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Type	Oral communication
Session	Protein structure and function
Title	Molecular docking simulations for the screening of putative ligands of SARS-CoV-2 proteins
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Motivation

On 11 March 2020, World Health Organization (WHO) officially declared the COVID-19 epidemic as pandemic and it is still today. Two years later, only two antiviral drugs have been authorized by EMA. The aim of our study is the screening of putative ligands of SARS-CoV-2 proteins whose 3D structure is available in PDB. In particular 77 selected ligands have been tested against NSP3 (PLpro and ADRP), NSP5 (M-pro), NSP7, NSP8, NSP9, NSP10, NSP12, NSP15, NSP16, ORF7A, N protein and SPIKE protein of SARS-CoV-2. The non-structural proteins M-pro and PLpro are the two major important cysteine proteases of SARS-CoV-2, quite conserved with SARS-CoV. The RNA-dependent RNA polymerase NSP12 (RdRp), with a NSP7-NSP8 heterodimer and an additional NSP8 subunit at a different binding site, form the polymerase complex, which mediates the replication of SARS-CoV-2 RNA. NSP9 seems able to mediate viral replication and bind RNA, NSP10 doesn’t possess any enzymatic activity but acts as a cofactor: together with other replicase subunits, NSP10, NSP14, and NSP16 are implicated in the formation of the CoV replication-transcription complex. NSP15 is an endoribonuclease specific for nidoviral RNA uridylate (NendoU) whose activity is responsible for protein interference with the innate immune response. NSP16 is a 2-O-MTase but probably its stability and activity are strictly correlated to the interaction with NSP10, which works as a “scaffold”. ORF7a is a transmembrane accessory protein that appears to be able to cause apoptosis of immune system cells. The nucleocapsid phosphoprotein (N) is the fourth structural protein of SARS-CoV-2 and is a multifunctional RNA-binding protein necessary for viral RNA transcription and replication. The spike glycoprotein is the first structural protein of SARS-CoV2 and is responsible of the receptor recognition and the membrane fusion. From this strongly summarized overview, it is evident that any of these molecules could be a useful target for the Sars-Cov-2 inactivation.

Methods

To perform molecular docking simulations of a large amount of putative ligands against these SARS-CoV-2 protein structures selected, we generated a semi-automatic procedure to produce, by AutoDock 4.2, a high number of protein-ligand simulations in few hours, depending on the computational power of the linux platform. It is important to underline that docking simulations have been performed exploiting two strategies: blind docking, considering whole protein structures, and focused docking, considering just relevant parts of the proteins. In some cases, different docking conditions have been adopted, as with or without cofactors, and considering monomeric or multimeric protein assembly.

Results

Results of the screening evidenced a number of ligands with potential ability to bind the viral proteins, with a perspective interest in the finding of molecules useful against the pandemic urgency. In particular, blind docking simulations between kempferol and M-pro produced the best binding energy (-7.35 kcal/mol) at the known binding site. Focused docking simulations on this site showed binding energy of -8.29 kcal/mol and 100 clustered poses. Interestingly, in both simulations, the ligand assumes the same orientation in the pocket, showing a possible interaction with one catalytic residue of the dyad, with a potential inhibition of the protease activity.
Due to the possibility of NSP7 and NSP8 to interact each other but also with NSP12, all these possibilities have been evaluated during the docking analysis and an important result was obtained by β-carotene. In fact this ligand seems to be able to bind NSP12 in the NSP8 binding surface and NSP7 and NSP8 in a site responsible of their heterodimerization. Particularly, β-carotene binds NSP7 on its NSP8-heterodimerization site with a lowest binding energy of -8.17 Kcal/mol and 78 poses in that pocket, and NSP8 on its NSP7-heterodimerization site with a mean binding energy of almost -7 Kcal/mol and a high cluster population.
Moreover, β-carotene seems to be also able to bind NSP12 in the NSP8 binding surface.
Crossing all the results was possible to notice the possible role of β-carotene in the inhibition of all these bindings necessary for the construction of the polymerase complex. Another interesting result concerning the β-carotene is related to the docking blind performed on the RBD of the Spike protein. Results show as this ligand is able to bind the RBD occupying a large part of the ACE2 interaction designated area.
The potential ligands found with our study will be proposed for experimental testing. Moreover, we are working to make our procedure a tool adaptable to perform fast screenings of potential protein ligands for targets in public health emergencies.

Info

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