (2020): 998-1002. DOI: https://doi.org/10.1093/nsr/nwaa041
9. Patel, C.N., Kumar, S.P., Pandya, H.A. et al. "Identification of potential inhibitors of coronavirus hemagglutinin-esterase using molecular docking, molecular dynamics simulation and binding free energy calculation." *Mol. Div.* 25 (2021): 421–433. DOI: https://doi.org/10.1007/s11030-020-10135-w
10. Abdellatiif M.H., Ali, A, Ali, A , Hussien, M.A. "Computational studies by molecular docking of some antiviral drugs with COVID-19 receptors are an approach to medication for COVID-19". *Open Chem.* 19 (2021): 245-264. DOI:https://doi.org/10.1515/chem-2021-0024
11. Khan, S.A., Komal Z, Sajda A, Reaz U, and Zaheer U. "Identification of chymotrypsin-like protease inhibitors of SARS-CoV-2 via integrated computational approach." *J. Biomol. Struc. Dyn.* 39, (2021): 2607-2616. DOI: https://doi.org/10.1080/07391102.2020.1751298
12. Berman, Helen M., John Westbrook, Zukang Feng, Gary Gilliland, Talapady N. Bhat, Helge Weissig, Ilya N. Shindyalov, and Philip E. Bourne. "The protein data bank." *Nucleic Acids Res.* 28, (2000): 235-242. DOI: https://doi.org/10.1093/nar/28.1.235
13. Kim, Sunghwan, Paul A. Thiessen, Evan E. Bolton, Jie Chen, Gang Fu, Asta Gindulyte, Lianyi Han et al. "PubChem substance and compound databases." *Nucleic Acids Res.* 44, (2016): D1202-D1213. DOI: https://doi.org/10.1093/nar/gkv951
14. Trott O, Olson A.J. "AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading." *J Comput. Chem.* 31(2010):455-461. DOI: https://doi.org/10.1002/jcc.21334
15. Wallace, A. C., R. A. Laskowski, J. Singh, and J. M. Thornton. "Molecular recognition by proteins: protein-ligand interactions from a structural perspective." *Biochem. Soc. Trans.* (1996): 280-284. DOI: http://doi.org/10.1042/bst0240280