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Identification of the Potent Inhibitors for a Coronavirus Protease- an *In-Silico* Approach

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Abstract - *In December 2019, the outbreak of novel coronavirus disease (COVID-19) has spared from Wuhan to every continent on the earth in every single generation. Till now, there is no treatment for severe disease COVID-19 and very hard to control the current situation, as WHO concerns pandemic. COVID-19 also belongs to genera β-CoVs shows similarity with SARS-CoV. Both use the ACE-2 receptor for their entry into the human host cell by interaction of spike glycoprotein which present on the surface of coronavirus. Some of the pre-existing drugs such as, Hydroxychloroquine, and Favipiravir that have shown effective results against COVID-19. Phytochemicals, especially flavonoids, also having anti-viral properties against CoVs have been reported in studies to inhibit COVID-19 virus main protease. I performed a molecular docking study using the drug Hydroxychloroquine and Favipiravir and 40 flavonoids molecules. This study suggested that, among these Silymarin, Quercetin, β-Naphthoflavone, and Apigenin can be the potential drug. These all having much higher binding affinity against target COVID-19 main protease and docked with similar binding pocket residues.*

Key Words: **Coronavirus, COVID-19, Beta coronaviruses, β-CoVs, SARS-CoV-2, Main proteases, Flavonoids, Docking, Drug discovery.**

1. INTRODUCTION

In December 2019, the outbreak of novel coronavirus disease (COVID-19), have originated in bats first in the Wuhan region, China. COVID-19 (transmitted from Bat to Human) has spared from Wuhan to every continent on the earth in every single generation. Thus, the World Health Organization (WHO) concerns Covid-19 to a global pandemic on 11 March 2020 [1, 2, 3].

Timeline of COVID-19: In India, according to India Fights Corona COVID-19, there are 80,722 peoples who have active Cases, 4,167 peoples were Death, and 60,490 peoples were Cured / Discharged on 26th May, 2020 [4]. As the World Health Organization (WHO) report, COVID-19 spread in 215 Countries, areas, or territories. Worldwide there are 5,370,375 peoples Confirmed cases and 344,454 peoples Confirmed death on 26th May, 2020 [5].

Beta coronaviruses (β-CoVs) are known to affect a wide range of birds and Mammals such as severe acute respiratory syndrome (SARS) in 2003 and the Middle East respiratory syndrome (MERS) in 2012. COVID-19 caused by SARS-CoV-2 shows similarity with SARS-CoV their origin in live animal (Bat) and transmitted to Human. SARS-CoV causes SARS & ARDS disease and SARS-CoV-2 cause SARS & COVID-19 disease. Both viruses show similar symptoms as fever, cough, and shortness of breath. The study also showed that both show 79% genomic sequence similarity and share conserved binding domain for their S-protein. The angiotensin-converting enzyme 2 (ACE2) receptor is common in both for their entry in the human host cell [7, 12].

COVID-19 also belongs to genera β-CoVs, uses single-stranded (positive-sense) RNA as their genetic material which associated with a nucleoprotein within a capsid comprised of matrix protein which makes a difference in their genomic and phenotypic structure from others. The length of the genome is around 30 kb, which codes for both structural proteins: spike (S), membrane (M), envelope (E), and nucleocapsid (N) and non-structural proteins [6].

Spike proteins play an essential role in viral entry into host cells. These protein binds to human cells through its spike glycoprotein, a trimeric class-1 fusion protein, making this protein a key target for potential therapies and diagnosis. This genome acts just like a messenger RNA when it infects a cell and directs the synthesis of two long polyproteins that include the machinery that the virus needs to replicate new viruses. These proteins include a replication/transcription complex that makes more RNA, several structural proteins that construct new virions, and two proteases. The main proteases (Mpro) play essential roles in cutting the polyproteins into all of these functional pieces [8].

Flavonoids are naturally occurring secondary metabolites widely found in Medicinal plants and rich in Dietary sources. Flavonoids have Pharmacological properties that include antioxidant, anti-inflammatory, anti-viral, anticancer, antimicrobial, and immunomodulatory functions. Different flavonoids have been found to antiviral activity against parainfluenza virus, poliovirus, herpes virus, HIV, Respiratory syncytial virus and etc. Preliminary studies indicate that flavonoids can inhibit viral infections by interfering with host factors that are essential for the virus for their survival in host cells [9,10].

Some of the pre-existing drugs (Chloroquine, Remdesivir, Lopinavir, Ritonavir, Arbidol, Hydroxychloroquine, Favipiravir) have been previously tested to test their efficacy and safety in the treatment of viral disease like Influenza, Ebola, SARS, and MERS-CoV. Hydroxychloroquine is used to prevent or treat malaria and Favipiravir is an antiviral medication used to treat influenza. As coronaviruses belongs

to SARS family and very closely related, some studies suggesting it may have some effect in patients with COVID-19 which generated promising result [11-12].

2. MATERIALS & METHOD

2.1 Retrieval of protein

Protein data bank (PDB) is a repository for 3-D structure of protein in detail. The 3-D structure of target protein COVID-19 main protease was obtained from PDB (PDB ID: 5R84).

2.2 Library and ligand structure preparation

PubChem is an open database of chemical molecules and their activities against biological assays. The structure of the drug (Hydroxychloroquine and Favipiravir) and 40 flavonoids phytochemical compound was retrieved from Pubchem in SDF format. The activities of all compounds were taken in terms of inhibitory activity, which satisfied the Lipinski's rule of 5.

Table -1: Drug and Flavonoids ligand molecule follow Lipinski's rule of 5

S. No.	Pubchem CID	Compound Name	Mol. Formula	Mol. Wt. (g/mol)	XlogP3	H-Bond Donor Count	H-Bond Acceptor Count
1.	5280442	Acacetin	$C_{16}H_{12}O_5$	284.2	2.1	2	5
2.	5280443	Apigenin	$C_{15}H_{10}O_5$	270.2	1.7	3	5
3.	5281605	Baicalein	$C_{15}H_{10}O_5$	270.2	1.7	3	5
4.	14236566	Bavachin	$C_{20}H_{20}O_4$	324.4	4.1	2	4
5.	2361	B-Naphthoflavone	$C_{19}H_{12}O_2$	272.3	4.4	0	2
6.	641785	Cardamonin	$C_{16}H_{14}O_4$	270.2	3.5	2	4
7.	73160	Catechin	$C_{15}H_{14}O_6$	290.2	0.4	5	6
8.	160237	Cirsiliol	$C_{17}H_{14}O_7$	330.2	2	3	7
9.	128861	Cyanidin	$C_{15}H_{11}O_6^+$	287.2	---	5	5
10.	5281708	Daidzein	$C_{15}H_{10}O_4$	254.2	2.5	2	4
11.	5281612	Diosmetin	$C_{16}H_{12}O_6$	300.2	1.7	3	6
12.	72276	Epicatechin	$C_{15}H_{14}O_6$	290.2	0.4	5	6
13.	440735	Eriodictyol	$C_{15}H_{12}O_6$	288.2	2	4	6
14.	492405	Favipiravir	$C_5H_4FN_3O_2$	157.1	-0.6	2	4
15.	5281614	Fisetin	$C_{15}H_{10}O_6$	286.2	2	4	6
16.	10251	Flavanone	$C_{15}H_{12}O_2$	224.2	3.2	0	2
17.	145858	Flavylium (Anthocyanins)	$C_{15}H_{11}O^+$	207.2	---	0	0
18.	5280961	Genistein	$C_{15}H_{10}O_5$	270.2	2.7	3	5
19.	124052	Glabridin	$C_{20}H_{20}O_4$	324.3	3.9	2	4
20.	6253344	Helichrysetin	$C_{16}H_{14}O_5$	286.2	3.1	3	5
21.	5280544	Herbacetin	$C_{15}H_{10}O_7$	302.2	2.2	5	7
22.	72281	Hesperetin (citrus-flavonoid)	$C_{16}H_{14}O_6$	302.2	2.4	3	6
23.	5281628	Hispidulin	$C_{16}H_{12}O_6$	300.2	1.7	3	6
24.	3652	Hydroxychloroquine	$C_{18}H_{26}ClN_3O$	335.9	3.6	2	4
25.	5318980	Icaritin	$C_{21}H_{20}O_6$	368.4	4.8	3	6
26.	3747	Ipriflavone	$C_{18}H_{16}O_3$	280.3	4	0	3
27.	5464170	Irigenin	$C_{18}H_{16}O_8$	360.3	2.6	3	8
28.	5281654	Isorhamnetin	$C_{16}H_{12}O_7$	316.2	1.9	4	7
29.	513197	Isoxanthohumol	$C_{21}H_{22}O_5$	354.4	4.1	2	3
30.	5280863	Kaempferol	$C_{15}H_{10}O_6$	286.2	1.9	4	6
31.	5280445	Luteolin	$C_{15}H_{10}O_6$	286.2	1.4	4	6
32.	159287	Malvidin	$C_{17}H_{15}O_7$+	331.2	---	4	6
33.	5281670	Morin	$C_{15}H_{10}O_7$	302.2	1.5	5	7
34.	439246	Naringenin	$C_{15}H_{12}O_5$	272.2	2.4	3	5
35.	73201	Pinostrobin	$C_{16}H_{14}O_4$	270.2	3.1	1	4
36.	5280459	Quercetin	$C_{15}H_{10}O_7$	302.2	1.5	5	7

37.	73571	Sakuranetin	$C_{16}H_{14}O_5$	286.2	2.7	2	5
38.	1548994	Silymarin	$C_{25}H_{22}O_{10}$	482.4	2.4	5	10
39.	124211	Skullcapflavone II	$C_{19}H_{18}O_8$	374.3	2.9	2	8
40.	439533	Taxifolin	$C_{15}H_{12}O_7$	304.2	1.5	5	7
41.	460715	Trihydroxychalcone	$C_{15}H_{12}O_4$	253.2	3.2	3	4
42.	5281703	Wogonin	$C_{16}H_{12}O_5$	284.2	3	2	5

2.3 Molecular docking

Study of molecular docking of COVID-19 main protease (PDB ID: 5R84) with the drug (Hydroxychloroquine and Favipiravir) and 40 flavonoids compound was done by using virtual screening tool PyRx AutodockVina v0.8. The cleaning of protein was done by removing the water molecule, heteroatoms, and bounded ligand molecules to prepare the protein for further docking by adding H atom to them. All the ligand molecules were docked with the selected targets to know their conformation in the binding pocket of protein and their binding energy. Binding pose with the highest docked energy of all ligand molecules was selected for analysis. Protein-ligand interaction and binding pocket was analysed by PyMOL and UCSF Chimera [13, 14].

3. RESULTS & DISCUSSION

3.1 Protein interaction with pre-existing drugs

The *in-silico* protein-ligand interaction gives the information about the interacting residue, H-bond along with the docking score. The picture shows the labelled residues interacting within 4 Ă of the protein (PDB ID: 5R84) with docked ligand namely, Hydroxychloroquine and Favipiravir.

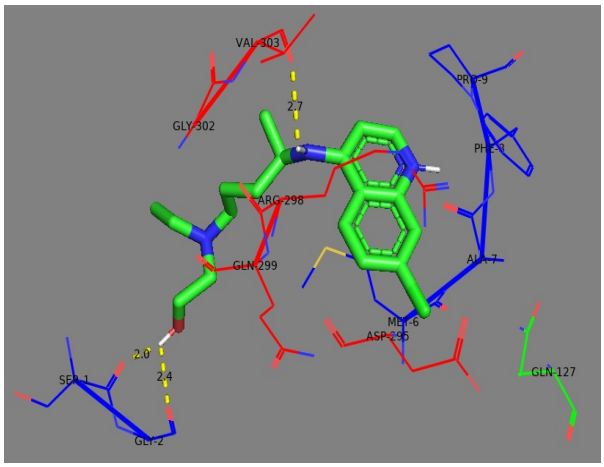


Fig -1: Representing the docking poses of Hydroxychloroquine with COVID-19 main protease (PDB ID: 5R84).

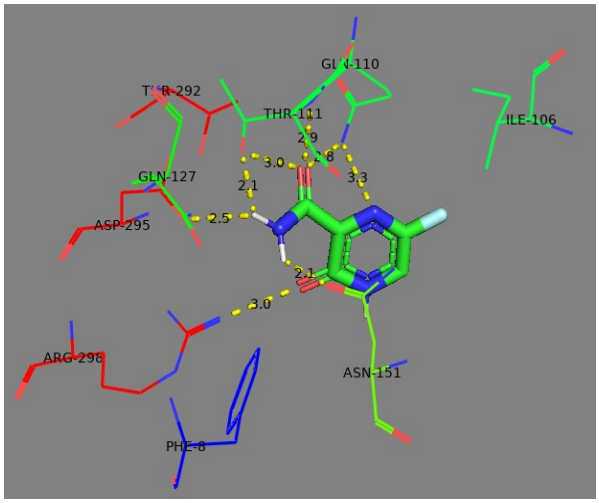
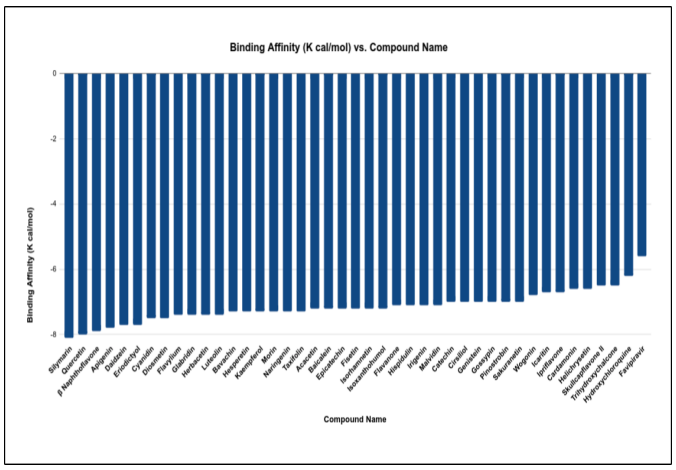


Fig -2: Representing the docking poses of Favipiravir with COVID-19 main protease (PDB ID: 5R84).

3.2 Binding affinity

Molecular docking study gives the binding pose (conformation) and binding affinity (docking score) of ligand. Molecules docked with a protein having a high affinity. Binding affinity of all ligands are shown in graph 1.



Graph -1: Binding affinity of ligand molecules with their target COVID-19 main protease (PDB ID: 5R84).

3.3 Visualization of protein-ligand interaction

In this work, the drug (Hydroxychloroquine, and Favipiravir) and 40 flavonoids molecule was docked to the target protein to predict the active site of the protein. The docking study shows the binding affinity which is summarized in Table 2. The PYMOL visualization of the docked pose of top 4 ligand showed the binding pocket of the protein where ligands are bonded. Interacting residue and the bonds were carefully observed in protein-ligands interaction.

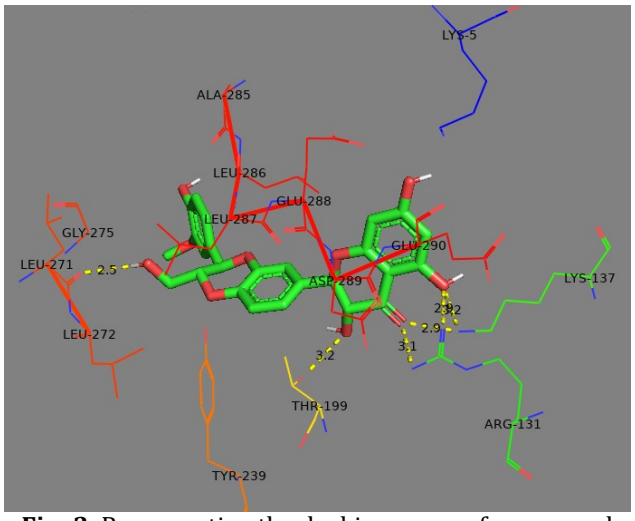


Fig -3: Representing the docking poses of compound Silymarin with COVID-19 main protease (PDB ID: 5R84).

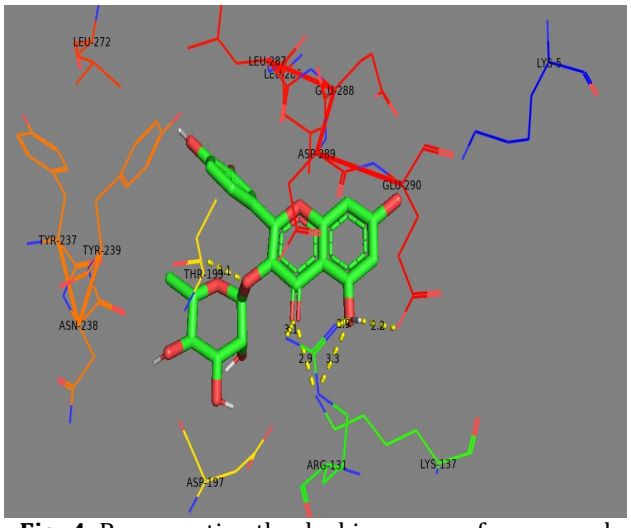


Fig -4: Representing the docking poses of compound Quercetin with COVID-19 main protease (PDB ID: 5R84).

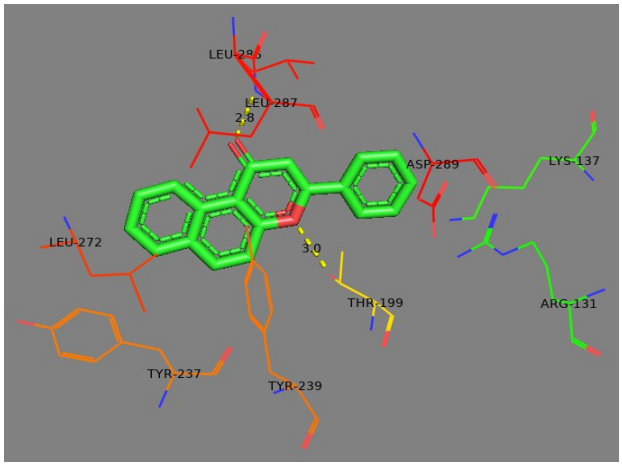


Fig -5: Representing the docking poses of compound β-Naphthoflavone with COVID-19 main protease (PDB ID: 5R84).

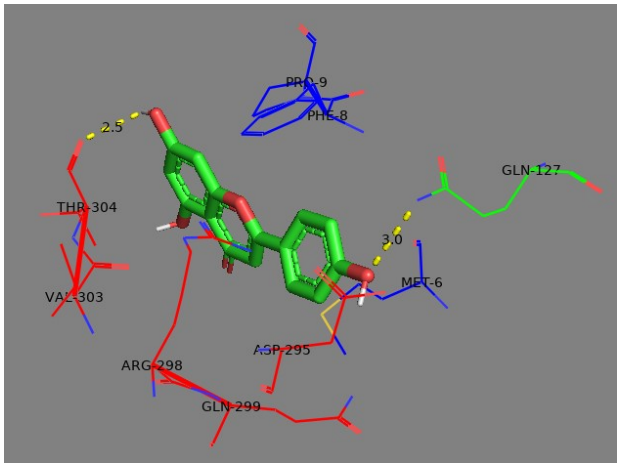


Fig -6: Representing the docking poses of compound Apigenin with COVID-19 main protease (PDB ID: 5R84).

3.4 Active site prediction

To visualize the binding site (where most the ligand molecules bind), the protein (PDB ID: 5R84) structure and all docked conformation of ligand molecules were open in UCSF Chimera and Maestro, which shows that, there are three regions in the protein where most of the ligand molecules binding. The *in-silico* protein-ligand interaction results showed that the protein (PDB ID: 5R84) was having the following Amino acid residues at the protein binding pocket which participate in the interaction. Some of the important residue are: THR-111, THR-199, ARG-131, LYS-137, GLN-110, and LEU-287, involved by forming H-bond with ligands.

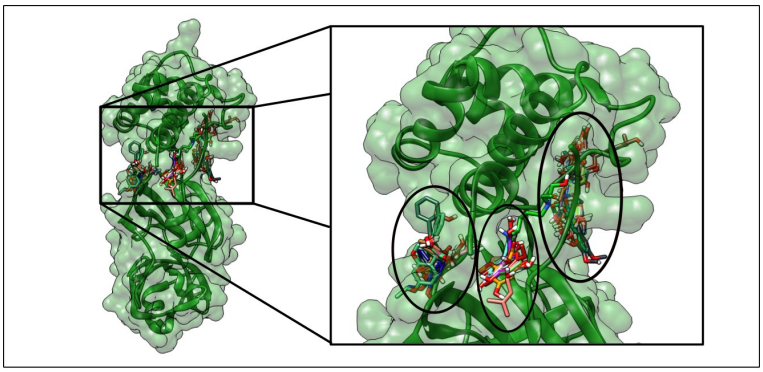


Fig -7: Representing the Surface of COVID-19 main protease (PDB ID: 5R84) with docked ligand molecules.

Table -2: Docking Result with COVID-19 main protease (PDB ID: 5R84)

Sl. No.	Compound Name	Binding Affinity (K cal/mol)	Interacting Residue within 4 Ă	Number of H-Bond	Length in Ă
1.	Silymarin	-8.1	LYS-5, LYS-137, ALA-285, LEU-286, LEU-287, GLU-288, GLU-290, ARG-131, ASP-298, THR-199, GLY-275, TYR-239, LEU-271, LEU-272	LEU-271 THR-199 ARG-131 LYS-137	2.5 3.2 2.9, 3.1 2.9, 3.2
2.	Quercetin	-8	ARG-131, ASP-197, THR-199, TYR-293, TYR- 237, ASN-238, LEU-272, LEU-286, LEU-287, GLU-288, LYS-5, GLU-290, LYS-137	GLU-290 THR-199 ARG-131 LYS-137	2.2 3.1 2.9, 3.1 2.0, 3.3
3.	B-Naphthoflavone	-7.9	LEU-287, LEU-285, LEU-272, TYR-237, TYR-239, THR-199, ASP-289, ARG-131, LYS-137	LEU-287 TYR-239	2.8 3.0
4.	Apigenin	-7.8	PRO-9, PHE-8, GLN-127, MET-6, ASP-295, GLN-299, ARG-298, VAL-303, THR-304	THR-304 GLN-127	2.5 3.0
5.	Daidzein	-7.7	GLN-189, MET-49, ARG-188, PRO-52, TYR-54, CYS-44, ASP-187, HIS-41, GLU-166, ASN-142, LEU-141, MET-165, PHE-140, HIS-164, CYS-145	TYR-54 GLU-166	2.9 3.3
6.	Eriodictyol	-7.7	ARG-298, VAL-303, ASP-153, ILE-152, ASN-151, THR-292, GLN-110, ILE-106, THR-111	ASP-153 ARG-298 GLN-110 THR-111	2.7 3.1, 3.3 2.9, 3.1
7.	Cyanidin	-7.5	GLN-299, GLY-302, ARG-298, MET-6, ASP-295, VAL-303, THR-304, PHE-8, PRO-9, ALA-7, GLN-127	THR-304 GLN-299 GLN-127	2.1 3.4 3.0
8.	Diosmetin	-7.5	LEU-286, LEU-287, ASP-289, GLU-290, LYS-137, ARG-131, THR199, ASP-197, TYR-239, TYR-27	THR-199 LEU-287 ARG-131 LYS-137	3.1 3.0 3.0, 3.0 3.1, 2.1
9.	Flavylium	-7.4	ASP-295, ARG-298, GLN-295, VAL-303, MET-6, THR-304,	---	---

			GLN-127, PHE-8, PRO-9		
10.	Glabridin	-7.4	LEU-287, LEU-286, LEU-272, TYR-237, TYR-239, THR-199, GLU-288, ASP-289, GLU-290, LYS-137	ASP-289 THR-199	2.9 3.0
11.	Herbacetin	-7.4	ARG-298, VAL-303, PHE-294, ASP-295, THR-292, ASP-153, GLN-110, THR-111, ILE-106, ILE-152, ASN-151, VAL-104	GLN-110, THR-111, ARG-298	3.1 2.9, 3.0 3.1, 3.1
12.	Luteolin	-7.4	LYS-137, GLU-290, LEU-286, LEU-287, ASP-289, ARG-131, THR-199, LEU-272, TYR-239, TYR-237, THR-198, ASP-197	LYS-137 LEU-287 THR-199 TYR-237 ARG-131	3.1, 3.0 3.0 3.1 2.0 3.0, 3.0
13.	Bavachin	-7.3	GLN-299, ARG-298, VAL-303, THR-304, ASP-295, MET-6, ALA-7, GLN-127, PRO-9, PHE-8	---	---
14.	Hesperetin	-7.3	ARG-131, ASP-197, LYS-137, THR-199, TYR-239, TYR-237, LEU-272, ASP-289, GLU-290, LEU-286, LEU-287	TYR-237 LEU-287 THR-199 LYS-137 ARG-131	2.1 3.0 3.0 3.0, 3.2 3.0, 3.1, 3.4
15.	Kaempferol	-7.3	LYS-5, LEU-286, LEU-287, GLU-288, ASP-289, GLU-290, LYS-137, THR-199, ARG-131, TYR-239	THR-199 ARG-131 LYS-137 GLU-290	3.1 2.9, 3.1 2.9, 3.2 2.2
16.	Morin	-7.3	ILE-152, ASP-153, PHE-8, ASN-151, VAL-104, VAL-303, ARG-298, THR-111, GLN-110, THR-292, ASP-295	GLN-110 THR-111 ILE-152 ARG-298	3.2 3.1, 3.2 2.1 3.0, 3.2, 3.4
17.	Naringenin	-7.3	LEU-286, LEU-287, GLU-288, TYR-239, THR-199, ASP-197, LYS-5, ARG-131, LYS-137, ASP-289	ARG-131 LYS-137	3.0, 3.0 2.9, 3.3
18.	Taxifolin	-7.3	ARG-131, ASP-197, TYR-239, TYR-237, THR-199, LYS-137, LEU-272, LEU-287, LEU-286, ASP-289, GLU-290,	ARG-131 LYS-137 THR-199 LEU-287	3.0, 3.1, 2.9, 3.1 3.2 2.9
19.	Acacetin	-7.2	LYS-5, LEU-287, LEU-286, GLU-290, ASP-289, TYR-239, THR-199, ARG-131, LYS-137, GLU-288	LYS-137 ARG-131	2.8, 3.2 2.3, 2.9, 3.2
20.	Baicalein	-7.2	TYR-239, THR-199, LEU-286, LEU-287, GLU-288, ASP-289, GLU-290, LYS-5, LYS-137, ARG-131,	LYS-137 GLU-290 ARG-131	2.9, 3.2 2.3 3.0, 3.1
21.	Epicatechin	-7.2	LEU-287, VAL-204, LEU-272, TYR-237, TYR-239, THR-199, ASP-289, GLU-290, LYS-137, ARG-131, ASP-197	LYS-137 THR-199 TYR-239 LEU-287 ARG-131	3.2 3.2 2.9 2.2 3.0, 3.1
22.	Fisetin	-7.2	ARG-298, VAL-303, THR-292, THR-111, GLN-110, ILE-152, ASP-151, ASP-153	ARG-298 GLN-110 THR-111	3.2 3.1 2.6, 2.9, 3.0
23.	Isorhamnetin	-7.2	LYS-137, LYS-5, ARG-131, ASP-	LYS-5	2.8, 3.1

			197, ASP-289, GLU-290, GLU-288, LEU-286, LEU-287, THR-199, THR-198,	GLU-288 ASP-289 ARG-131 THR-199	3.4 2.9 3.1 2.9, 2.9
24.	Isoxanthohumol	-7.2	LYS-137, GLU-290, LEU-286, LEU-287, ASP-289, ARG-131, ASP-197, THR-199, TYR-237, TYR-239, LEU-271, LEU-272	THR-199 ARG-131 LEU-287	3.2 3.2 3.2
25.	Flavanone	-7.1	MET-6, ALA-7, PRO-9, PHE-8, GLN-299, ARG-298, VAL-303, THR-304	---	---
26.	Hispidulin	-7.1	LEU-272, LEU-286, LEU-278, GLU-288, ASP-289, GLU-290, THR-199, TYR-239, ARG-131, LYS-137	ARG-131 LYS-137 GLU-290	3.0, 3.0 3.0, 3.2 2.6
27.	Irigenin	-7.1	ARG-131, LYS-137, ASP-197, THR-199, ASP-289, GLU-290, GLN-127, LYS-5, LEU-287, LEU-286	LYS-5 THR-199 GLU-290 ARG-131 LYS-137	2.9 2.7, 3.2 2.5, 3.5 2.8, 3.3 2.7, 3.2
28.	Malvidin	-7.1	THR-304, VAL-303, GLY-302, ARG-298, GLN-299, ASP-295, PRO-9, PHE-8, SER-113, ALA-7, GLN-127	GLN-127 GLN-299 MET- 6	2.9 3.4 2.0
29.	Catechin	-7	VAL-303, ARG-298, ASP-153, ILE-152, ASN-151, PHE-112, ILE-106, THR-11, GLN-110, THR-292	ARG-298 GLN-110 THR-111	3.3, 3.3, 3.1 3.0, 2.9, 2.1
30.	Cirsiliol	-7	LEU-286, LEU-287, LEU-272, TYR-237, TYR-239, THR-199, THR-198, ASP-197, ARG-131, LYS-137, ASP-289	THR-199 LEU-287 ASP-197 LSY-137 ARG-131	3.2 2.8 2.7 3.1, 3.0 3.4, 3.0
31.	Genistein	-7	LEU-287, LEU-286, GLY-275, LEU-271, LEU-272, TYR-237, TYR-239, ASP-197, THR-199, ARG-131, LYS-137, ASP-298,	THR-1993 LYS-137 LEU-271 LEU-287 ARG-131	3.1 3.2 2.6 3.4 3.2
32.	Pinostrobin	-7	LEU-286, LEU-287, GLU-288, ASP-289, GLU-290, LYS-5, TYR-239, THR-199, ASP-197, ARG-131, LYS-137	GLU-290 LYS-137 ARG-131	2.4 2.9, 3.2 2.9, 3.0
33.	Sakuranetin	-7	LEU-286, LEU-287, GLU-288, ASP-289, GLU-290, LYS-5, LYS-137, THR-199, TYR-239, ASP-197, ARG-131	LYS-137 ARG-131	3.0, 3.2 2.8, 3.0, 3.3
34.	Wogonin	-6.8	ARG-298, GLN-107, GLN-110, ILE-106, SER-158, ASN-151, ASP-153, ILE-152, CYS-156, PHE-8	ARG-298 ASP-153 SER-158	2.8, 3.0 3.3 3.0, 3.1
35.	Icaritin	-6.7	LEU-286, LEU-287, LEU-272, TYR-237, ASN-238, THR-199, ASP-289, GLU-290, LYS-137, ARG-131	TYR-237 LYS-137 THR-199 LEU-287	2.0 2.8 3.3 2.0, 3.2, 3.3
36.	Ipriflavone	-6.7	ILE-152, VAL-303, ASN-151, ASP-153, ARG-298, SER-158,	SER-158 ARG-298	2.7 2.9

			VAL-104, PHE-294		
37.	Cardamonin	-6.6	GLN-107, GLN-110, PRO-108, PRO-132, ILE-200, GLU-240, VAL-202, HIS-246, PRO-293, ILE-249, PHE-294	GLU-240 HIS-246	2.7 3.0
38.	Helichrysetin	-6.6	PRO-9, ALA-7, MET-6, GLN-127, PHE-8, THR-304, VAL-303, ARG-298	GLN-127, MET-6	2.9 2.3
39.	Skullcapflavone II	-6.5	ASN-84, MET-82, ARG-40, VAL-186, ASP-187, ARG-188, GLU-55, TYR-54, ASN-153, PRO-52	ARG-188 ARG-40 GLU-55 TYR-54	3.0, 3.0 3.2 2.9 3.0, 3.4
40.	Trihydroxychalcone	-6.5	PHE-8, ASN-151, ARG-298, VAL-297, ASP-295, PHE-294, ILE-106, GLN-110	PHE-294 GLN-110 ARG-298	2.2 3.3 3.1, 3.2
41.	Hydroxychloroquine	-6.2	PRO-9, PHE-8, ALA, -7, GLN-127, MET-6, ASP-295, ARG-298, GLN-299, SER-1, GLY-2, VAL-303	GLY-2 VAL-303	2.0, 2.4 2.7
42.	Favipiravir	-5.6	ARG-298, ASP-295, THR-292, GLN-110, THR-111, ILE-106, GLN-127, ASN-151, PHE-8	ARG-298 ASP-295 ASN-151 GLN-110 THR-111	3.0 2.5 2.1 2.8 2.1, 2.9, 3.0

3. CONCLUSIONS

Drug designing is the inventive process of finding new medications based on the knowledge of a biological target. This molecule will interact with the protein or binds on their active site and activates or inhibits the function of this biomolecule protein.

I have performed a molecular docking study using 40 potential naturally occurring flavonoids against the COVID-19 main protease and compared their affinity and amino acid residues at the protein binding pocket which participate in the interaction with the drug Hydroxychloroquine and Favipiravir. Docking results showed that all the flavonoids have high binding affinity against target COVID-19 main protease and docked with similar binding pocket residues.

This study suggested that, among these 4 flavonoid molecules Silymarin, Quercetin, β-Naphthoflavone, and Apigenin can be the potential drug for COVID-19 main protease. This in-*silico* approach can be further investigated to generate more effective and potential drugs through ligand-based drug designing approaches.

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