In Silico Analysis of 716 Natural Bioactive Molecules Form Atlantic Ocean Reveals Candidate Molecule to Inhibit Spike Protein

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Abstract

COVID-19, a new pandemic of coronavirus (CoV), was reported in Wuhan, China, in 2019. No specific drugs are available and investigations regarding COVID-19 treatment are proceeding. Lan et al. (2020) successfully crystallized the COVID-19 spike receptor-binding domain bounding to the ACE2 receptor, which is a potential drug target. The present study aimed to assess 716 bioactive compounds found in the South Atlantic Ocean as potential COVID-19 Spike inhibitors, using a molecular docking study. Molecular docking was performed using Autodock Vina to analyze the probability of docking. COVID-19 Spike was docked with several compounds, and docking was virtually screened by Chimera, Pymol, and Biovia Discovery Studio and test for draggability using SWISSADME. The analysis shows that 11 NPs out of 716 are predicted to be Spike inhibitors by blocking the amino acids responsible for binding Spike to ACE2. However, further findings are necessary to experimentally investigated for their potential medicinal use.

Introduction

A global health catastrophe has been created by SARS CoV-2 (COVID-19) This pandemic-threatening situation closely resembles the 2003 SARS CoV outbreak (Walls et al. 2020). But with an extremely higher degree of virulence, the current one is highly spreading. As of today, it has killed over 2,169,344 thousand people in 210 countries out of a total of 100,913,073 infected people until the time of this paper (https://www.worldometers.info/coronavirus/). The world economy in most places of the globe has been in a jerk under 4 months or even more of a quarantine period. Thus therapeutic/preventive action is an immediate necessity and a challenging act against this highly stable and often mutable viral strain. No therapeutics are developed against this infection. A few of the old medications are used from similar types of diseases, based on previous observations. In some in vitro models, some experiments were performed with inclusive findings. For instance, some recent study suggests that in an experimental in vitro model, remdesivir and chloroquine effectively inhibit this infection (Wang et al., 2020; Cortegiani et al. 2020; Gao and Tian, 2020) . But chloroquine may have high toxicity, and it is predicted that hydroxychloroquine is less toxic than it is (Colson, Rolain, and Raoult 2020) . Hydroxychloroquine treatment is strongly correlated with viral load reduction in COVID-19 patients in a trial and survey-type experiment with very limited sample size, and its effect is enhanced by azithromycin (Gautret et al. 2020) . Out of a few combinations of medication, presently HCQ is being used in COVID-19 cases (Wang et al., n.d.). Apart from that, this drug is also used in systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) among other autoimmune diseases. Other drugs such as remdesivir, lopinavir/ritonavir combination, Favipiravir have demonstrated effectiveness in inhibiting coronavirus in vitro. It has been shown that teicoplanin, an antibiotic used to treat staphylococcal infections, inhibits MERS-CoV in the human cells. In the current pandemic, this medication can also be rechecked (Baron et al. 2020) . Studies on molecular docking propose sofosbuvir, galidesivir, and tenofovir to inactivate SARS-CoV2 RNA Dependent RNA Polymerase (Elfiky 2020).

In terms of its biological diversity, South Africa ranks third in the world (Griffiths et al. 2010) , and it is estimated that 3,000 medicinal plant species are used for therapeutic purposes in this region, mostly as part of traditional medicines (Cragg and Newman 2013) . Nearly every documented disease has been treated with natural products (NPs), with reports from civilizations all over the world going back as far as 4,600 years ago (Cragg and Newman 2013; Dias, Urban, and Roessner 2012) . NPs are the natural consequence of evolutionary processes that provide them with a level of structural complexity, chemical diversity, and biological proprieties not seen in simply synthetic compounds (Pelay-Gimeno, Tulla-Puche, and Albericio 2013; Mishra and Tiwari 2011) . NPs are considered essential for the drug development process (Mishra and Tiwari 2011) and about 64 percent of approved drugs were derived from or influenced by NPs between 1981–2010 (Newman and Cragg 2012) . There has been one since 2008. 25 Newly authorized drugs derived from NPs, with 31 additional drugs whether in phase III clinical trials or past phase III (Butler, Robertson, and Cooper 2014).

Clarkson (Clarkson et al. 2004) reported that 49 percent of the 134 different South African medicinal plant extracts tested had at least moderate antispasmodic activity. Similar manner, Besson (Bessong et al. 2005) documented a series of South African plant extracts that showed action against HIV. van Vuuren (Van Vuuren 2008) discusses the antimicrobial activity of South African plant life, including examples of different compounds isolated from these plants and their antimicrobial activity as measured. Marine NPs are a fairly new origin of pharmaceutical agents (Glaser and Mayer 2009) but they exhibit complex and special chemistry (Haefner 2003). Despite early research efforts, Southern African aquatic chemistry work only really took off in the 1990s with isolated molecules showing great potential as anticancer agents (Davies-Coleman and Beukes 2004).

The methodology of molecular docking explores the behavior of small molecules at a target protein's binding position. With more protein structures being experimentally determined using spectroscopy of X-ray crystallography or nuclear magnetic resonance (NMR), molecular docking is increasingly being used as a method in drug discovery. It also becomes possible to dock against homology-modeled targets for proteins whose structures are not known. For further lead optimization processes, the docking strategies can be used to measure the druggability of the compounds and their specificity against a given target. Molecular docking programs carry out a search algorithm in which the ligand conformation is evaluated continuously until the minimum energy state is reached. Finally, an affinity scoring method, ΔG [U total in kcal/mol], is used to rate the candidate as the sum of the electrostatic energies and van der Waals. The driving forces in biological systems for these specific interactions aim at the complementarities between the shape and electrostatics of the binding site surfaces and the ligand or substratum.

Molecular docking shows massive potentials in discovery of several molecules have the ability inhibit Coronavirus proteins. Sharma (Sharma and Kaur 2020) suggest Jensenone to be main protease (Mpro) inhibitor. Ghosh (Ghosh et al. 2020) report significant inhibition potential of three polyphenols from green tea against Mpro. In another studies, FDA approved antiviral drug against COVID-19 shows IDX-184 is superior compared to Ribavirin (Elfiky, Mahdy, and Elshemey 2017). flavonoid from medicinal plant

(Adem et al. 2020) and eucalyptol oil component from eucalyptus oil (Sharma and others 2020) have activity against Mpro.

In this study, we used Chimera(Pettersen et al. 2004), OpenBabel (O'Boyle et al. 2011), Pymol (DeLano and others 2002), Autodock Vina (Trott and Olson 2010), and LigPlot+ (Laskowski and Swindells 2011) to virtually screened docked 716 NPs against the binding domain of Spike protein that bound to ACE2 domain. We docked the NPs to the area in which the amino acids responsible for binding to the ACE2 receptor.

Material And Methods

Spike and Ligands Download

We collect the 716 ligand downloaded from SANCDB (Hatherley et al. 2015), Pubchem (Kim et al. 2016), ChemSpider (Pence and Williams 2010), and chEMBL (Gaulton et al. 2012) in form of PDB format. energy minimized using default Chimera parameters. Spike Domain PDB file downloaded from PDB (Berman et al. 2000) database ID: 6M0J and separated from the ACE2 domain in a different file. while the 6M0J is the complex of Spike domain bounded to the ACE2 domain. Spike extracted, minimized, and converted to PDBQT format in a separate file.

Converting and Docking

To loop and dock the 716 ligands, we build python script as shown in figure(1) to convert PDB ligand files to PDBQT using OpenBabel, export the converted file to Autodock Vina and docking against the Spike domain, and finally store each docked ligand with different orientation in the same file. All molecules docked against the whole Spike domain and the surface of Spike domain the containing the amino acids responsible for binding. Docking area dimensions which are center_x, center_y, center_z, size_x, size_y, and size_z for -38.833, 29.0981, -1.26252, 32.9627, 63.5716, and 19.2879 respectively in the two processes determined using Chimera as shown in figure(2).

Results And Discussion

Deep investigation

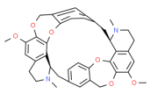
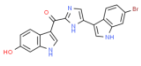
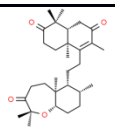
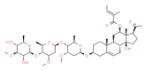
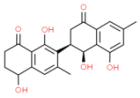
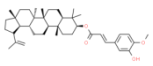
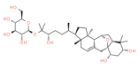
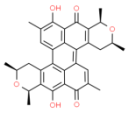
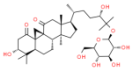
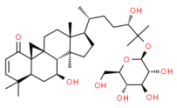
we scanned the binding of the Spike domain with the ACE2 domain figure(3) to discover amino acid responsible for connecting the two domains figure(4-6). The investigation shows the main players in the binding process as shown in table(1). the table shows that Glycin is the most present amino acid in Spike and Glutamine in ACE2.

In Spike	In ACE2
THR 500	TYR 41
GLN 498	GLN 42
GLY 446	GLN 42
GLY 496	LYS 353
ASN 501	LYS 353
GLY 502	LYS 353
TYR 505	GLU 37
GLN 493	GLU 35, HIS 34
ASN 487	GLN 24, TYR 83
LYS 417	ASP 30
TYR449	ASP 38, GLN 42

Table 1: list of amino acids responsible of binding to ACE2

Docked NPs

Molecular docking of 716 NPs reveals 12 candidate molecules to be used as Spike inhibitor with affinity <= -8.0 listed in the table(2) and shown in figure(7).

Name	Formula	2D Structure	Affinity (kcal/mol)
Cissacapine	$C_{38}H_{38}N_2O_6$		-8.0
Bromotopsentin	$C_{20}H_{13}BrN_4O_2$		-8.2
Sodwanone R	$C_{30}H_{46}O_4$		-8.0
P57 (glycoside)	$C_{47}H_{74}O_{15}$		-8.3
Octahydroeuclein	$C_{22}H_{22}O_6$		-8.3
20(29)-Lupene-3β-isoferulate	$C_{40}H_{58}O_4$		-8.2
Sutherlandioside A	$C_{36}H_{60}O_{10}$		-8.0
Scutiaquinone B	$C_{32}H_{30}O_6$		-8.0
Sutherlandioside C	$C_{36}H_{58}O_{10}$		-8.0
Sutherlandioside D	$C_{36}H_{58}O_9$		-8.1
Saundersioside G	$C_{46}H_{66}O_{15}$		-8.1

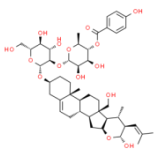
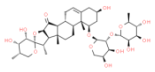
			
Ornithosaponin A	$C_{38}H_{58}O_{15}$		-8.2

Table 2: selected molecule and their binding affinity to Spike

NPs-Spike Interaction

By performing the docking procedure, it is clear that ligands can interact with amino acids as shown in figure (7) that generated by Chimera and Ligplot+ to show interacted amino acids using hydrogen and hydrophobic bonds between the Spike domain and selected molecules.

Druggability Assessment

After docking, we test the druggability of the 12 molecules using SwissADME (Daina, Michielin, and Zoete 2017) with is a web tool to determine drug-likeness and medicinal chemistry friendliness of each molecule as shown in figure (8). SwissADME also hosts the Brain Or Intestinal Estimated permeation method (BOILED-Egg) (Daina and Zoete 2016) which is a method proposed as an accurate predictive model that calculating the lipophilicity and polarity of small molecules to determine its permeation both brain and intestine as shown in figure (9) and the rest of analysis provided in supplementary(1).

Target Prediction and Network Construction

To identify the possible target macromolecule for each NPs we used SwissTargetPredict (Daina, Michielin, and Zoete 2019) give a probability for the query molecule - assumed as bioactive - to have this protein as a target. The analysis reveals that Bromotopsentin has a 100% probability to target for Alpha-1b adrenergic receptors, and Octahydroeuclein has no targets. The rest of each molecule probabilities provided in supplementary(2). to build the network, We used SNPector's (Habib et al. 2020) Network construction python script to build and visualize a network show the unique and shared targets between different molecules and generate an HTML interactive network as shown in figure (10). we also built a network to show the unique and shared target classes, probabilities, and genes.

Having activity on alpha receptors in the human body predicts a spectrum of adverse effects, related mainly to the cardiovascular system, whereas Octahydroeuclein is expected to be safe. Octahydroeuclein was previously reported in the literature only in few publications. It was widely used for curing bronchitis,

pleurisy, chronic asthma, and urinary tract infections as traditional medicine, by the Zulus, in South Africa. Also, octahydroeuclein was found to be significantly effective against Phytophthora (Lall et al. 2006), antifungal activity against A. niger, and Cladosporium cladosporioides respectively (Kothari et al. 2010; Aqil et al. 2010; Karthikeyan et al. 2020), and Antimycobacterial activity against Mycobacterium tuberculosis(Maroyi 2017). Docking against Spike revealed the best affinity with -8.3 Kcal/Mol and best physicochemical proprieties which lead to recommending it as a possible drug for Coronavirus.

Conclusion

Novel Coronavirus represents a new formula of virulence and a real challenge to scientists all over the world. Natural products have shown their capacity to treat different diseases specially marine compounds . After docking 716 molecule, only 12 candidate molecules/compounds shows promising affinity in inhibiting or blocking Spike binding domain. in this study, we suggest Octahydroeuclein be one of the highest druggability and promising effects as a novel antiviral agent against SARS-CoV-2. Octahydroeuclein is photochemical has anti-fungal activity and shows potential to block Spike protein which may drive the efforts over the world to investigate and test with molecular docking of marine compounds against invulnerable viruses such as Coronavirus.

Declarations

Data Availability: Results and Scripts along with Supplementary Files 1 and 2 freely available on Github: zenodo.org/record/3888898#.XuE6TnUzZnw

Competing interests: The authors have declared that no competing interests exist.

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