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In silico Docking for Inhibition Neuropilin-1 (Sars-Cov-2 Receptor) by Some Natural Compound and Approved Drugs

Mohamed Gomaa Seadawy[1*], Mohamed Shamel Eldesoky[2], Aya Ahmed[2] and Abdel Rahman Nabwi Zekri[2]

[1]Main Laboratories, Chemical Warfare, Egyptian Army Forces, Cairo, Egypt

[2]National Cancer Institute, Cairo University, Giza, Egypt

Abstract

Background: Neuropilin-1 (NRP-1) is a multifunctional transmembrane receptor for ligands that affect developmental axonal growth and angiogenesis. Beside its role in cancer, NRP-1 is a reported entrance for several viruses, including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causal agent of coronavirus disease 2019 (COVID-19).

Methods: 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. Then by using molecular docking, we test nine compounds against Neuropilin-1 for its inhibition.

Results and Conclusion: 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.

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

Abbreviations: NRP-1: Neuropilin-1; COVID-19: Coronavirus disease 2019; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; S Protein: Spike Protein; SAVES: Structural Analysis and Verification Server; rep :Repulsive; att :Attractive; elec :Electrostatic; DARS :Decoys as the Reference State

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 Spike (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 [1].

Materials and Methods

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 [2]. 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 [3,4]. After model building, the models were validated through the Structural Analysis and Verification Server (SAVES) webserver of the UCLA and Molprobity from Duke University [5].

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 [6]. Following equation has been used to compute cluster scores as well as to predict the lowest binding energy (using ClusPro 2.2 online server) [7].

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

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 [7].

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 [8,9]. Docking experiments were performed using AutoDock Vina software [10]. 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 (Table 1).

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.

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

Corresponding Author: *Seadawy MG, Main Laboratories, Chemical Warfare, Egyptian Army Forces, Cairo, Egypt, E-mail: biologist202054@yahoo.com*

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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 (Figure 1). By using ClusPro27 web server, docking structure of a chain of human NRP-1 receptor binds with SARS CoV-2 spike protein fragment with binding energy -1219.1 kcal/mole.

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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 Figures 2 and 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.s.

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. But 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 Figures 2 and 3.

Conclusion

Since most of the drug candidates presently available for COVID-19 significantly act on viral spike protein and other studies reports that NRP-1 is an entrance for several viruses, including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causal agent of coronavirus disease 2019 (COVID-19), by using molecular docking analysis. We have predicted the inhibitor activity of several natural products that can emerge as potential drug candidates inhibiting the binding between virus spike protein and NRP-1. A promising binding of natural products and drugs with the NRP-1 was revealed by docking analysis. Among the several natural products and drugs screened by docking analysis, hesperidine, ravidasvir, daclatasvir, remdesivir and sofosbuvir were found to exhibit a higher degree of interaction with the human receptor accompanied by lowest binding energy with favourable drug like properties. Thus, these natural products and drugs may emerge as potential Neuropilin-1 inhibitor. However, additional exploration is predictable for the investigation of the essential use of the drugs and herbs containing these natural products and their *in-vivo* activity.

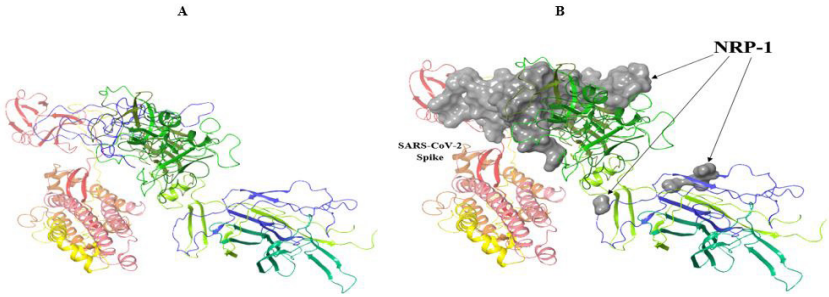

Figure 1. A and B are the 3D structures of the spike protein of SARS-CoV-2 docked with Neuropilin-1 human receptor.

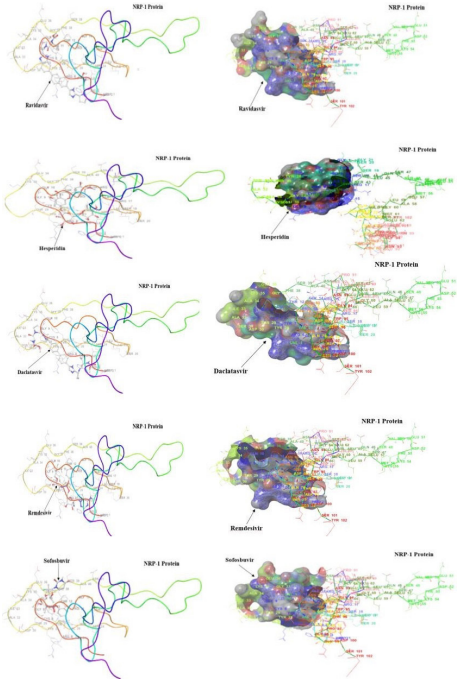

Figure 2. The docking complexes formed after the docking of (A) Ravidasvir, (B) Hesperidin, (C) Daclatasvir, (D) Remdesivir, and (E) Sofosbuvir into the Neuropilin-1 human receptor active site.

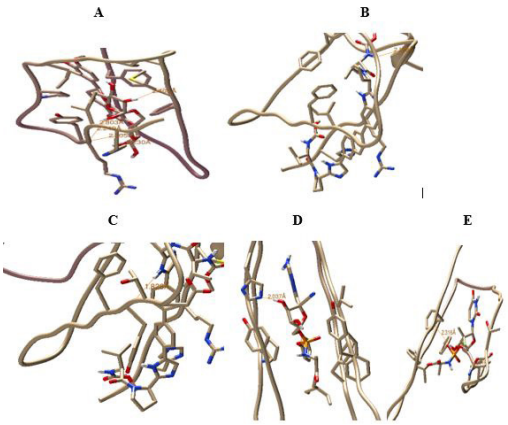

Figure 3. The Docked complexes of (A) Hesperidine, (B) Ravidasivir, (C) Daclatasvir, (D) Remdesivir and (E) Sofosbuvir with Neuropilin-1 model using Chimera software.

Competing Interests

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

Authors' Contributions

Mohamed Gomaa Seadawy-Writing, Editing and Molecular Docking, Mohamed Shamel Eldesoky-Data analysis, Aya Ahmed Saeed Mohamed-Molecular docking and data analysis, Abdel Rahman Nabwi Zekri-Revising.

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