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Molecular Docking Studies of Coronavirus Proteins with Medicinal Plant-Based Phytochemicals

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ABSTRACT

In this study, we presented an *in silico* molecular docking between the SARS-CoV-2 four proteins [(a) SARS-CoV-2 nucleocapsid protein N-terminal RNA binding domain (6M3M), (b) Nsp9 RNA binding protein of SARS CoV-2 (6W4B), (c) The crystal structure of COVID-19 main protease in apo form (6M03), and (d) Structure of the 2019-nCoV HR2 Domain (6LVN)] available in the PDB (Protein Data Bank), and the medicinal plant-based phytochemicals (retrieved from PubChem database) as ligand molecules i.e. Piperine (Black Pepper), Eugenol (Clove), Alliin (Garlic), Gingerol (Ginger) and Curcumin (Turmeric). All these ligand molecules showed good docking with their respective receptor molecules and their scores range from -8.195 to -5.263. DockThor Portal (a receptor ligand-docking server) which was recently developed and published this year were used in the current study. The obtained results might help in the wet lab conditions to develop better antiviral compounds against SARS-CoV-2.

Keywords: SARS-CoV-2; COVID-19; Docking; Coronavirus; Proteins; Medicinal plants; Phytochemicals; Ligand; DockThor'; Antivirals

1. INTRODUCTION

Currently, the entire world is facing the lockdown type situation caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), identified as the novel coronavirus (nCoV, family: Coronoaviridae) responsible for causing the Coronavirus Disease in 2019 designated as COVID-19[1]. The recent outbreak of novel coronavirus (nCoV-2019) or SARS-CoV-2 has raised a challenged to design a drug for this deadly virus. However, to date, no approved drug is available for this pathogenic virus (infectious pathogen transmitted through Human to Human). Computational drug discoveries against SARS-CoV-2 from natural sources has been suggested and tried by many scientist across the globe this year. This includes several *in silico* studies and few wet lab trials[2-4].

This novel coronavirus marked its origin from Wuhan, the capital of Central China's Hubei province. Bats, birds, camels, and pangolins are considered as the potential natural reservoir of SARS-CoV-2 and the virus was later transmitted to humans. The COVID-19 virus is fatal to humans in most of the cases and the mortality rate is increasing day by day (killed over 45,000 people and infected over 9,00,000)[5]. Symptoms related to COVID-19 includes Sore Throat, Fever, Pneumonia, Sneezing, Headache, Cough, Acute Respiratory Distress Syndrome, Acute Cardiac Injury, Rhonorrhea, Fatigue, Sputum Production, Haemoptysis, Ground Glass Opacities, Hypoxemia, Dysponea, RNAaemia, Lymphopenia and Diarrhoea[6]. Every country is devising different strategies to minimise the outbreak of SARS-CoV-2 responsible for the COVID-19 pandemic[7]. Several medicines and vaccines are under trial to find the possible cure against the SARS-CoV-2[8], meanwhile, precautionary measures and social distancing have been suggested and the only way to limit the spread of coronavirus[9-10].

The genome of SARS-CoV-2 consists of a positive single-stranded RNA [(+) ssRNA]. Various proteins present in the viral structure are Spike (S) glycoprotein, Nucleocapsid (N) phosphoprotein, Membrane (M) glycoprotein and Small Envelope (E) glycoprotein[11]. Teams of doctors and scientists are working day and night to find a possible cure to tackle this virus. Keeping this in view, here we have presented a study which might be helpful for scientists and doctors. One such computational molecular docking approach has been taken up by us which might be helpful in developing antiviral compounds against this deadly virus.

2. MATERIAL AND METHODS

Protein and ligand interactions play a crucial role, wherein the latter is responsible for limiting/diminishing the activity of the former in many human cellular and biological functions. In our study, we have taken the assistance of online freely available DockThor Portal (www.dockthor.lncc.br) designed for receptor-ligand docking, developed by Grupo de Modelagem Molecular de Sistemas Biológicos (GMMSB) (www.gmmsb.lncc.br) situated at Laboratório Nacional de Computação Científica (LNCC) Petrópolis – Brazil, which runs virtual screening experiments on Santos Dumont supercomputer. DockThor

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Portal is well equipped with software's like MMFFLigand, PdbThorBox, DockThor, and Dtstatistic[12].

For docking, we have considered four SARS-CoV-2 proteins as receptor molecules and the same were mined from the PDB database (www.rcsb.org/) in the .pdb format i.e. (a) SARS-CoV-2 nucleocapsid protein N-terminal RNA binding domain (6M3M), (b) Nsp9 RNA binding protein of SARS CoV-2 (6W4B), (c) The crystal structure of COVID-19 main protease in apo form (6M03), (d) Structure of the 2019-nCoV HR2 Domain (6LVN). These four SARS-CoV-2 proteins were docked separately against five ligand molecules i.e. Piperine (Black Pepper: *Piper nigrum*), Eugenol (Clove: *Syzygium aromaticum*), Alliin (Garlic: *Allium sativum*), Gingerol (Ginger: *Zingiber officinale*) and Curcumin (Turmeric: *Curcuma longa*). Avoiding the harmful effects of chemical based compounds, selection of phytochemicals were made based on a green approach. These medicinal plant-based phytochemicals were considered and their 3 D structure files were retrieved from the PubChem (pubchem.ncbi.nlm.nih.gov/) database in the .sdf format, later converted to .pdb format. The retrieved receptors and ligand files were uploaded / submitted to the DockThor Portal for docking study. Parameters taken up during the docking procedure were Number of Evaluations: 1000000, Population Size: 750, Initial Seed: -1985, Number of Runs: 24, Docking: Soft, Spatial discretisation of the energy grid: 0.25Å, Grid points: <1,000,000. Water molecules were excluded from the structure and the results were downloaded, analysed and viewed on JSmol (View 3D) option provided by the server.

3. RESULTS AND DISCUSSION

The submitted project on the DockThor Portal employs the computational facilities provided by the Brazilian SINAPAD (Sistema Nacional de Alto Desempenho) having a high-performance platform. Upon completion, the DockThor Portal generated twenty-four different models for each docking experiment (4 x 5 x 24 = 480 in total) between the SARS-CoV-2 protein receptors and phytochemical ligands and the best ones were selected. This virtual screening method initially docks and then scores individual ligand molecules. Their Total Energy (T. Energy) [Total Energy = Intermolecular ligand-receptor + Intramolecular ligand energies], Interaction Energy (I. Energy), van der Waals energy (vdW), Coulomb energy

Table 1. Docking data generated by DockThor server between various ligands molecules and Coronavirus proteins as receptor molecules available in the PDB (Protein Data Bank) database.

S. No.	Ligand	Plant	T. Energy	I.Energy	vdW	Coul	Num Rotors	RMSD	Score
6M3M	Piperine	Pepper	8.352	-23.093	-0.158	-2.935	4	0.000	-8.118
	Eugenol	Clove	7.558	-20.325	-11.632	-8.693	3	0.000	-7.331
	Alliin	Garlic	-10.510	-25.844	-2.279	-23.565	5	0.000	-6.355
	Gingerol	Ginger	-3.213	-31.300	-18.842	-12.458	10	0.000	-7.897
	Curcumin	Turmeric	30.841	-34.224	-19.053	-15.171	8	0.000	**-8.195**
6W4B	Piperine	Pepper	29.771	-1.488	-1.194	-0.294	4	0.000	-5.925
	Eugenol	Clove	26.386	-1.335	-1.265	-0.070	3	0.000	-5.966
	Alliin	Garlic	12.292	-1.377	-1.129	-0.248	5	0.000	-5.859
	Gingerol	Ginger	24.488	-1.213	-1.100	-0.113	10	0.000	-5.878
	Curcumin	Turmeric	59.240	-1.422	-1.338	-0.084	8	0.000	**-5.969**
6M03	Piperine	Pepper	0.686	-30.939	-17.942	-12.997	4	0.000	**-8.167**
	Eugenol	Clove	6.843	-23.038	-3.559	-19.479	3	0.000	-6.625
	Alliin	Garlic	-14.407	-29.422	-6.038	-23.384	5	0.000	-6.461
	Gingerol	Ginger	-5.959	-41.082	-11.427	-29.655	10	0.000	-6.957
	Curcumin	Turmeric	25.169	-43.148	-14.385	-28.763	8	0.000	-7.045
6LVN	Piperine	Pepper	31.226	-0.032	-0.001	-0.031	4	0.000	**-5.705**
	Eugenol	Clove	27.686	-0.022	-0.001	-0.021	3	0.000	-5.640
	Alliin	Garlic	13.641	-0.026	-0.001	-0.025	5	0.000	-5.332
	Gingerol	Ginger	25.801	-0.023	-0.001	-0.022	10	0.000	-5.263
	Curcumin	Turmeric	60.633	-0.023	-0.001	-0.022	8	0.000	-5.440

T. Energy = Total Energy; I. Energy = Interaction Energy; vdW = van der Waals energy; Coul = Coulomb energy; NumRotors = Number of rotatble chemical bonds; RMSD = Root Mean Square Deviation

(Coul), Number of rotatable chemical bonds (NumRotors) and Root Mean Square Deviation (RMSD) values are given in Table 1. The best scores are given in the last column of the table on which these models were selected.

In all the screened ligands, a minimum number of NumRotors were found in Eugenol ligand and maximum in the case of Gingerol. These values give an idea of the conformational difference between the alternative ligand binding modes. All the suggested ligand molecules showed docking with their respective receptor molecules and their detailed three-dimensional view can be seen perfectly in (Annexure I). SARS-CoV-2 proteins can be visualised in their secondary structure and ribbon form, whereas ligands molecules are presented in Grey colour at the centre of each docking results. Cases of COVID-19 patients are increasing across the globe and even diagnosed in those humans which had no travel history to China suggesting the seriousness of this pandemic and demands for curing at earliest[13]. In the race of various clinical trials on several vaccines that are underway and using traditional medicine against the coronavirus, there is a great demand to find its cure[14, 15]. The performed study showed the synergistic nature of the compounds within each medicinal plant. Combination of the most enriched plants in the created network could be chosen for mitigation of SARS-CoV-2. Further molecular dynamic simulation studies, in vitro and in vivo analyses are required to confirm the results of our study, however, the insights provided by the present study may authenticate valuable investigation and development of anti-SARS-CoV-2 compounds having natural origin with therapeutic properties.

4. CONCLUSION

We have done a green approach based on docking studies previously on plant viruses[16-17]. This time we have applied this tactic on animal virus Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) which considered humans, bats, pangolins as its host. All the ligand molecules used in this *in silico* experiment (dry lab) have strong antioxidant and medicinal properties and they can be coupled/conjugated with drug molecules in wet lab conditions to develop better antiviral compounds. This might be a solution against the pandemic caused by the deadly novel coronavirus (COVID-19). This manuscript will help scientists and doctors to consider such ligands in their future drug development and targeting experiments against SARS-CoV-2.

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He designed the experiments and edited the first draft.

Annexure I

Figures 1 to 24: 3 D (Three dimensional) Ribbon views of the Docking results generated by DockThor server between various ligands molecules and Coronavirus proteins as receptor molecules available in the PDB (Protein Data Bank) database. Ligands molecules are presented in Grey colour at the centre of each docking results.

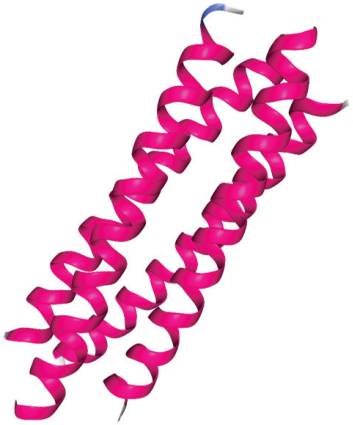

Figure 1. Structure of the 2019-nCoV HR2 Domain (6LVN).

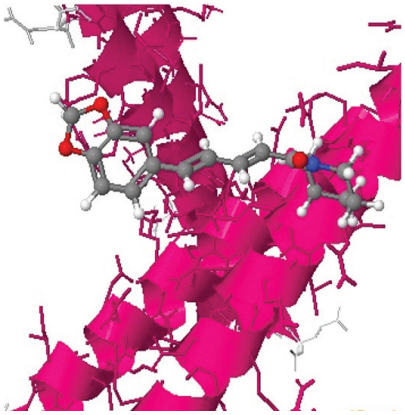

Figure 2. 6LVN vs Piperine.

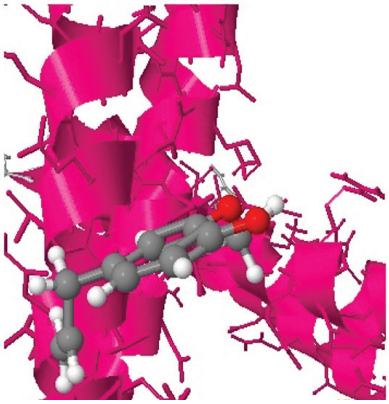

Figure 3. 6LVN vs Eugenol.

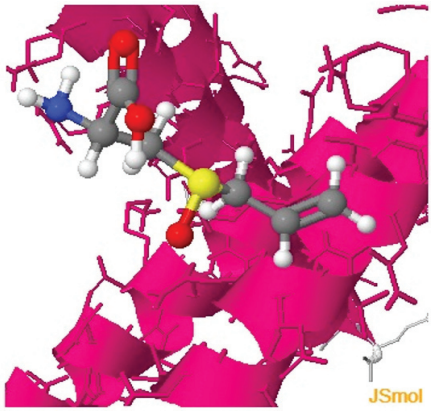

Figure 4. 6LVN vs Alliin.

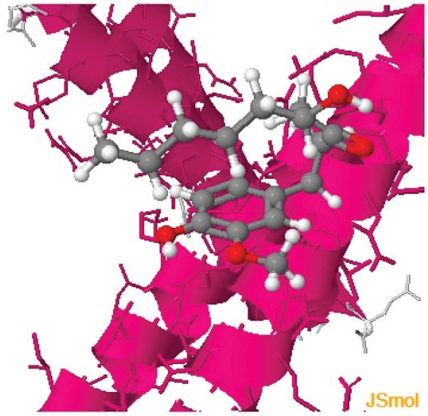

Figure 5. 6LVN vs Gingerol.

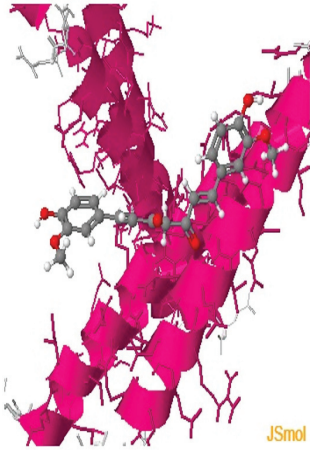

Figure 6. 6LVN vs Curcumin.

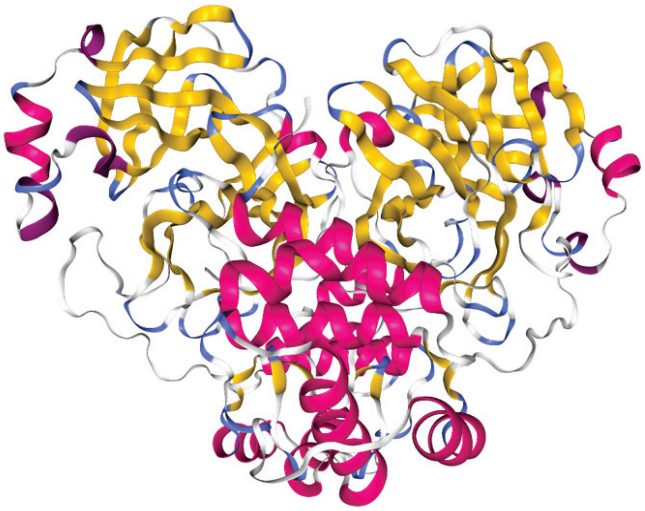

Figure 7. Structure of the COVID-19 main protease in apo form (6M03).

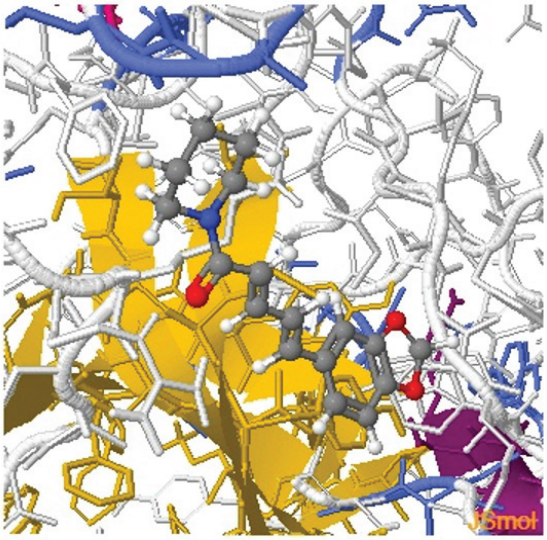

Figure 8. 6M03 vs Piperine.

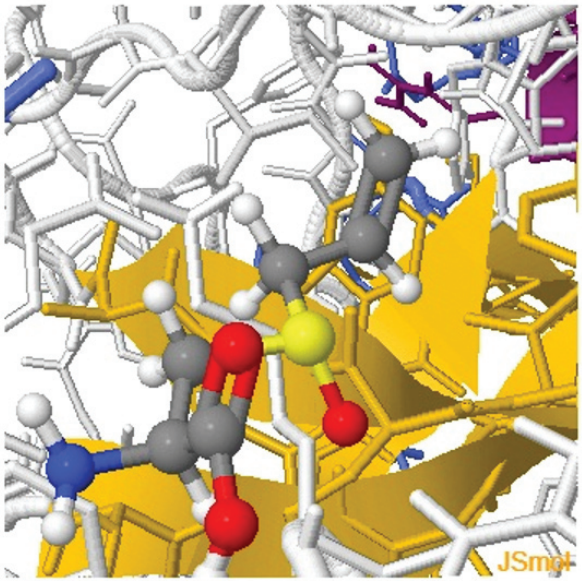

Figure 9. 6M03 vs Eugenol.

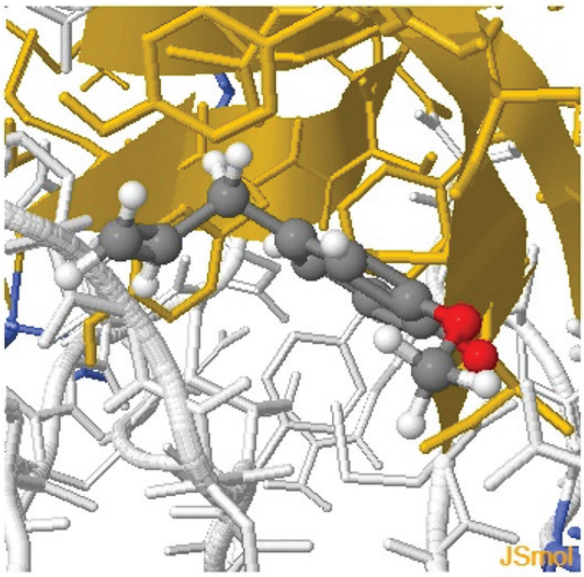

Figure 10. 6M03 vs Alliin.

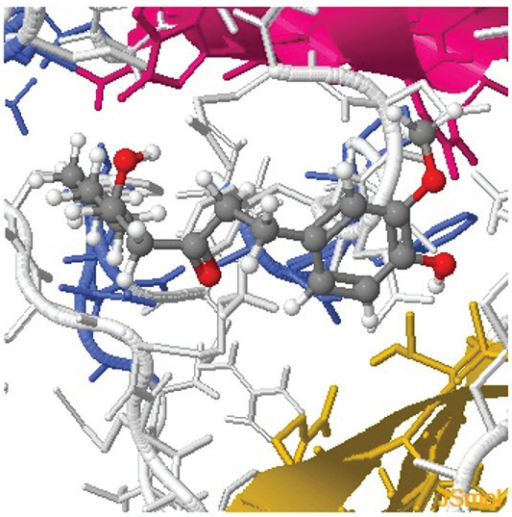

Figure 11. 6M03 vs Gingerol.

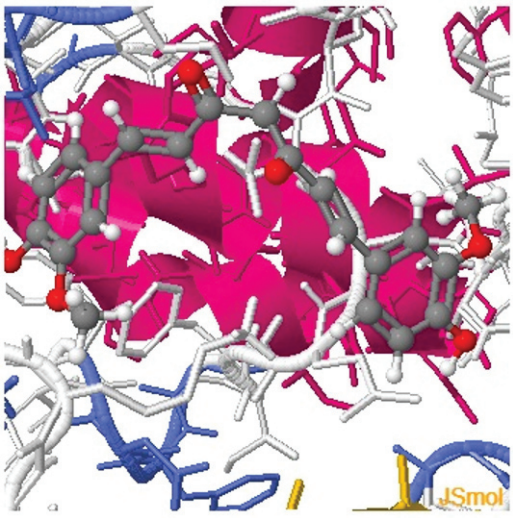

Figure 12. 6M03 vs Curcumin.

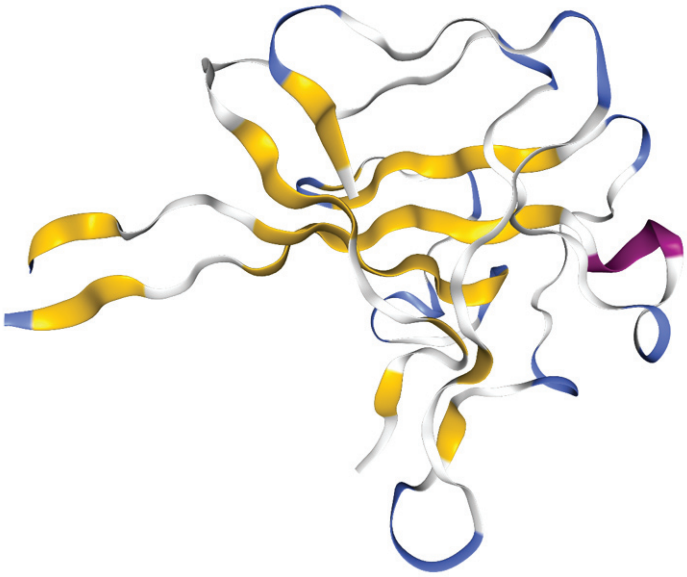

Figure 13. Structure of the SARS-CoV-2 nucleocapsid protein N-terminal RNA binding domain (6M3M).

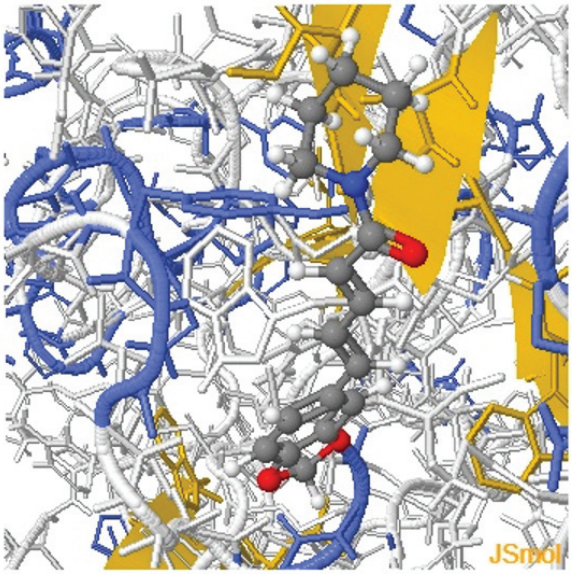

Figure 14. 6M3M vs Piperine.

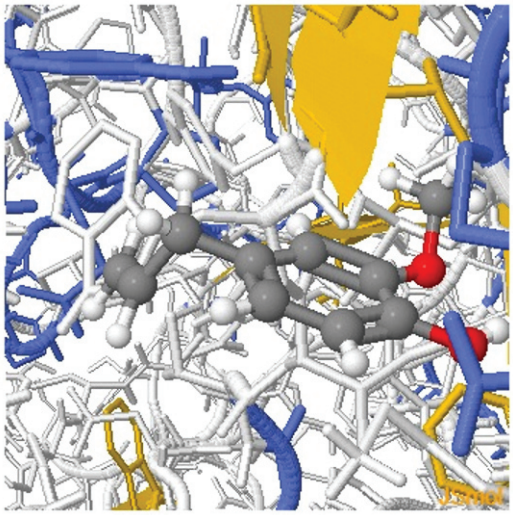

Figure 15. 6M3M vs Eugenol.

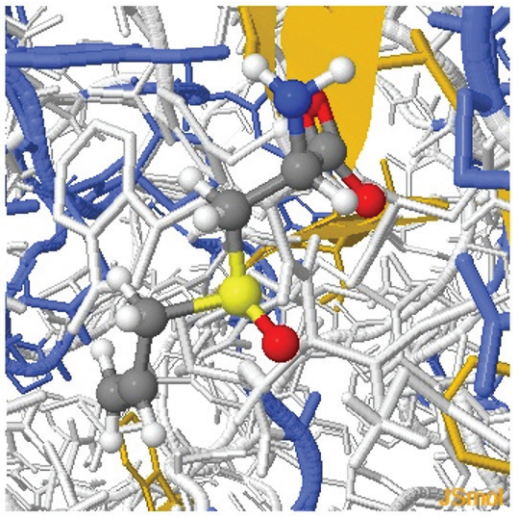

Figure 16. 6M3M vs Alliin.

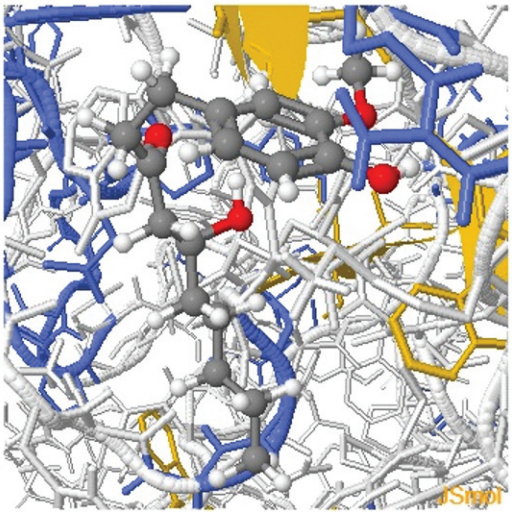

Figure 17. 6M3M vs Gingerol.

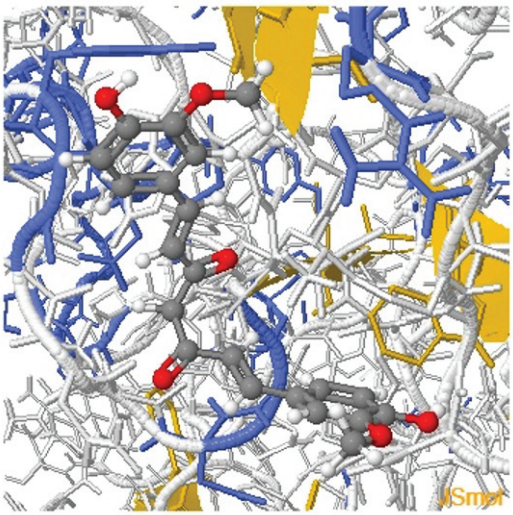

Figure 18. 6M3M vs Curcumin.

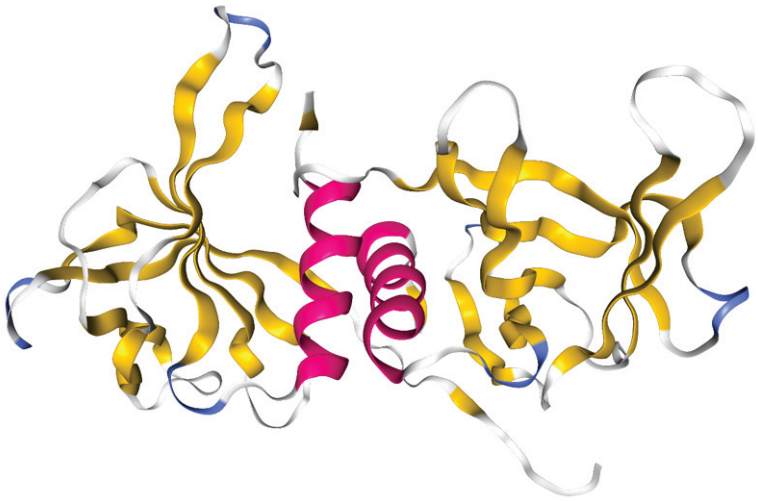

Figure 19. Structure of the Nsp9 RNA binding protein of SARS CoV-2 (6W4B).

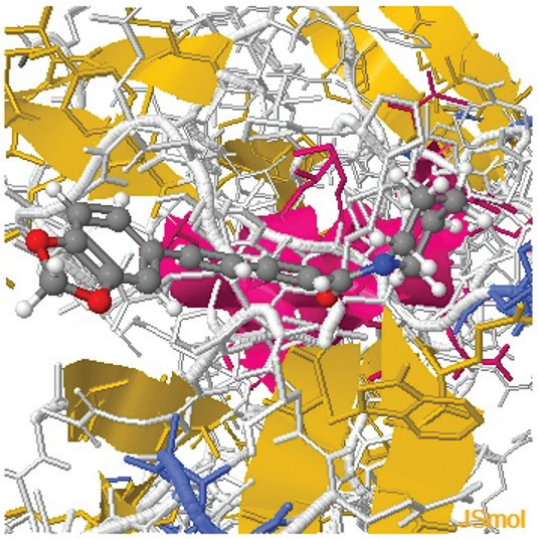

Figure 20. 6W4B vs Piperine.

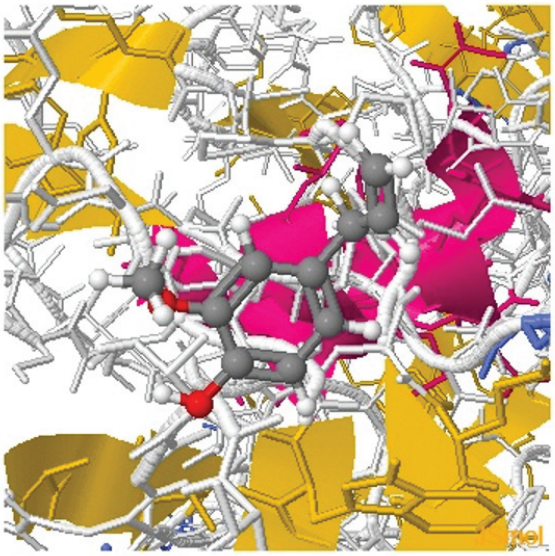

Figure 21. 6W4B vs Eugenol.

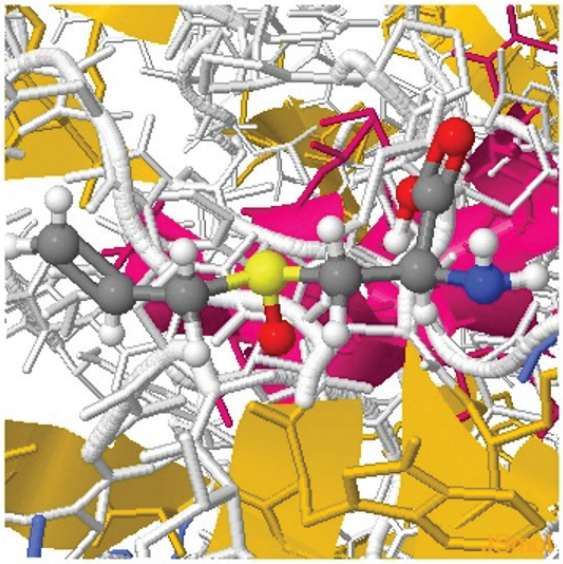

Figure 22. 6W4B vs Alliin.

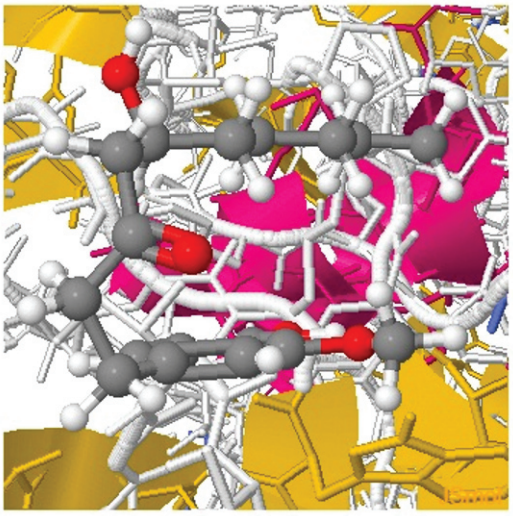

Figure 23. 6W4B vs Gingerol.

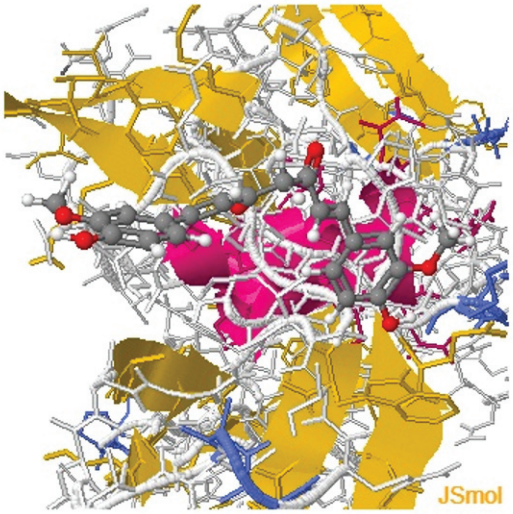

Figure 24. 6W4B vs Curcumin.