In Silico Docking for Inhibition Neuropilin-1 (SARS-CoV-2 Receptor) by Some Natural and Approved Drugs

Mohamed G. Seadawy (✉ biologist202054@yahoo.com)

Main chemical laboratories, Egypt Army

Mohamed Shamel

Main chemical laboratories, Egypt Army

Aya Ahmed

National Cancer Institute, Cairo University, Giza, Egypt

Abdel Rahman N. Zekri

National Cancer Institute, Cairo University, Giza, Egypt

Research Article

Keywords: SARS-CoV-2, Spike (S) protein, Neuropilin-1

Posted Date: November 20th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-111160/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

Abstract

Severe Acute Respiratory Syndrome Coronavirus2 (SARS-CoV-2) attached to Angiotensin Converting Enzyme 2 (ACE2) as human receptor. The Spike (S) protein of this virus is responsible for host cell penetration and attachment. This viral glycoprotein is synthesized as a precursor in infected cells and, to be active, must be cleaved to two associated polypeptides: S1 and S2^{1,2}. We made Insilco docking between the spike protein and Neuropilin-1 using Cluspro 2.0 software. Therefore, Neuropilin-1 becomes host factor for SARS-CoV-2 infection. Our study revealed that some drugs and natural compounds success in inhibition of binding between the virus and its new receptor with Insilco docking data.

Introduction

NEUROPILIN-1 (NRP-1) is the receptor involved in the development of the cardiovascular system. It mediates the chemorepulsant activity of semaphorins. It involved in the formation of certain neuronal circuits. It also binds to semaphorin 3A. It Regulates mitochondrial Iron. SARS-CoV-2 attachment with host cell receptor is catalyzed by Furin, which cleaves the S protein at a specific sequence motif that generates a polybasic (Arg-Arg-Ala-Arg) C-terminal sequence on S1. The sequence motif conforms to the C-end rule, which means that the C-terminal sequence may allow the protein to bind with cell receptor neuropilin-1 and neuropilin-2 receptors⁽³⁾.

Material And Method

Protein molecular modeling of spike protein fragment and NRP-1 protein:

Swiss Model web server was utilized to build the 3D structural model for Egyptian sequences for NRP-1 and the spike protein⁽⁴⁾. The two solved structures with PDB ID: 7QQm and 6XR8 were chosen to be the homolog solved structures for NRP-1 and the spike protein since they share a sequence identity of 100% and 99.84%, respectively^(5,6). After model building, the models were validated through the Structural Analysis and Verification Server (SAVES) webserver of the UCLA and Molprobit from Duke University⁽⁷⁾.

Molecular docking between S protein fragment and NRP-1.

Molecular docking studies between S protein fragment and human NRP-1 receptor are performed using ClusPro⁽⁸⁾. Following equation has been used to compute cluster scores as well as to predict the lowest binding energy (using ClusPro 2.2 online server⁽⁸⁾)

$$E = 0.40E_{\text{rep}} + -0.40E_{\text{att}} + 600E_{\text{elec}} + 1.00E_{\text{DARS}}$$

The repulsive (rep), attractive (att), electrostatic (elec) forces and interactions extracted from the decoys as the reference state (DARS), are measured using molecular docking study⁽⁹⁾.

Molecular docking study of some natural compounds and FDA approved drugs

The tested compounds are retrieved from the PubChem database and prepared using PyMOL software^(10, 11). Docking experiments were performed using AutoDock Vina software⁽¹²⁾. Model built for NRP-1 was used in this study, and its binding affinities against, Carvacrol, Thymol, Amantadine, Daclatasvir, Ravidasvir, Remdesivir, Sofosbuvir, Hesperidine, and Thymoquinone were tested using the Vina scoring function. Chimera software was used to represent and analyze the docking complexes.

Results And Discussion

Molecular docking between spike protein fragment and human NRP-1 receptor.

Human NRP-1 receptor (PDB ID 2QQM) is considered as receptor protein for molecular Docking study of spike protein fragment with its receptor in human host. By using ClusPro27 web server, docking structure of A chain of human NRP-1 receptor binds with SARS CoV2 spike protein fragment with binding energy -1219.1 kcal/mole.

Hesperidine, Ravidasvir, Daclatasvir, Remdesivir and Sofosbuvir for inhibition of NRP-1

There are 9 natural and FDA approved drugs tested against NRP-1 human receptor for its inhibition. Hesperidin binds with NRP-1 protein fragment with binding energy -9 kcal/mole. This docked structure is stabilized by four H binding (shown in Figure 3 with orange lines) at SER 24 of NRP-1 with O atom of hesperidin, with bond length 2.403 °A and three H binding at GLY 5 with O atom of hesperidin with a distance 2.305, 2.2 and 2.803 °A.

Ravidasvir binds with human receptor NRP-1 protein, at GLY 9. But with higher binding energy -10.3 kcal/mole compared to that of hesperidin -9 kcal/mole, with bond length 2.198 °A.

Daclatasvir, Remdesivir and Sofosbuvir bind with human receptor NRP-1 protein, at TYR 28, HIS 3 and GLY 37 respectively. However, with less binding energy -8, -7.6, -7.3 kcal/mole respectively compared to that of hesperidin and Ravidasvir, with bond length 1.828, 2.037 and 2.316 °A as shown in figure 2 and 3.

Tables

Ligand	Affinity (kcal/mole)
Amantadine	-5.6
Carvacrol	-5.4
Daclatasvir	-8.0
Hesperidine	-9.0
Ravidasvir	-10.3
Remdesivir	-7.6
Sofosbuvir	-7.4
Thymol	-5.3
Thymoquinone	-5.4

Table 1. The binding affinity (in kcal/mole) of tested compounds against the NRP-1 as a SARS-CoV2 target calculated using AutoDock Vina software.

Declarations

Competing Interest

All the authors declare that there is no competing interest in this work.

Data Availability

The docking structures are available upon request from the corresponding author.

References

1. Wrapp, D. et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. *Science* 367, 1260-1263 (2020).
2. Walls, A. C. et al. Structure, Function, and Antigenicity of the SARS-CoV-2 Spike Glycoprotein. *Cell* 181, 281-292.e6 (2020).
3. Hoffmann, M. et al. A multibasic cleavage site in the spike protein of SARS-CoV-2 is essential for infection of human lung cells. *Mol Cell* 78, 779-784 (2020).
4. Biasini M, Bienert S, Waterhouse A, Arnold K, Studer G, Schmidt T, et al. SWISS-MODEL: modelling protein tertiary and quaternary structure using evolutionary information. *Nucleic Acids Research*. 2014;42:W252-W8.

5. Chi X, Yan R, Zhang J, Zhang G, Zhang Y, Hao M, et al. A neutralizing human antibody binds to the N-terminal domain of the Spike protein of SARS-CoV-2. *Science* (New York, NY). 2020;369:650-5.
6. Wang Q, Wu J, Wang H, Gao Y, Liu Q, Mu A, et al. Structural Basis for RNA Replication by the SARS-CoV-2 Polymerase. *Cell*. 2020;182:417-28.e13.
7. Williams CJ, Headd JJ, Moriarty NW, Prisant MG, Videau LL, Deis LN, et al. MolProbity: More and better reference data for improved all-atom structure validation. *Protein Science*. 2018;27:293-315.
8. Kozakov, D. *et al.* The ClusPro web server for protein–protein docking. *Protoc*. **12**(2), 255–278 (2017).
9. Kozakov, D. *et al.* How good is automated protein docking? *Struct. Funct. Bioinf*. **81**(12), 2159–2166 (2013).
10. 7.6 V. The PyMOL Molecular Graphics System, Version 1.7.6 Schrödinger, LLC.
11. Kim S, Thiessen PA, Bolton EE, et al. PubChem substance and compound databases. *Nucleic acids research* 2015; **44**(D1): D1202-D13.
12. Trott O, Olson AJ. AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. *J Comput Chem*. 2010;31:455-61.

Figures

A

B

Figure 1

A and B The 3D structures of the Spike protein of SARS-CoV-2 docked with Neuropilin-1 human receptor.

A

B

Figure 1

A and B The 3D structures of the Spike protein of SARS-CoV-2 docked with Neuropilin-1 human receptor.

Figure 2

The docking complexes formed after the docking of (A) Ravidasvir, (B) Hesperidin, (C) Daclatasvir, (D) Remdesivir, and (E) Sofosbuvir into the Neuropilin-1 human receptor active site.

Figure 2

The docking complexes formed after the docking of (A) Ravidasvir, (B) Hesperidin, (C) Daclatasvir, (D) Remdesivir, and (E) Sofosbuvir into the Neuropilin-1 human receptor active site.

Figure 3

The Docked complexes of (A) Hesperidine, (B) Ravidasivir, (C) Daclatasvir, (D) Remdesivir and (E) Sofosbuvir with Neuropilin-1 model using Chimera software.

Figure 3

The Docked complexes of (A) Hesperidine, (B) Ravidasivir, (C) Daclatasvir, (D) Remdesivir and (E) Sofosbuvir with Neuropilin-1 model using Chimera software.