Finding Potential Inhibitors of COVID-19

Angela Kralevska[1], Marija Velichkovska[1], Viktor Cicimov[1], Tome Eftimov[1,2] and Monika Simjanoska[1]

[1]*Ss. Cyril and Methodius University, Faculty of Computer Science and Engineering, Skopje, North Macedonia*
[2]*Computer Systems Department, Jožef Stefan Institute, Ljubljana, Slovenia*

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Abstract: COVID-19 is an infectious disease caused by virus SARS-CoV-2 that spread globally due to its high contagious nature and became an ongoing pandemic. The lack of vaccines and drugs to treat infected patients is a great problem in the fight against this pandemic. Molecular docking is one of the best approaches to search for potential drugs in real time with possibilities to apply at COVID-19. In this experiment, molecular docking studies of fourteen ligands were carried out with three important proteins of SARS-CoV-2, i.e. main protease, ACE2, and spike glycoprotein. From the obtained results, we observed that many of the tested molecules showed better dock score in comparison to remdesivir and dexamethasone, drugs that are claimed to be effective against COVID-19. Combining the dock score and other properties, we believe that auranetin can be further explored for potential use against COVID-19.

1 INTRODUCTION

Year 2020 has brought along with itself a global tragedy in a form of pandemic named COVID-19. It has proven to be a highly pathogenic and transmittable viral infection causing the severe acute respiratory syndrome. Started in Wuhan, China, it has rapidly spread throughout the world. SARS-CoV-2 has caused around 50 million infections and more than one million deaths (Yamin, 2020).

Despite the worsening trends of COVID-19, large-scale studies report that no drugs are validated to have significant efficiency in clinical treatment of patients diagnosed with COVID-19. So far, remdesivir has been approved by the Food and Drug Administration Agency, only for the treatment of COVID-19 patients that require hospitalization (FDA, 2020). The world at the moment is in a dire need for new drugs against COVID-19, ones that combine efficiency with minimal side effects, but also are inexpensive and readily available.

In the fight against coronavirus, scientists have come up with three strategies for developing new drugs. The first strategy is testing existing broad-spectrum anti-virals. This category encompass interferons, ribavirin, and cyclophilin inhibitors used to treat coronavirus pneumonia. Using existing molecular databases to screen for molecules that may have therapeutic effect on coronavirus is the second strategy, and the third strategy is based on the pathological characteristics and genomic information of different coronaviruses with the aim to develop new targeted drugs from scratch. Theoretically, the drugs found through these approaches would exhibit better anti-coronavirus effects, however, the research procedure might last for more than 10 years (Wu et al., 2020).

For the development of medicines for treating SARS-CoV-2, the fastest way is to find potential molecules from the marketed drugs. Remdesivir is considered the most promising antiviral agent. It works by inhibiting the activity of RNA-dependent RNA polymerase to stop the virus from reproducing and making copies of itself. RdRp inhibitor favipiravir is also being clinically evaluated for its efficacy at treating COVID-19 patients. Lopinavir/ritonavir, the protease inhibitor, plus ribavirin were shown to be effective against SARS-CoV in vitro. Hydroxychloroquine plus azithromycin is another promising alternative, that showed excellent clinical efficacy on Chinese patients against COVID-19. Many other inhibitors, such as monoclonal and polyclonal antibodies and teicoplanin, which inhibits the viral genome exposure in cytoplasm, are under investigation for the treatment of SARS-CoV-2 (Jean et al., 2020).

Corticosteroid called dexamethasone was the first shown to reduce Covid-19 deaths. A study of more

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than 6,000 people found that dexamethasone reduced deaths by one-third in patients on ventilators, and by one-fifth in patients on oxygen (Peter et al., 2020). This drug was recommended for people hospitalized with COVID-19 who are on mechanical ventilators or need supplemental oxygen by the U.S. National Institutes of Health. If dexamethasone and other corticosteroids are given for less severe COVID-19 infection, they may be harmful (Sparks, 2020).

Disrupting this virus's self-replication machinery could be one of the ideal targets without causing any harm to the host. SARS-CoV-2 has an active site for the inhibitors. The spikes are responsible for the attachment of the viruses on the surface and their subsequent entry into the host cells. One of the major causes behind the virus infecting multiple hosts is because of its loosely bound receptor-binding domains (Singh et al., 2020).

In this research, we are exploring some ligands with the aim to determine the level up to which they inhibit main protease, ACE2 and spike glycoprotein.

The rest of the paper is organized as follows. We review related work in Section 2. The methods are presented in Section 3. In Section 4 is explained the process of retrieving and preprocessing the data for this project. The whole process of performing molecular docking is briefly explained in Section 5. The results are reported in Section 6, followed by the conclusions from this study in Section 7.

2 RELATED WORK

The molecular docking has been actively researched to find potential drugs that can be used for COVID-19 (Narkhede et al., 2020). In (Omar et al., 2020), the authors used molecular docking and showed that Quercetin, Hispidulin, Cirsimaritin, Sulfasalazine, Artemisin and Curcumin showed better potential inhibition than Hydroxy-Chloroquine against COVID-19 main protease active site. Another study was focused on molecular docking of 18 ligands with three three therapeutic target proteins of SARS-CoV-2, i.e. RNA-dependent RNA polymerase (RdRp), angiotensin-converting enzyme 2 (ACE2) and spike glycoprotein (SGp), where phytochemicals has better dock score compared to the paracetmol and hydroxychloroquine (Vardhan and Sahoo, 2020). Ribavirin, remdesivir, chloroquine and luteolin have been also studied, where it was shown that luteolin bind with a high affinity to the same sites of the main protease of SARS-CoV-2 as the control molecule (Yu et al., 2020). Finding potential inhibitors for SARS-CoV-2 main protease (Mpro) using a combination of molecular docking and fast pulling of ligand (FPL) simulations has been also researched in (Pham et al., 2020). It was shown that 20 compounds were able to bind well to SARS-CoV-2 Mpro, among them five top are: are periandrin V, penimocycline, cis-p-Coumaroylcorosolic acid, glycyrrhizin, and uralsaponin B.

3 METHODS

The problem with the coronavirus can be viewed as a typical chemical problem while we are trying to obtain potential medicines that will work as inhibitors in the process of transcription. Computer-aided drug design (CADD) is a rational drug design technology, which enables drug discovery based on knowledge of target structures, functional properties and mechanisms. When the target protein structure is known, structure-based approaches, such as molecular docking, can be used (Hung and Chen, 2014).

The path to drug discovery is long and challenging. This process starts with the discovery of molecules that show efficacy in a simple screen, called hits. The interaction between two molecules can happen in a form of interaction of a protein and protein, or, a protein and small molecule. Molecular docking helps in predicting the intermolecular framework and suggest the binding modes responsible for inhibition of the protein (Aaftaab et al., 2019).

There are two basic components which distinguish the variety of docking softwares available to choose from. These are the sampling algorithm and scoring function. After doing some research we have found that most appropriate software for our research would be AutoDock Vina since it is newly designed and improved version of the AutoDock program. This version adopted a new knowledge-based scoring function with a Monte Carlo sampling technique and the Broyden–Fletcher–Goldfarb–Shanno (BFGS) method for local optimization (Nataraj et al., 2017).

AutoDock Vina (Oleg and Arthur, 2010) tends to be much faster than AutoDock, and can take advantage of multiple CPUs or CPU cores to significantly shorten its running time.

The first step in performing docking studies is to find the appropriate compounds that would be fetched from PubChem. There are many compounds to be chosen from in PubChem, since it is the world's largest free chemistry database (PubChem, 2020), however, we will pay attention to the ones that have not been yet explored for COVID-19 in the previous researches. Also, we will rely on the information that the spike glycoprothein (Huang et al., 2020), main

protease (Ullrich and Nitsche, 2020), or ACE2 (Gheblawi et al., 2020) are regions that can be used to inhibit the transcription of the virus. Each compound will be docked and depending on the affinity that is produced, the one with highest rank will be chosen as a candidate. Those compounds that form a bond and as a result have higher energy, will be chosen.

Virtual screening based on molecular docking will be used in order to explore all compounds that are able to bind with the proteins and inhibit the virus.

4 DATA AND PREPROCESSING

In the process of molecular docking, the first step is to obtain proteins and ligands from online databases. Next step is preprocessing the molecules and transforming them to the format needed for the process of molecular docking.

4.1 Proteins and Ligands Selection

To study the protein-ligand interactions, we retrieved proteins in '.pdb' format from RSCB protein data bank (RCSB, 2020). We downloaded the crystallographic 3D protein structures of main protease with PDB ID: 6LU7, spike glycoprotein with PDB ID: 2GHV and ACE2 (Angiotensin Converting Enzyme 2) with PDB ID: 1R42.

The ligands were chosen after performing a thorough literature research (Kouznetsova et al., 2020). Also, we used the similarity structure search option that is offered by the PubChem database. Components with similar structure to ones that have already shown significant docking affinity with the proteins were taken into consideration.

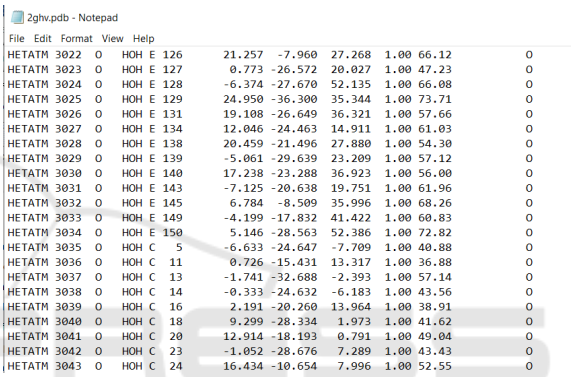
Therefore, we decided to use the following ligands in our research: Sinensetin, Alnetin, Auranetin, Hesperetin, Nobiletin, Obacunone, Pedalitin, Pomiferin, Tangeretin, Eucalyptin, Citromycetin, Trifluoperazine, Beta D Mannose and Dimetylsulphoxide. The affinity of these components will be also compared to the affinity of Remdesivir and Dexamethasone that are already used as treatment for COVID-19.

4.2 Protein Preparation

The protein structures we are using are crystal structures complexes with ligand(s). Therefore, to dock the desired ligand with the protein in that particular position we need to remove the bound ligand by removing hetatoms from the PDB file. If the docking with our ligand is done without removing the already complexed ligand, the obtained results will be incorrect. During the preprocessing step, except removing hetatoms, water molecules were deleted, and we optimized hydrogen bonds structures.

Fig. 1 depicts '2ghv.pdb' file, i.e. the spike glycoprotein. It can be noticed that the hetatoms are binding with only two chains: Chain E and Chain C. These are the only chains we will need for docking. The preprocessing is done with MGLTools (MGLTools, 2020) software developed at the Molecular Graphics Laboratory (MGL) and AutoDock Tools.

As the final preprocessing step, the files are transformed from '.pdb' to a '.pdbqt' format that is required for docking in AutoDock Vina. The look of the molecule after preprocessing is shown in Fig. 2.


2ghv.pdb - Notepad

File Edit Format View Help

```
HETATM 3022  O   HOH E 126      21.257  -7.960  27.268  1.00 66.12           O
HETATM 3023  O   HOH E 127       0.773 -26.572  20.027  1.00 47.23           O
HETATM 3024  O   HOH E 128      -6.374 -27.670  52.135  1.00 66.08           O
HETATM 3025  O   HOH E 129      24.950 -36.300  35.344  1.00 73.71           O
HETATM 3026  O   HOH E 131      19.108 -26.649  36.321  1.00 57.66           O
HETATM 3027  O   HOH E 134      12.046 -24.463  14.911  1.00 61.03           O
HETATM 3028  O   HOH E 138      20.459 -21.496  27.880  1.00 54.30           O
HETATM 3029  O   HOH E 139      -5.061 -29.639  23.209  1.00 57.12           O
HETATM 3030  O   HOH E 140      17.238 -23.288  36.923  1.00 56.00           O
HETATM 3031  O   HOH E 143      -7.125 -20.638  19.751  1.00 61.96           O
HETATM 3032  O   HOH E 145       6.784  -8.509  35.996  1.00 68.26           O
HETATM 3033  O   HOH E 149      -4.199 -17.832  41.422  1.00 60.83           O
HETATM 3034  O   HOH E 150       5.146 -28.563  52.386  1.00 72.82           O
HETATM 3035  O   HOH C   5      -6.633 -24.647  -7.709  1.00 40.88           O
HETATM 3036  O   HOH C  11       0.726 -15.431  13.317  1.00 36.88           O
HETATM 3037  O   HOH C  13      -1.741 -32.688  -2.393  1.00 57.14           O
HETATM 3038  O   HOH C  14      -0.333 -24.632  -6.183  1.00 43.56           O
HETATM 3039  O   HOH C  16       2.191 -20.260  13.964  1.00 38.91           O
HETATM 3040  O   HOH C  18       9.299 -28.334   1.973  1.00 41.62           O
HETATM 3041  O   HOH C  20      12.914 -18.193   0.791  1.00 49.04           O
HETATM 3042  O   HOH C  23      -1.052 -28.676   7.289  1.00 43.43           O
HETATM 3043  O   HOH C  24      16.434 -10.654   7.996  1.00 52.55           O
```

Figure 1: Spike protein hetatoms binding chains.

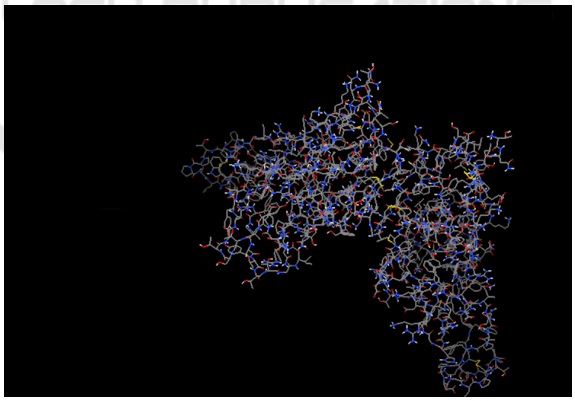


Figure 2: Spike protein after preprocessing.

4.3 Ligand Preparation

Ligands were taken in '.sdf' format directly from the PubChem Database (National Library of Medicine), and converted into '.pdb' format using the PyMOL software (PyMOL, 2020). After that, with AutoDock tools the files were transformed to '.pdbqt'. Example of prepared ligand is shown in Fig. 3.

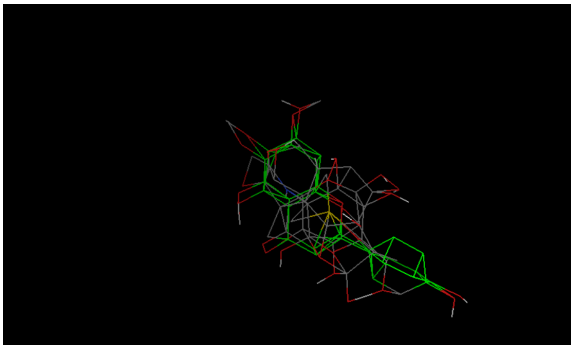


Figure 3: Ligand hispidulin after preprocessing.

5 MOLECULAR DOCKING

5.1 Defining Binding Site

There are two ways in which docking can be done: specific site docking or blind docking. In blind docking, because the binding sites are unknown, the whole protein is used. For specific site docking, expert chemistry knowledge is needed to define the binding site in the protein. Information about the place where other ligands are binded is necessary, because another ligand is suposed to be binded in the same position. If the amino acids are known, the region we are interested at can be found with AutoDock tools. Therefore, since we have the information describing the docking sites, we are going to do specific site docking.

Targeted docking sites for ACE2 are (375, 505, 273, 345, 371, 30 to 41, 82 to 84, and 353 to 357). For molecular docking of the main protease, the selected cavity is the binding site of inhibitor N3. Binding sites for the spike glycoprotein in chain E are (361 to 368, 391 to 399, 401, 414, 416, 420, 422, 489, 490 and 494), and in chain C they are (361 to 368, 391 to 395, 397 to 401, 414, 416, 420, 422, 489, 490 and 494).

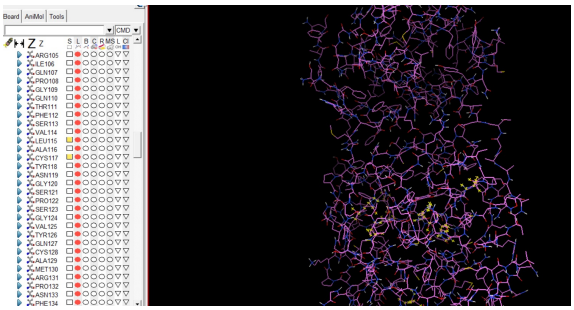


Figure 4: Defining binding site of main protease with AutoDock Tools.

Fig. 4 presents an example of main protease with selected amino acids. They are represented with yellow crosses on the picture and it can be noticed that all of them are in particular part of the molecule. That part should be taken into consideration for the process of docking.

5.2 Grid Box for Docking

Next step is enclosing the binding site for the ligand in a grid box. We used AutoDock tools software to position the grid box because there we can select the binding site amino acids and place the box at the most appropriate location of the protein. Spike glycoprotein with selected amino acids, enclosed in a grid box is shown on Fig 5. This way we defined the following boxes.

Grid box of size (74, 70, 80) centered at (4.166, -23.345, 14.697) was used for the *Spike glycoprotein*. Grid box with center at (-13.309, 14.415, 61.16), and size (30, 40, 40) was used for the *main protease*. For *ACE2* the grid box we used was with size (126, 88, 68), and centered at (68.719, 73.5, 26.656).

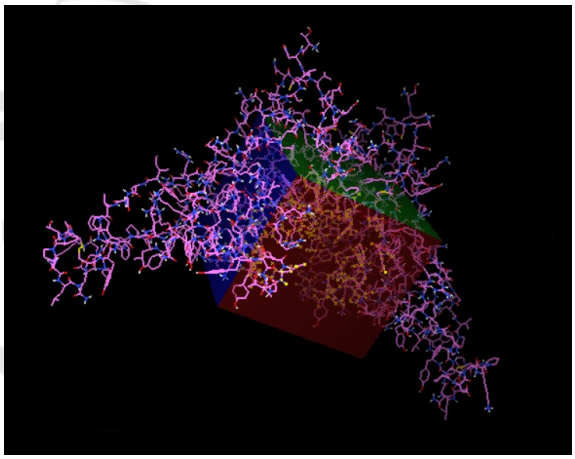


Figure 5: Grid box with AutoDock tools.

5.3 Running AutoDock Vina

As a result from the experiments AutoDock Vina, produces log file. This file consists of all the poses generated by the AutoDock Vina along with their binding affinities and RMSD scores. The first pose is considered to be the best pose, since it has more binding affinity than the other poses and is without any RMSD value. The structure of the file is presented in Fig. 6.

```
mode |   affinity | dist from best mode
     | (kcal/mol) | rmsd l.b.| rmsd u.b.
-----+------------+----------+----------
   1         -7.3      0.000      0.000
   2         -7.2      1.166      1.345
   3         -7.1      2.907      6.346
   4         -6.8      9.618     13.792
   5         -6.7      8.731     13.334
   6         -6.7      1.709      7.266
   7         -6.6      6.695     10.515
   8         -6.6     14.255     17.428
   9         -6.5      2.889      6.963
```

Figure 6: Example of log file that is result from AutoDock Vina.

6 RESULTS

Tables 1, 2, and 3 present the results obtained from the experiments. The molecular docking results showed best dock score with Auranetin with all three proteins. It has shown affinity of -11.3 with Spike protein, -12.5 with ACE2 and -9.1 affinity with main protease. This is a good indication to propose Auranetin for further investigation in developing treatments against COVID-19. Auranetin belongs to the class of organic compounds known as 8-o-methylated flavonoids. These are flavonoids with methoxy groups attached to the C8 atom of the flavonoid backbone. Thus, Auranetin is considered to be a flavonoid lipid molecule. Auranetin is a very hydrophobic molecule, relatively neutral and practically insoluble in water. Outside of the human body, auranetin has been detected, but not quantified in, citrus (Yannai, 2003).

Obacunone, Pomiferin, Eucalyptin and Hesperetin showed lower binding energy to Spike protein active site compared to Remdesivir and Dexamethasone. Obacunone is a natural compound present in citrus fruits. It has been demonstrated for various biological activities including anti-cancer and anti-inflammatory properties (Xiang et al., 2015) (Jing et al., 2019).

Pomiferin can be found along with osajin in the fruits and female flowers of the osage orange tree (Maclura pomifera). It is a prenylated isoflavone that has demonstrated efficacy as an antioxidant, cardioprotectant, antimicrobial, antidiabetic, PDE5 inhibitor and cytotoxicity for several cancer cell lines (Gruber et al., 2014).

Eucalyptin has antioxidant and antimicrobial properties, and also is natural compound. Hesperetin is also flavonoid, same as Auranetin. This compound, in the form of its glycoside hesperidin, is the predominant flavonoid in lemons and oranges. It has antioxidative, antiinflammatory, and neuroprotective effects (Hwang et al., 2015).

Most of the compounds that showed highest affinity with these three proteins are natural compounds that display a large variety of biological activities.

Table 1: Results of molecular docking with *Spike protein*.

Spike protein	
Ligand	Affinity (kcal/mol)
Auranetin	-11.3
Obacunone	-8.1
Pomiferin	-7.7
Eucalyptin	-7.5
Hesperetin	-7.5
Dexamethazone	-7.5
Alnetin	-7.2
Pedalitin	-7.2
Remdesivir	-7.2
Citromycetin	-7.0
Trifluoperazine	-6.8
Tangeretin	-6.6
Nobiletin	-6.6
Sinensetin	-6.5
Beta D Mannose	-5.4
Dimetylsulphoxide	-2.7

Table 2: Results of molecular docking with *ACE2*.

ACE2	
Ligand	Affinity (kcal/mol)
Auranetin	-12.5
Obacunone	-10.0
Pomiferin	-8.9
Dexamethasone	-8.3
Pedalitin	-8.2
Hesperetin	-8.0
Trifluoperazine	-7.8
Eucalyptin	-7.8
Sinensetin	-7.8
Tangeretin	-7.7
Remdesivir	-7.7
Alnetin	-7.6
Nobiletin	-7.2
Citromycetin	-6.8
Beta D Mannose	-5.9
Dimetylsulphoxide	-2.4

6.1 Analysing AutoDock Vina Results with PyMOL

After getting the results from AutoDock Vina, they can be analysed by using the PyMOL software (PyMOL, 2020). It allows the analysis of all the poses generated from our docking study, starting from the pose with highest affinity, to the one with lowest affinity (Yuan et al., 2017).

Inspecting the ligand sites, we can see the bonds that exist between the ligand and the residues of the protein. If the residue that is part of the interaction is one of the binding sites of the protein, it means that the ligand is situated well in the protein's cavity.

Table 3: Results of molecular docking with *Main protease*.

Main Protease	
Ligand	Affinity (kcal/mol)
Auranetin	-9.1
Pomiferin	-7.2
Obacunone	-7.1
Dexamethazone	-6.8
Remdesivir	-6.3
Pedalitin	-6.2
Trifluoperazine	-6.2
Hesperetin	-6.1
Sinensetin	-6.0
Alnetin	-5.9
Citromycetin	-5.7
Eucalyptin	-5.7
Nobiletin	-5.7
Tangeretin	-5.5
Beta D Mannose	-5.2
Dimethylsulphoxide	-2.4

Auranetin forms bond with Trp423 amino acid of the spike glycoprotein. Unfortunately, it is not part of the active site of the protein. It may be allosteric site, but this needs to be confirmed by additional experiments and analysis. In biochemistry, regulation of an enzyme by binding an effector molecule at a site other than active site, is called allosteric regulation (Cooperman, 2013). Effectors that decrease the protein's activity are called allosteric inhibitors. The interaction of Auranetin and spike glycoprotein is shown in Fig. 7.

The bonds formed between the main protease and auranetin are with the three residues: Lys137, Val202 and Glu288, that again are not part of the active site. This is shown in Fig. 8. Auranetin forms bond with Tyr158 amino acid of ACE2, and this can be seen on Fig. 9.

Analysis of obacunone, the second compound that showed highest affinity after auranetin, was also done. It formed two bonds with active site of spike glycoprotein, more precisely with Arg495 and Gln401 amino acids. This is shown in Fig. 10. Except auranetin, we suggest doing additional experiments of obacunone. This compound may also be considered in developing suitable drug for Sars-CoV-2.

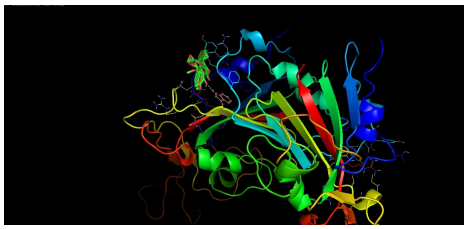


Figure 7: Complex of Spike protein and Auranetin with selected ligand sites in PyMOL.

Figure 8: Complex of main protease and Auranetin with selected ligand sites in PyMOL.

Figure 9: Complex of ACE2 and Auranetin with selected ligand sites in PyMOL.

7 CONCLUSIONS

In summary, we have performed the molecular docking studies of ligands, mostly natural components, chosen randomly with three important proteins (main protease, ACE2, and spike glycoprotein) and compared the dock score results with remdesivir and dexamethasone. Our results revealed that many of the

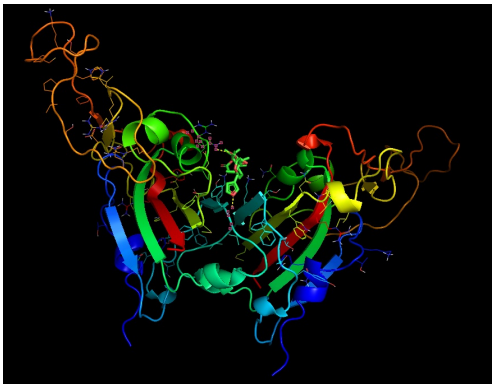


Figure 10: Complex of Spike protein with Obacunone with selected ligand sites in PyMOL.

tested ligands showed higher dock score than remdesivir and dexamethasone, with the maximum dock score shown by auranetin. Therefore, with the combined docking results and the medical importance of auranetin, we propose that auranetin and other flavonoids can be further studied with the aim to get suitable drugs against COVID-19.

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