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Research Article

Molecular dynamics simulation study on the drug discovery in covid-19 disease

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ABSTRACT

In this study, drug discovery of SARS-CoV-2 nsp-16 effective in Coronavirus (COVID-19) has been accomplished by pharmacophore-based virtual screening among some analogs (FDA approved drugs) and marine natural plants (MNP). The comparison of the binding energies and the inhibition constants was determined using molecular docking method. Between selected drugs, three compound were selected for further investigation using the molecular dynamics simulations. The results indicated that Ibrutinib and Idelalisib are oral medications while Kumusine, with proper hydrophilic and solubility properties, is an appropriate candidate for nsp-16 inhibitor and can be effective to control COVID-19 disease. It seems that Kumusine due to its better drug properties including the highest binding, the ability of destroying the secondary structure of the protein can be proposed as the best drug candidate among screened drugs in this research, for further investigations.

Keywords: Coronavirus (COVID-19); SARS-CoV-2 nsp-16; molecular dynamics simulations; Kumusine.

1. Introduction

Coronavirus (COVID-19) was first reported in December 2019 in China. Previously, some members of the virus family, such as (SARS or MERS)-CoV caused acute respiratory illness in humans [1,2] which among them, SARS-CoV-2 is the newest group of this family and due to mutations in the receptor binding domain (RBD), its spike protein introduces itself as a potent respiratory pathogen and causes high binding of ACE2 receptors in humans [3,4]. During this period, many researchers from around the world have conducted basic studies related to this disease, despite all these extensive efforts, so far no useful treatment has been discovered [5]. Recently, various studies have been conducted to discover the effective drug for SARS-CoV-2 using this method [6-8] in parallel with using lots of clinical drugs [9,10]. In this study, the nonstructural protein nsp-16 (S-adenosyl-l-methionine (SAM)-dependent 2^0-O-MTase) was used as the target, in which its activity is regulated by nsp10 binding and prevents virus detection by cell innate immunity mechanisms consequently. Therefore, significant antiviral responses to SAM analogues such as sinefungin via the SAM binding site and activity inhibition of 2-O-MTase of nsp-16 are expected [11,12]. Thus, if a suitable drug can be found to inhibit the activity of this protein, the immune system will be able to detect and eliminate this virus, swiftly. Recently, some researchers have identified the promising drug candidates against NSP16 of SARS-CoV-2 through computational drug repurposing study [13]. This study attempts to introduce some effective nsp-16 inhibitors among some compounds by pharmacophore-based virtual screening and drug design approaches such as molecular docking and molecular dynamics simulation (MD) that play a significant role in understanding the biological systems, recently [14].

2. Experimental

All computation in this study was performed using by molecular docking and molecular dynamics simulations (MD). Molecular docking was done by using Auto-Dock 4.2 software

[15] to find the appropriate binding site, binding energies and inhibition constants of a ligand in complexes with the protein. The structure of the receptor was created using Polak-Ribiere conjugate gradient algorithm and AMBER95 force field by Hyper Chem software and then optimized [16,17]. By removing all water molecules and adding the missing hydrogen atoms, Kollman united atom charges and polar hydrogens, then by merging non-polar hydrogens to the corresponding carbon atoms, and finally by assigning desolvation parameters to each atom, grid box was built. The box size was adjusted to 48 X, 48 Y and 50 Z grid points, with spacing between grid points kept at 0.375 Å and the coordinate of central grid point of maps was set to 8.278 x, 14.333 y and 8.250 z points. To find the best conformers, Lamarckian genetic algorithm was used. The selected structures from molecular docking between nsp-16 protein and the studied drugs were placed in the path of molecular dynamics simulation calculations for more investigations. The topology file for studied drugs was created by Automated Topology Builder (ATB) server [18]. All processes of the simulations were accomplished using the newest version of GROMACS package by gromos 53a6 force field. The simulation boxes were fulfilled with a SPC/E model of water and by adding appropriate numbers of sodium or chlorine ions, the neutralization of the simulation system was performed [19]. After that, energy minimization process was performed by the steepest descend algorithm. Then, in equilibrium process, NVT ensemble for temperature and NPT ensemble for pressure were coupled in 310K and 1bar, respectively, using v-rescale thermostat [20] and Parinello-Rahman barosta [21]. LINCS algorithm was used for all bonds. The cut off was 1nm for Electrostatics and van der Waals interactions. Finally, leap frog algorithm was exerted for production process of MD simulations [22].

3. Results and discussion

Molecular docking method is one of the powerful tools to investigate the ligand binding interactions at the active site of the substrates [23]. In this study, the interactions that

established after docking the drugs against COVID-19 nsp-16. The binding energies, inhibitory constants has been reported in Table 1. Furthermore, Sinefungin as a known inhibitor of nsp 16 was docked to compare with selected compounds. As shown in Table 1, Ibrutinib, Idelalisib and Kumusine with more negative binding energy and the lowest inhibition constant was selected for more molecular interaction investigations by molecular dynamics simulation study. Recently, computational methods such as molecular dynamics simulation have made a lot of progress to predict the protein-drug binding parameters [24-26]. In order to more accurately investigate the extent of changes in protein structure in combination with studied drugs, molecular dynamics simulations were performed for 60 ns. In order to further investigate the accuracy of the simulation, the root-mean-square deviation (RMSD) of the protein backbone as a depending on time for the free protein and protein in complex with mentioned drugs were performed and result. Dictionary of the Secondary Structure of the Protein (DSSP) is one of the most important analyses to investigate the secondary structure of the proteins [27]. Dssp analysis show that in the protein complexes to Kumusine, in several regions of protein, the secondary structures of alpha helix and beta sheets are destroyed. These findings indicating the adverse effects of the drugs on the protein secondary structures.

Table 1. Binding energies, inhibitory constants, and type of residues involved in binding selected drugs to NSP16.

Ligand	$\Delta G_{binding}$ (kcal.mol^{-1})	Inhibition Constant (K_i)	H-Bond Interaction
Cladribine	-6.79	10.49 µM	Asp 6897, Cys 6913, Tyr 6930
Clofarabin	-6.05	36.77 µM	Tyr 6930, Cys 6913, Gly 6911, Leu 6898
Tubercidin	-6.33	22.78 µM	Tyr 6930, Asp6897, Leu6898

7-Nitrobenzoxadiazole-6-Aminohexanoic acid	-5.53	88.7 µM	Cys 6913, Tyr 6930, Asp 6931
2-deoxyadenosine	-6.02	38.65 µM	Tyr 6930, Asp 6897
Ibrutinib	-8.95	272.84 nM	phe 6947, Cys 6913
Idelalisib	-7.58	2.79 µM	Tyr 6930 Gly 6911
Kumusine	-7.65	2.47 µM	Cys 6913, Tyr 6930, Leu6898, Gly 6911
Sinefungin (reference molecule)	-7.24	4.93 µM	Asp6897, Asp 6912, Asp 6928, Tyr 6930, Asn6899, Leu6898

4. Conclusions

Based on molecular docking results, Ibrutinib along with Kumusine have the highest binding energy among other compounds compared with Sinefungin. Furthermore, MD calculations showed that Kumusine has destroyed the secondary structure of the protein more than others. Generally, it seems that Kumusine due to its better drug properties including the highest binding, the ability of destroying the secondary structure of the protein and its suitable ADME properties can be proposed as the best drug candidate among screened drugs in this research, for further investigations.

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References

[1] V. M. Corman, D. Muth, D. Niemeyer, C. Drosten, *Adv. in Virus Res.* 100 (2018) 163-188.

[2] C. I. Paules, H. D. Marston, A. S. Fauci, *JAMA* 323(8) (2020) 707-708.

[3] K. G. Andersen, A. Rambaut, W. I. Lipkin, E. C. Holmes, R. F. Garry, *Nature Med.* 26 (2020) 450-452.

[4] A. Hasan, B. A. Paray, A. Hussain, F. A. Qadir, F. Attar, F. M. Aziz, M. Sharifi, H. Derakhshankhah, B. Rasti, M. Mehrabi, K. Shahpasand, A. A. Saboury, M. Falahati, *J. Biomol. Struct. Dyn.* 39 (2020) 3025-3033.

[5] A. Remuzzi, G. Remuzzi, *Lancet* 395 (2020) 1225-1228.

[6] A. D. Elmezayen, A. Al-Obaidi, A. T. Sahin, K. Yelekci, *J. Biomol. Struct. Dyn.* 39 (2020) 2980-2992.

[7] P. Sang, S. H. Tian, Z. H. Meng, L. Q. Yang, *RSC Adv.* 10 (2020) 15775-15783.

[8] B. Shah, P. Modi, S. R. Sagar, *Life Sci.* 252 (2020) 117652.

[9] E. Tazikeh-Lemeski, S. Moradi, R. Raoufi, M. Shahlaei, M. A. M. Janlou, S. Zolghadri, *J. Biomol. Struct. Dyn.* 39 (2021) 4633-46.

[10] H. H. Fan, L. Q. Wang, W. L. Liu, X. P. An, Z. D. Liu, X. Q. He, L. H. Song, Y. G. Tong, *Chin. Med. J. (Engl)* 133 (2020) 1051-1056.

[11] W. Aouadi, A. Blanjoie, J. J. Vasseur, F. Debart, B. Canard, E. Decroly, *J. Virol.* 91(5) (2017) e02217-16.

[12] Y. Chen, D. Guo, *Virologica Sinica* 31 (2016) 3-11.

[13] V. Vijayan, P. Pant, N. Vikram, P. Kaur, T. P. Singh, S. Sharma, P. Sharma, *J. Biomol. Struct. Dyn.* 39 (2021) 6713-6727.

[14] J. Ewald, P. Sieber, R. Garde, S. N. Lang, S. Schuster, B. Ibrahim, *Cell. Mol. Life Sci.* 77 (2020) 467-80.

[15] D. S. Goodsell, *Cold Spring Harb. Protoc.* 5: (2009) pdb.prot5200.

[16] H. De Waard, A. Amani, J. Kendrick, W. L. Hinrichs, H. W. Frijlink, J. Anwar, *J. Phys. Chem. B* 114 (2010) 429-436.

[17] M. Froimowitz, *Biotechniques* 14 (1993) 1010-1013.

[18] A. K. Malde, L. Zuo, M. Breeze, M. Stroet, D. Poger, P. C. Nair, A. E. Mark, *J. chem. theory and computation* 7 (2011) 4026-4037.

[19] K. Binder, *Rep. Prog. Phys.* 60 (1997) 487-559.

[20] G. Bussi, D. Donadio, M. Parrinello, *J. Chem. Phys.* 126 (2007) Article ID 014101.

[21] M. Parrinello, A. Rahman, *J. Appl. Phys.* 52 (1981) 7182-7190.

[22] D. M. van Aalten, A. Amadei, R. Bywater, J. B. Findlay, H. J. Berendsen, C. Sander, P. F. Stouten, *Biophys. J.* 70 (1996) 684-692.

[23] X. Y. Meng, H. X. Zhang, M. Mezei, M. Cui, *Curr. Comput. Aided Drug Des.* 7 (2011) 146-157.

[24] S. Tayyebi, E. Tazikeh-Lemeski, *Iran J. Sci. Technol. Trans. Sci.* 41 (2017) 329-335.

[25] L. Karami, E. Tazikeh-Lemeski, A. A. Saboury, *Phys. Chem. Res.* 5 (2017) 483-496.

[26] E. Tazikeh-Lemeski, *Binding J. Theor. Comput. Chem.* 15 (2016) 1650045.

[27] W. Kabsch, C. Sanders, *Biopolymers* 22 (1983) 2577-2637.