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Role and applicability of *In silico* molecular interactional studies and analysis in relation to Covid-19 pandemic

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Abstract
From December 2019 up till today, COVID-19 has caused a big Havoc across the globe, not to mention the economic crisis it has caused in the nations and has brought everything to a temporary hold. Till date no viable treatment option is available but computational approaches like molecular interactional and docking studies are giving all the researchers a hope. Since the beginning of the pandemic there has been a huge number of researches done on molecular docking and drug repurposing which have upgraded the potential of drugs like lopinavir and remdesivir. These techniques have also targeted protein receptors like ACE2 receptor thus targeting entry of virus particle to the host cells. In this article we have tried to highlight such major points about molecular interactional studies along with its role and applicability in finding a viable and potential treatment option.

Keywords: COVID-19, molecular docking, drug repurposing, applicability, treatment

Introduction

Towards the end of the year 2019, in December, a group of patients were identified in Wuhan, Hubei province, China with Pneumonia for which the origin was unknown to all. Among these patients, most of the patients witnessed the history of stopping over at the famous Huanan seafood wholesale market [1]. By now all of us have witnessed the horrors of COVID-19 and the whole world has suffered greatly from that but now, we are all recouping from it, though it seems as if every time the virus comes with even more force. Thus, the researchers around the world and healthcare professionals are still working on it to get a permanent cure of this disorder. Unlike any respiratory disorder, COVID-19 is also characterized by shortness of breath, coughing, sneezing, difficulty in breathing etc. which makes it even more complicated to distinguish it from other respiratory disorders. In advanced stages, it can cause ARDS-Acute Respiratory Distress Syndrome – i.e., a condition in which lungs get swollen and there is accumulation of fluid in them which causes septic shock and causes sudden drop in oxygen levels which in turn can cause organ failure [2, 3]. As of now, there is no single explicit antiviral treatment for COVID-19 and the primary medicines are steady. Nonetheless, drug repositioning has been a system embraced by a few scientists to look for compelling treatment in a brief period. Other than that, a virtual screening dependent on atomic mooring arises as a significant device for acquiring new antiviral particles, where analysts can utilize this instrument as a corresponding methodology so the amalgamation of new mixtures or the repositioning of medications can be doled out [4, 5]. In silico Docking studies are very helpful in drug repurposing studies and are able to give potent results in a lesser time compared to any wet lab experiments. Despite the fact that at first, back in 2019 and 2020, the circumstance was extremely difficult with no conceivable fix and antibody for COVID-19 yet now in the year 2021, circumstances have become significantly more irksome with numerous new and novel variations of SARS-CoV-2 becoming visible [6]. There is an urgent need to build up an alternative strategy to forestall novel SARS-CoV2 infection. Traditional techniques for drug discovery could require years, while in silico-docking analysis empowers enormous scope in screening fast and less expensive than traditional medication [7]. In in silico analysis, we survey the binding capacity of a ligand to protein at an active site as well as to analyze the binding methods of various ligands to the active site-pocket [8].

In silico molecular docking and the basic workflow

Molecular docking technique investigates the conduct of small particles in the active site of an objective protein. As more protein structures are resolved tentatively utilizing X-Ray crystallography or NMR spectroscopy, atomic docking is progressively utilized as an apparatus in drug disclosure. Docking against homology modeled targets likewise gets feasible for proteins whose structures are not known. With the docking techniques, the druggability of the mixtures and their particularity against a specific objective can be determined for additional lead streamlining measures. Molecular Docking programs play out a hunt calculation in which the conformity of the ligand is assessed recursively until the intermingling to the base energy is reached. At long last, a fondness scoring capacity, ΔG [U all out in kcal/mol], is utilized to rank the competitor acts like the whole of the electrostatic and van der Waals energies. The driving powers for these particular communications in organic frameworks point toward complementarities between the shape and electrostatics of the limiting site surfaces and the ligand or substrate [9].

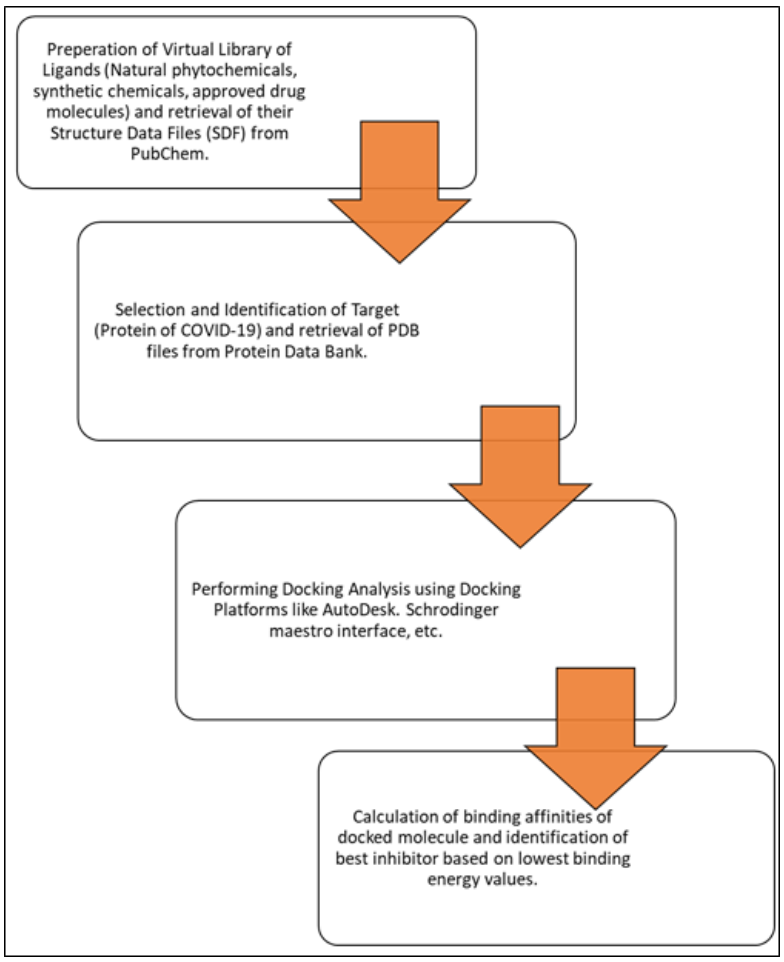

Fig 1: Basic workflow of an in silico molecular docking experimentation.

Software platforms available to perform *in silico* molecular interactional studies

There are hundreds of docking softwares available for commercial and/or academic purposes which one can easily use to perform molecular docking experiments. Each software is designed in a certain way to perform certain specific kinds of docking for example – In order to perform Rigid body docking one can use platforms like MEGADOCK, ZDOCK, BiGGER, etc. [9], similarly to perform specific type of docking, specific platforms and softwares are available which one can use. Some of the best platforms that are widely used among the computational biologist and bioinformatics community include – *(See table – 1)*

Table 1: Some Most commonly used Docking platforms

S.no.	Name	Organization	Year	License type	Website link
1.	Auto Dock	The Scripps Research Institute	1990	Open Source	http://autodock.scripps.edu/
2.	Auto Dock Vina	The Scripps Research Institute	2010	Open Source	http://vina.scripps.edu/
3.	Glide	Schrödinger	2004	Commercial	https://www.schrodinger.com/products/glide
4.	GOLD	The University of Sheffield, GlaxoSmithKline plc and CCDC	1995	Commercial	https://www.ccdc.cam.ac.uk/solutions/csd-discovery/Components/Gold/
5.	Swiss Dock	Swiss Institute of Bioinformatics	2011	Free for Academic Usage	http://www.swissdock.ch/

Role of Docking in Covid-19 Treatment

Molecular docking is a structure-based drug-design to distinguish the fundamental amino acids connections between the chosen protein and generated ligands with low energy adaptation [10]. It assists with foreseeing the binding affinity between protein and ligand by using scoring functions [11]. In order to study the effect of Indian phytochemicals on spike protein fragment, Basu, A. *et al*. [12] used molecular docking study for spike glycoprotein fragment with human ACE2 receptor. The phytochemicals were considered as modulators whereas the bound design of spike glycoprotein with human ACE2 receptor was considered as target molecule for treatment of COVID-19. These bind with ACE2 as non-competitive particle and impart their anti-viral activity by destabilizing spike protein binding with ACE2 receptor.

B. Shah, *et al* [13] used Glide Standard precision (SP) as docking protocol. In order to predict the binding affinity and ligand efficiency as inhibitor, Flexible docking with Glide Standard precision (SP) protocol was performed [14]. Dock score was used

to evaluate the concluding energy. Representation of docked ligands was done by Maestro interface (Schrödinger Suite, LLC, NY) [15].

R.R. Deshpande *et al*. [16] used PyMOL version 2.3.3 [The PyMOL Molecular Graphics System, Version 2.0 Schrodinger, ¨ LLC] for ligand and protein optimization. Pymol and Bio via Discovery Studio 4.5 was used for docking analysis.

Drug Repurposing

Computational screening of the FDA-approved drugs with the capability of focusing on SARS-CoV-2 is a cost savvy and less tedious system and can rapidly distinguish promising applicants. Recently, molecular docking has been endeavoured to distinguish possible drugs for COVID-19 by protein-ligand binding energy expectation [17].

Hosseini *et al*. [17] directed molecular docking examination on five drugs that have been proposed as promising SARS-CoV-2 inhibitors: Remdesivir, Chloroquine, Hydroxychloroquine, Lopinavir, and Ritonavir. Remdesivir was the only supported drug that has been proposed to restrain RdRp and Mpro [18, 19]. Chloroquine/hydroxychloroquine and lopinavir/ritonavir have been eliminated from the COVID-19 treatment protocols due to potential dangers and vulnerability with respect to their advantages [20, 21]. There molecular docking has identified some potential new ligands, e.g., rolapitant, leucal, and labetalol, as promising inhibitors against SARS-CoV-2. There molecular docking have recognized some new ligands, e.g., rolapitant, leucal, and labetalol, as promising inhibitors against SARS-CoV-2.

R.R. Deshpande *et al*. [16] concluded that drug repurposing is the best methodology for discovering answer for treatment of novel Covid-19 infection. If the targets and activity of these drugs are known, treatment would be simpler. Consequently, the broad work is carried out in this examination to comprehend the association of numerous viral proteins and diverse drug ligands which are considered for treatment in COVID-19. Proteins significant in viral replication were chosen in the examination in light of the fact that hindering these proteins may be helpful to obstruct the inception of disease and chain of replication. In silico molecular docking study improved the capability of Lopinavir, Ritonavir, Remdesivir as an up-and-comer drugs for treatment of COVID-19. Eriodictyol due to its efficient binding energy and its anti-inflammatory activity has emerged as a promising candidate for treatment of corona infection.

Bhumi Shah *et al.* selected total 61 reported antiviral agents to carry out the molecular docking studies to recognize the potent antiviral agents explicitly for COVID-19. Each one of these 61 particles was docked against the target enzyme and positioned them on the basis of their dock score [13]. Known antiviral drugs like Indinavir, Ritonavir, Lopinavir, Remdesivir, Marboran/ Methisazone and Simeprevir as well as Galidesivir, Saquinavir, Hydroxychloroquine (HCQ), Pemirolast, which are used to treat other diseases, were selected as ligands for docking against target proteins [16]. Out of these 61 molecules, 37 molecules were found to interact with >2 protein structures of COVID-19. The docking results indicate that amongst the reported molecules, HIV protease inhibitors and RNA-dependent RNA polymerase inhibitors showed promising features of binding to COVID-19 enzyme. Along with these, Methisazone an inhibitor of protein synthesis, CGP42112A an angiotensin AT2 receptor agonist and ABT450 an inhibitor of the non-structural protein 3-4A might become convenient treatment option as well against COVID-19. 37 molecules out of 61 molecules were found to interact with >2 protein structure of COVID-19. HIV protease inhibitors and RNA-dependent RNA polymerase inhibitors showed promising features of restricting COVID-19 enzyme. Other than this, Methisazone, CGP42112A and ABT450 may become advantageous treatment choice against COVID-19.

Donald C. Hall *et al*. [22] concluded that Zanamivir, Indinavir, Saquinavir, and Remdesivir are highly effective on the $3CL^{PRO}$ main proteinase. Thay also concluded that Flavin Adenine Dinucleotide (FAD) Adeflavin, and Coenzyme A, can also be used for the treatment of SARS-CoV-2 infections.

Das S. *et al*. [23], blind molecular docking study proposed a possible methodology for the use of natural products, anti-virals, anti-fungals, anti-nematodal, and anti-protozoal drugs as forthcoming inhibitors of SARS-CoV-2 Mpro. The inhibition activity of rutin was found to be the elevated as its Δ*G* value is the minimum, trailed by ritonavir, emetine, hesperidin and indinavir (Table – 2).

Table 2: Drugs along with their properties and ΔG value. Data taken from [23]

Drug	Property	Δ*G* value [23]
Rutin	A natural compound that enhances the action of Vitamin C and treats allergies, virues and other inflammatory conditions.	−9.55 kcal/mol
Ritonavir	A control drug used in the treatment of HIV	−9.52 kcal/mol
Emetine	anti-protozoan drug used for the treatment of amebiasis	−9.07 kcal/mol
Hesperidin	A natural compound used for blood vessel conditions like hemorrhoids.	−9.02 kcal/mol
Indinavir	anti-viral drug decreases the chances of contractions AIDS and HIV-related diseases	−8.84 kcal/mol

Conclusion

As of now, Coronavirus has become a major challenge for every country. The outbreak is spreading worldwide and causing several deaths. As we realize that no medications are accessible for the prevention of the disease, we can utilize repurposed drugs, which can be useful to stop the spread of Coronavirus. To battle the life-threatening corona virus infection, several studies on antiviral drug therapies are going on. Despite of a flood of SARS-CoV-2 research published every now and then, current knowledge of this novel coronavirus is a hint of something larger. In-silico molecular docking upgraded the capability of Lopinavir, Ritonavir, Remdesivir as a candidate drugs for treatment of COVID-19. Drug repurposing is the best methodology for discovering answer for treatment of infection. If mechanism of action of these drugs and the targets are known then planning treatment would be simpler. Therefore, to understand the interaction of various viral proteins and different drug ligands, extensive work is carried out. Proteins significant in viral

replication were chosen for molecular interactional analyses because hindering these proteins may be useful to block the initiation of infection and chain of replication. Tus, it is evident that molecular docking studies are very important from treatment point of view for COVID-19 and more and more such studies should be carried out to understand the interaction of potential drug lead molecules and repurposed drugs with the viral proteins.

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