Research Square

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Phytomolecules having flavone and napthofuran nucleus exhibited better binding G-score against protease and SPIKE protein of novel corona virus COVID-19

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Research Article

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Abstract

The present study aims to screen the different phytoconstituents and drugs for potential treatment of the corona virus COVID-19 and for specificity through virtual screening. The plant molecules selected were based upon traditional knowledge and are prescribed in the Indian system of medicine for infectious/ respiratory conditions. The three target proteins selected for the study are 3CLpro, PLpro, and SPIKE. These proteins have defined pathological roles in disease transmission. The virtual screening was carried out in these proteins using the GLIDE Schrödinger Maestro software version 11.9.011. The efficacy was assessed by the calculated G-score of the ligand interaction with the amino acid side chains of the ligand binding domain. Molecules such as saponarin, mangiferin, and hesperidin exhibited better G-score with 3CLpro and PLpro. Similarly, diphyllin and tuberculatin exhibited better G-score for SPIKE protein. The reference anti malarial drug hydroxychloroquine showed better interactions with 3CLpro and PLpro. Similarly, protease inhibitors and antiviral drugs have shown interaction with 3CLpro specific protease protein. Interestingly, SPIKE protein ligands, diphyllin and tuberculatin from *Justicia adhatoda* (vasaka), were found to be unique and did not show affinity to protease inhibitor. It can be concluded, that the molecules having flavone scaffolds show better binding affinity with protease proteins 3CLpro and PLpro. SPIKE protein scaffold is different and showed better binding affinity with molecules having naptho-furan ring. The traditionally used plant phytoconstituents did not exhibit good binding affinity; however, we believe that a combination of these herbs might induce human immune system against microbial infection.

1. Introduction

The pandemic of the novel corona virus infection (COVID-19) started from Wuhan, China and currently spreading to several countries **[1].** COVID-19 is highly homologous to the 2003-SARS (severe acute respiratory syndrome) corona virus **[2]**. Corona viruses (CoV) are enveloped viruses with a positive RNA genome, belonging to the *Coronaviridae* family that mainly causes respiratory and gastrointestinal tract infections in mammals and predominantly in birds **[3].** CoV did not attract worldwide attention until the 2003-SARS pandemic, followed by the 2012-MERS, and most recently, the COVID-19 outbreaks **[4]**. RNA genome of CoV is the largest one among all the RNA viruses and the genetic material of CoV is susceptible to frequent recombination process, which enabled the virus to become a new strain with alteration in virulence **[5, 6].**

CoV transmits mainly through droplet infection (respiratory secretions) and close person-to-person contact. Severe Acute Respiratory Syndrome Corona Virus-2 (SARS-CoV-2) infects human by primarily targeting enterocytes, pneumocytes, and thereby establishing a cycle of infection and replication **[7]**. SARS-CoV-2 attaches to the target cell by interacting with host cell protein (such as angiotensin converting enzyme-2) and releases the viral genome into the cytoplasm of host cells. It acts just like a messenger RNA and directs the host cell to synthesize two long polyproteins, which enables the virus to take command over host ribosomes for their own translation process **[8].**

There are no approved therapies currently available for COVID-19. Current drugs having indications for other diseases have been tried in these patients. The viral load in these patients has come down with the treatment of anti-malarial drug like hydroxyl chloroquine, anti-viral drugs, and protease drugs. There are also discussions within the healthcare system that for individuals having a good immune system, the infection rate will be less. Consequently, recommendation has also been made to boost the immune system. It is a pandemic and no specific drugs are available, which has made researchers to focus on drug re-purposing and also natural products. The objective is to stop or delay the infection to minimize the future socioeconomic disruption due to this global health-care burden.

Secondary metabolism is a complex defence phenomenon of plants and still serves as a source of countless medicinal compounds in pharmaceutical drug discovery. In comparison to chemical drugs, herbal medicines are less understood mechanistically due to poly-pharmacological interactions by compounds present in the herb. Even now, in the combat of COVID-19 pandemic, the National Health Commission of China recommended traditional Chinese medicine as an early defence treatment option **[9]**.When it comes to infectious diseases, Indian traditional systems of medicine (like Ayurveda and Siddha) emphasizes not only anti-microbials but also on enhancing immunity boosting activities **[10]**.

Hence, in the present study, virtual screening of the drugs and phytochemicals were made on three important protein targets of COVID-19 virus SARS-CoV-2 to elucidate the most potentially active molecules. The phytoconstituents selected are the chemical and/ or functional markers of herbs, which are being recommended in the Indian System of medicine for either the management of infectious/ respiratory disorders or strengthening of the immune system **[11, 12]**. This approach will also validate the use of herbal preparations in infectious condition.

2. Methodology

All the *in-silico* simulations were performed in Maestro v11.9.011 modelling package provided by Schrödinger, LLC, New York, NY, 2019-1, installed on an Intel Core i7-4770 processor, kernel GNOME™ Linux 2.6 Centos 6.5.

2.1.Molecular docking and binding free energy

GLIDE v7.7 module was used to carry out the molecular docking simulation. Crystal structures of SARS-CoV-2 Main Protease(3CLpro) , Papain like protease (PLpro),& 2019-nCoV SPIKE receptor were taken from the RCSB protein data bank (PDB ID: 6LU7, Resolution: 2.16Aº;PDB ID: 3E9S, Resolution: 2.5Aº;PDB ID: 6M0J, Resolution: 2.45Aº, respectively) and have been depicted in **Fig.1**. The force field used during the protein preparation was OPLS3.Proteins were pre-processed to add hydrogen and delete waters beyond 5Å , reviewed , modified, and finally minimized using the Protein Preparation Wizard module in Maestro. Ligands were prepared to desalt, generate stereoisomers & generate possible states at target pH 7±2 using LigPrep module in Maestro. A receptor grid was generated at the binding site using the receptor grid generation tool in Maestro. All the ligands were docked within the grid-generated area. Standard

precision (SP), followed by extra precision (XP) mode of docking were performed for selection of top hit ligands.

2.2.Selection of the molecules

Virtual Screening of 82 compounds comprising of phytoconstituents of herbal plants *Solanum trilobatum, Mukia maderaspatana, Andrographis paniculata, Justicia adhatoda, Mangifera indica, Ocimum tenuiflorum, Prosopis cineraria, Grindelia argentina, Azadirachta indica)*, Anti-Viral drugs,& Standard WHO approved drugs for COVID-19 were performed using the Schrodinger Maestro v.11.9.011 Ligand docking and the resultant G-scores were obtained for the three COVID-19 target proteins 3CLpro , PL pro &SPIKE.

2.3.Protein description

3CLpro and PLpro are protease enzymes present in the SARS-CoV-2 bearing molecular weight of 34.51kDa & 36.17kDa, respectively. They have a residue count of 312 & 317 respectively. These two proteins are the main proteases which cleave and process the polyproteins pp1a and pp1ab into 15 non-structural proteins. These non-structural proteins help in viral replication, transcription, and assembly.ORF1ab encodes pp1ab, whereas, ORF 2 encodes viral structural proteins such as the SPIKE, membrane, envelope, and nucleocapsid protein. SPIKE protein of SARS-CoV-2 has a molecular weight of 97.14 kDa. SPIKE protein helps in the fusion of virus into the host cell by binding with the ACE2 enzyme. These defined functions of these three proteins provide an attractive target for potential drugs to inhibit the viral entry and replication in host cell **[13, 14].**

3CLpro(PDB ID:6LU7): The crystal structure of COVID-19 main protease in complex with an inhibitor N3.Resolution: 2.16 Å,R-Value Free: 0.235,R-Value Work: 0.202.Chain A: SARS-CoV-2 main protease (306 sequence length),Chain C: N-[(5-METHYLISOXAZOL-3-YL) CARBONYL]ALANYL-L-VALYL-N~1~-((1R,2Z)-4-(BENZYLOXY)-4-OXO-1-{[(3R)-2-OXOPYRROLIDIN-3-YL]METHYL}BUT-2-ENYL)-L-LEUCINAMIDE(6 sequence length)**[15]**.**PLpro(PDB ID:3E9S):** A new class of papain-like protease/deubiquitinase inhibitors blocks SARS virus replication**.** Resolution: 2.5 Å, R-Value Free: 0.26, R-Value Work: 0.196**.**Chain A: Non-structural protein 3 (318 sequence length)**[16].Spike (PDB ID:6M0J):**Crystal structure of 2019 n-CoV SPIKE receptor – binding domain bound with ACE2.Resolution: 2.45 Å, R-ValueFree: 0.237, R-Value Work: 0.196.Chain A: Angiotensin-converting enzyme 2 (603 sequence length),Chain E: 2019-nCoV receptor-binding domain (209 sequence length)**[17] Fig.1**

3. Results

The screening of phytochemicals and drugs currently used to treat COVID19 with three different proteins having pathological function indicates effective interactions of compounds with the targeted proteins. The G score for all the compounds are given in **Table 1**. The ligand binding domain of the three different proteins 6LU7, 3E9S, & 6M0J and possible amino acids interacting with the targeted proteins are

represented in the **Fig. 2-4 and Table 2-4.** Chemical structures of selected molecules of better G-scores are depicted in **Fig.5**

3.1. Ligand Interaction of compounds with 3CL pro (3C-like main protease-6LU7)

The currently used protease inhibitors and other Anti-viral drugs have shown interactions with amino acids Glu 166, Gly 143, Asn 142, Arg 188,& Gln 189 and these ligand interactions showed better G-score. Remdesivir showed interactions with Gly 143, Glu 166, Ser 144,& Gln 189, which gained it a better G-score, while hydroxychloroquine &remdesivir interacted majorly with Glu 166. Valganciclovir &mangiferin interacted with Thr 190 & HID 41, which improved their G-score -7.556 & -7.435 respectively. Saponarin & mangiferin interacted with Ser 144 and their G-scores were found to be -7.326 & -7.435, respectively. Saponarin, and mangiferin, with highest G-scores of -7.326 and -7.435,respectively, interacted with Glu 166, Gly 143, Ser 144,& Gln 189 &.Hence, from the data, Glu 166 & Thr 190 constitute a centre point of interaction to have better G-score and further interactions with Gly 143, Asn 142, Thr 190, Ser 144,& Gln 189 provide additional significance to maintain the G-score. In addition, hydrophobic interactions & π-π stacking also favour the ligand interaction outcome **(Table 2; Fig.2).**

3.2. Ligand Interactions of Compounds with PLpro (Papain like protease-3E9S):

The currently used protease inhibitors and antiviral drugs have shown interaction with Asp 165, Gln 270, Tyr 274, Leu 163, Glu 168, Arg 167, Asp 303, Tyr 269. Ligand interactions with these amino acids have shown good G-scores. Among the binding sites, interaction with Asp 165, Gln 270, Tyr 274, Gly 267, Arg 167 might be important for molecules to exhibit anti-viral activity through this protein. In addition, π-π stackingat Tyr 269 (π-π) &hydrophobic interactions at Pro 248 & Pro 249 were commonly observed **(Table 3; Fig. 3).**

3.3. Ligand Interactions of Compounds with SPIKE protein of SARS-CoV-2(6M0J):

The ligand interaction site for these protein molecules has been developed by our group. Earlier, no reports were available on ligand protein interactions with this target. It has been observed that two sets of interactions favour 6M0J ligand binding. Almost all the compounds interacted with Gly 496. The two sets of interactions observed are as follows: the first set of molecules interacted with Tyr 449, Gln 498, and Glu 406 and the second set of molecules interacted with Tyr 453, Ser 494, and Gly 496. Molecules, which have shown interactions with either of these two sets of amino acids showed better G-scores. Hydrophobic interactions at Tyr 505 & Tyr 495 were commonly observed. The standard drugs hydroxychloroquine, oseltamivir, and remedisivir were found to be least active as indicated by their lower G-scores **(Table 4; Fig. 4).**

4. Discussion

The objective of the present study is to identify a suitable ligand to interact with the different target proteins of the novel corona virus COVID-19. The study was carried out with virtual screening of the

molecules using Schrodinger Maestro v11.9.011. The viral proteins targeted to have therapeutic value are 3CLpro (PDB ID: 6LU7), PLpro (PDB ID: 3E9S) & SPIKE (PDB ID: 6M0J) of nCOVID-19. These proteins have definite function like protease activity, which helps the virus RNA transcription, translation, protein synthesis, and replication. SPIKE protein help in fusion and entry of virus into the host cell. Targeting these proteins were mediated through the binding pockets involving amino acids **3CLpro** (Cys 145, HID 41, Gly 143, Asn 142, HID 163, Glu 166,Thr 190, Arg 188, Ser 144, Gln 189) ; **PLpro** (Gly 164, Gln 270, Tyr 274, Asp 303, Gly 267, Asp 165, Glu 168, Arg 167, Ala 247, Tyr 269, Pro 248, Pro 249) ; **SPIKE** (Tyr 449, Gln 498, Thr 500, Val 445, Lys 417, Asn 501, Gly 446, Gly 502,Tyr 505, Leu 455, Gln 493,Gln 506, Lys 444, Phe 486, Ser 477, Tyr 473,Arg 403,Gly 496,Tyr 453). Our study revealed that chemical molecules having flavonoid nucleus, namely saponarin, mangiferin, & hesperidin, had better binding scores with 3CLpro protein (PDB ID: 6LU7). Similarly, for the target SPIKE protein (PDB ID: 6M0J), chemical molecules like diphyllin & tuberculatin showed better G-scores than the standard drugs and these molecules are from the plants *Mukia maderaspatana, Justicia adhatoda, and Mangifera indica.* While for the target PLpro (PDB ID: 3E9S), chemical molecules like mangiferin& aspartame showed good G-scores.

FNQ3 naptho-quinone derivatives have shown antiviral property against Japanese encephalitis virus through inhibition of viral replication by blocking viral RNA and transcriptional activities [18]. One of our hit compound diphyllin has also been reported to have antiviral property. Glycosylated diphyllin prevented zika virus during fusion with host cell, preventing the release of viral RNA into the target cells. This effect was attributed to acidification of the cytoplasmic content by glycosylated diphyllin. So, these results support that the napthofuran molecules like diphyllin may exhibit antiviral property by blocking structural protein (SPIKE protein) **[19]**.

Quercetin, a flavone derivative, has shown antiviral property against enterovirus 71(EV71). Quercetin exhibited antiviral property by preventing the early post attachment, inhibition of protease enzymes, RNA polymerase. Quercetin also has shown to bind with the substrate binding pocket of enterovirus 3Cpro **[20]**.However, in the present study we did not observe any interaction of quercetin with the targets. It might be protein specific. Another flavone mangiferin has shown antiviral property in clinical strains of HIV1. It was also found to be effective against resistant HIV1 strain through inhibition of peptide protease. It also possesses HIV protease enzyme inhibition in HIV strain **[21].** The significant role of flavonoids for antiviral property has been reviewed recently by **[22]**. So, these observations also support the present finding that flavonoids can block the protease enzyme activity of COVID-19.

Interestingly, the phytoconstituents from neem, tulsi & andrographis (Nila-Vembu) did not show any binding scores with these protein targets. Likewise, other chemical molecules studied include curcumin, liquitrigenin, iso-liquitrigenin, glabridin, piperine, glycyrrhizic acid, vasicine & vascinone and these showed no or low binding scores. The clinically used protease inhibitors, anti-viral drugs, ivermectin & chloroquine were also docked with these proteins; the results show lower G-scores comparatively with saponarin, mangiferin, hesperidin, diphyllin, and tuberculatin. Hydroxychloroquine and remedesivir showed better G-scores for 3CLpro & PLpro, but these two drugs showed lesser G-scores for SPIKE protein in comparison to diphyllin & tuberculatin. 6M0J can also be targeted, being it a SPIKE protein. But, as the binding site is

quite large it is difficult to block it with small molecules and it would be better if it can be blocked with larger molecules with better g-scores and binding affinity, However, this target can be tried for prophylactic purpose.

Formulations of traditional system of medicine contain multiple herbs and generally natural products act on either additive or synergistic mechanism to elicit the poly-pharmacological action **[23].** The current work was designed based on the hypothesis on antiviral activities of these compounds from selected herbs. However, compounds like curcumin (from *Curcurma longa*) and azadirachtin (from *Azadirachta indica*) are well-documented for their immuno-modulatory responses, including its effect on lymphoid cell populations, antigen presentation, humoral and cell-mediated immunity, and cytokine production **[24, 25].** Hence, studying the effect of these compounds on immune modulation targets is also needed to elucidate the complete potential of these compounds.

It can be concluded, that the molecules having flavone scaffolds show better binding affinity with protease proteins 3CLpro and PLpro. SPIKE protein scaffold is different and showed better binding affinity with molecules having napthofuran ring. The traditionally used plant phytoconstituents did not exhibit good binding affinity; however, we believe that a combination of these herbs might induce human immune system against microbial infection.

Declarations

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References

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, Zhao X, Huang B, Shi W, Lu R, Niu P, Zhan F, Ma X, Wang D, Xu W, Wu G, Gao GF, Tan W, China Novel Coronavirus Investigating and Research Team (2020) A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med 382:727–733 . https://doi.org/10.1056/NEJMoa2001017
2. Chen Y, Liu Q, Guo D (2020) Emerging coronaviruses: Genome structure, replication, and pathogenesis. J Med Virol 92:418–423 . https://doi.org/10.1002/jmv.25681
3. Tang Q, Song Y, Shi M, Cheng Y, Zhang W, Xia XQ (2015) Inferring the hosts of coronavirus using dual statistical models based on nucleotide composition. Sci Rep 5:undefined-undefined . https://doi.org/10.1038/srep17155

4. Song Z, Xu Y, Bao L, Zhang L, Yu P, Qu Y, Zhu H, Zhao W, Han Y, Qin C (2019) From SARS to MERS, Thrusting Coronaviruses into the Spotlight. Viruses 11: . https://doi.org/10.3390/v11010059
5. Belouzard S, Millet JK, Licitra BN, Whittaker GR (2012) Mechanisms of coronavirus cell entry mediated by the viral spike protein. Viruses 4:1011–1033 . https://doi.org/10.3390/v4061011
6. Hilgenfeld R (2014) From SARS to MERS: crystallographic studies on coronaviral proteases enable antiviral drug design. FEBS J 281:4085–4096 . https://doi.org/10.1111/febs.12936
7. Guo Y, Korteweg C, McNutt MA, Gu J (2008) Pathogenetic mechanisms of severe acute respiratory syndrome. Virus Res 133:4–12 . https://doi.org/10.1016/j.virusres.2007.01.022
8. Stobart CC, Sexton NR, Munjal H, Lu X, Molland KL, Tomar S, Mesecar AD, Denison MR (2013) Chimeric exchange of coronavirus nsp5 proteases (3CLpro) identifies common and divergent regulatory determinants of protease activity. J Virol 12611–8
9. Ho LTF, Chan KKH, Chung VCH, Leung TH (2020) Highlights of traditional Chinese medicine frontline expert advice in the China national guideline for COVID-19. Eur J Integr Med. https://doi.org/10.1016/j.eujim.2020.101116
10. Tripathi JS, Singh RH (1999) The Concept and Practice of Immunomodulation in Ayurveda and the Role of Rasayanas as Immunomodulators. Anc Sci Life 19:59–63
11. Kumar D, Arya V, Kaur R, Bhat ZA, Gupta VK, Kumar V (2012) A review of immunomodulators in the Indian traditional health care system. J Microbiol Immunol Infect 45:165–184 . https://doi.org/10.1016/j.jmii.2011.09.030
12. Jadhav P, Kapoor N, Thomas B, Lal H, Kshirsagar N (2012) Antiviral potential of selected Indian medicinal (ayurvedic) plants against herpes simplex virus 1 and 2. North Am J Med Sci 4:641–647 . https://doi.org/10.4103/1947-2714.104316
13. Wu C, Liu Y, Yang Y, Zhang P, Zhong W, Wang Y, Wang Q, Xu Y, Li M, Li X, Zheng M, Chen L, Li H (2020) Analysis of therapeutic targets for SARS-CoV-2 and discovery of potential drugs by computational methods. Acta Pharm Sin B. https://doi.org/10.1016/j.apsb.2020.02.008
14. Pillaiyar T, Meenakshisundaram S, Manickam M (2020) Recent discovery and development of inhibitors targeting coronaviruses. Drug Discov Today. https://doi.org/10.1016/j.drudis.2020.01.015
15. Jin Z, Du X, Xu Y, Deng Y, Liu M, Zhao Y, Zhang B, Li X, Zhang L, Peng C, Duan Y, Yu J, Wang L, Yang K, Liu F, Jiang R, Yang X, You T, Liu X, Yang X, Bai F, Liu H, Liu X, Guddat LW, Xu W, Xiao G, Qin C, Shi Z, Jiang H, Rao Z, Yang H (2020) Structure of M pro from COVID-19 virus and discovery of its inhibitors. Nature 1–9 . https://doi.org/10.1038/s41586-020-2223-y
16. Bank RPD RCSB PDB - 3E9S: A new class of papain-like protease/deubiquitinase inhibitors blocks SARS virus replication. https://www.rcsb.org/structure/3E9S. Accessed 17 Apr 2020
17. Lan J, Ge J, Yu J, Shan S, Zhou H, Fan S, Zhang Q, Shi X, Wang Q, Zhang L, Wang X (2020) Structure of the SARS-CoV-2 spike receptor-binding domain bound to the ACE2 receptor. Nature. https://doi.org/10.1038/s41586-020-2180-5
18. Takegami T, Simamura E, Hirai K, Koyama J (1998) Inhibitory effect of furanonaphthoquinone derivatives on the replication of Japanese encephalitis virus. Antiviral Res 37:37–45 .

https://doi.org/10.1016/s0166-3542(97)00058-2

19. Martinez-Lopez A, Persaud M, Chavez MP, Zhang H, Rong L, Liu S, Wang TT, Sarafianos SG, Diaz-Griffero F (2019) Glycosylated diphyllin as a broad-spectrum antiviral agent against Zika virus. EBioMedicine 47:269–283 . https://doi.org/10.1016/j.ebiom.2019.08.060
20. Yao C, Xi C, Hu K, Gao W, Cai X, Qin J, Lv S, Du C, Wei Y (2018) Inhibition of enterovirus 71 replication and viral 3C protease by quercetin. Virol J 15:116 . https://doi.org/10.1186/s12985-018-1023-6
21. Wang R-R, Gao Y-D, Ma C-H, Zhang X-J, Huang C-G, Huang J-F, Zheng Y-T (2011) Mangiferin, an anti-HIV-1 agent targeting protease and effective against resistant strains. Mol Basel Switz 16:4264–4277 . https://doi.org/10.3390/molecules16054264
22. Lalani S, Poh CL (2020) Flavonoids as Antiviral Agents for Enterovirus A71 (EV-A71). Viruses 12: . https://doi.org/10.3390/v12020184
23. Lacerda-Neto LJ, Barbosa AG, Quintans-Junior LJ, Coutinho HD, da Cunha FA (2019) The complex pharmacology of natural products. Future Med Chem 11:797–799 . https://doi.org/10.4155/fmc-2018-0327
24. Gautam SC, Gao X, Dulchavsky S (2007) Immunomodulation by curcumin. Adv Exp Med Biol 595:321–341 . https://doi.org/10.1007/978-0-387-46401-5_14
25. Baral R, Chattopadhyay U (2004) Neem (Azadirachta indica) leaf mediated immune activation causes prophylactic growth inhibition of murine Ehrlich carcinoma and B16 melanoma. Int Immunopharmacol 4:355–366 . https://doi.org/10.1016/j.intimp.2003.09.006

Tables

Table 1 G-score for various phytomolecules and currently indicated drugs on three target proteins of SARS CoV-2 virus

S. No	Pubchem ID	Name of the compound	3CLpro (6LU7)	PLpro (3E9S)	SPIKE (6M0J)
1	441381	Saponarin	-7.326	-5.237	-3.568
2	10621	Hesperidin	-7.312	-5.779	-3.947
3	5281647	Mangiferin	-7.435	-6.643	-4.200
4	437080	β Solamarine	-4.024	-2.066	-1.995
5	114776	Iso-orientin	-6.940	-5.326	-4.286
6	493570	Riboflavin	-8.156	-6.477	-5.4
7	64982	Baicalin	-8.106	-6.018	-5.055
8	442439	Neohesperidin	-7.312	-5.779	-3.947
9	392622	Ritonavir	-7.405	-5.354	-3.822
10	5280443	Apigenin	-7.218	-5.237	-3.294
11	44593583	Andrographiside	-7.032	-4.483	-5.562
12	135413535	Valganciclovir	-7.556	-6.356	-2.807
13	5281607	Chrysin	-6.55	-4.36	-2.83
14	44257586	Prosogerin A	-6.772	*	*
15	5281628	Hispidulin	-6.459	-4.303	-3.165
16	667639	Piceatannol	-6.381	-5.253	-4.908
17	54707177	Lymecycline	-6.239	-6.83	-3.632
18	3002977	Maraviroc	-6.043	-4.513	-1.922
19	37542	Ribavirin	-5.988	-6.001	-4.159
20	134601	Aspartame	-6.505	-7.174	-4.83
21	5281416	Esculetin	-5.198	-5.327	*
22	2719	Chloroquine	*	-5.144	*
23	441300	Abacavir	*	-4.112	*
24	447043	Azithromycin	*	-5.329	*
25	6537493	α-Solanine	*	*	-1.834
26	162859	Platcyodin-D	*	*	-7.975
27	5280441	Vitexin	-7.326	-4.894	-3.568
28	163859	Diphyllin	*	*	-5.501
29	103582194	Tuberculatin	*	*	-5.028
30	114829	Liquiritigenin	*	*	*
31	638278	Isoliquiritigenin	*	*	*
32	124052	Glabridin	*	*	*
33	638024	Piperine	*	*	*
34	76316558	Isomeldenin	*	*	*
35	108058	Nimbin	*	*	*
36	44715635	Nimbinene	*	*	*
37	10505484	Deacetylnimbin	*	*	*
38	157277	Nimbandiol	*	*	
39	13875741	Nimbocinol	*	*	*
40	5280343	Quercetin	*	*	*
41	5318517	Andrographolide	*	*	*
42	12000062	Bisandrographolide	*	*	*
43	5708351	12-Didehydroandrographolide	*	*	*
44	9848024	Neoandrographolide	*	*	*
45	5320315	Oroxylin A	*	*	*
46	5281703	Wogonin	*	*	*
47	10364	Carvacrol	*	*	*
48	3314	Eugenol	*	*	*
49	1794427	Chlorogenic acid	*	*	*

50	12411	Tritriacontane	*	*	*
51	969516	Curcumin	*	*	*
52	162464	Cirsilineol	*	*	*
53	188323	Cirsimaritin	*	*	
54	630253	Isothymusin	*	*	*
55	5315615	Rosmarinic acid	*	*	*
56	14194023	Nimbanal	*	*	*
57	12308714	Azadiradione	*	*	*
58	177090	Nimbosone	*	*	*
59	6442484	Nimbilin	*	*	*
60	6443005	Nimbolin	*	*	*
61	5281303	Azadirachtin	*	*	*
62	16126804	Azadirachtin B	*	*	*
63	10906239	Azadirone	*	*	*
64	100017	Nimbolide	*	*	*
65	5281876	Azadirachtinin	*	*	*
66	8815	Estragole	*	*	*
67	5281553	Ocimene	*	*	*
68	521569	Bergamotene	*	*	
69	10657	Beta -Cadinene	*	*	*
70	6431302	Alpha-Cadinol	*	*	*
71	637520	Methyl Cinnamate	*	*	*
72	64945	Ursolic Acid	*	*	*
73	3084407	Vicenin 2	*	*	*
74	14982	Glycyrrhizic acid	*	*	*
75	72610	Vasicine	-4.372	-4.475	-3.407
76	442935	Vasicinone	-4.292	-4.243	-2.552
77	3652	Hydroxychloroquine	-7.135	-6.704	-2.852
78	65028	Oseltamivir	-4.792	-4.12	-3.117
79	92727	Lopinavir	-7.642	-4.169	-4.582
80	121304016	Remdesivir	-7.061	-4.636	-3.823
81	492405	Favipiravir	-3.753	-3.807	-3.748
82	6321424	Ivermectin	-5.682	*	-2.672

Table 2 The best fit phytomolecules and currently indicated drugs interaction with the amino acids of the target proteins 3CLpro (6LU7) of SARS CoV-2 virus

PubChem-ID	Compound Name (G Score)	Gly 143	Asn 142	HID 163	Glu 166	Thr 190	HID 41	Arg 188	Ser 144	Gln 189	Leu 141
441381	Saponarin (-7.326)				*				*		
10621	Hesperidin (-7.312)	*			*						
5281647	Mangiferin (-7.435)				*				*		*
135413535	Valganciclovir (-7.556)					*	*				
114776	Isoorientin (-6.940)					*	*				
493570	Riboflavin (-8.156)	*			**				*	*	
92727	Lopinavir (-7.642)		*		*					*	
3652	Hydroxychloroquine (-7.135)				*			*			
65028	Oseltamivir (-4.792)										
121304016	Remdesivir (-7.061)	*			***						

Table 3 The best fit phytomolecules and currently indicated drugs interaction with the amino acids of the target proteins PLpro(3E9S) of SARS-CoV-2 virus

3CL pro(6LU7)Hydrophobic interactions & π-π stacking		
441381	Saponarin	Pro 52, Tyr 54, HID 163(π-π)
10621	Hesperidin	NA
5281647	Mangiferin	HID 41(π-π),Met 165,HID 164,HID 163,Tyr 54 , Pro 52 ,Met 49
135413535	Valganciclovir	HID 41(π-π)
114776	Isoorientin	HID 41(π-π)
493570	Riboflavin	Met 49,Pro 52 ,Tyr 54
92727	Lopinavir	Met49,Met 165,Leu 167, Pro 168 ,HID 41 (π-π)
3652	Hydroxychloroquine	Asp 187,Met 165,Glu 166,Thr 190,Gln 189
65028	Oseltamivir	NA
121304016	Remdesivir	NA

PubChem-ID	Compound Name (g Score)	Asp 303	Gly 267	Asp 165	Gln 270	Tyr 274	Leu 163	Glu 168	Arg 167	Ala 247	Asp 303	Tyr 269	Asn 268
5281647	Mangiferin (-6.643)	**											
134601	Aspartame (-7.174)			**	*	*							
442439	Neohesperidin (-5.779)		*										
114776	Isoorientin (-5.326)		*	**									*
493570	Riboflavin (-6.477)			**		*			*	*			
10621	Hesperidin (-5.779)		*										
92727	Lopinavir (-4.169)							*	*				
3652	Hydroxychloroquine (-6.704)					*	*		*		*		
65028	Oseltamivir (-4.12)				*			*	*				
121304016	Remdesivir (-4.636)			**					*			*	

PLpro(3E9S)- Hydrophobic interactions & π-π stacking		
5281647	Mangiferin	Tyr 265 , Asp 165, Val 166, Tyr 269 (π-π),Pro 248, Pro 249
134601	Aspartame	Gln 270,Tyr 269 (π-π),Met 209
442439	Neohesperidin	Tyr 265 (π-π), Ala 247, Tyr 274 Gly267
114776	Isoorientin	Tyr 269(π-π)*2
493570	Riboflavin	Tyr 269(π-π),Pro 248
10621	Hesperidin	Tyr 265(π-π), Ala 247
92727	Lopinavir	Tyr 269 (π-π),Tyr 274
3652	Hydroxychloroquine	Asp 165, Tyr 269(π-π),Gly 164
65028	Oseltamivir	-
121304016	Remdesivir	Tyr 269(π-π),Pro 248,Pro 249,Ala 247

Table 4 The best fit phytomolecules and currently indicated drugs interaction with the amino acids of the target proteins SPIKE (6M0J) of SARS CoV-2 virus

PubChem-ID	Compound Name (g Score)	Gly 502	Arg 403	Gln 498	Glu 406	Gln 493	Ser 494	Gly 496	Tyr 453	Lys 417	Tyr 449	Asn 501
493570	Riboflavin (-5.4)						**	*	*			
64982	Baicalin(-5.055)			*				*	**		*	
44593583	Andrographiside(-5.562)				*			*				
163859	Diphyllin(-5.501)	*				*						*
103582194	Tuberculatin(-5.028)			**							*	
3652	Hydroxychloroquine (-2.852)				*	*	*					
65028	Oseltamivir (-3.117)		*				*	*				
121304016	Remdesivir (-3.823)		*		**			*				

SPIKE(6M0J) Hydrophobic interactions , π-π stacking & Halogen bonding		
493570	Riboflavin	NA
64982	Baicalin	Tyr 505,Arg 403
44593583	Andrographiside	Arg 403
163859	Diphyllin	Tyr 495, Gly 496, Phe 497, Gln 498
103582194	Tuberculatin	Tyr 495, Gln 493
114776	Isoorientin	Tyr 505 (π-π)
3652	Hydroxychloroquine	Lys 417:Halogen bonding
65028	Oseltamivir	Ty4 505
121304016	Remdesivir	Ser 494

Figures

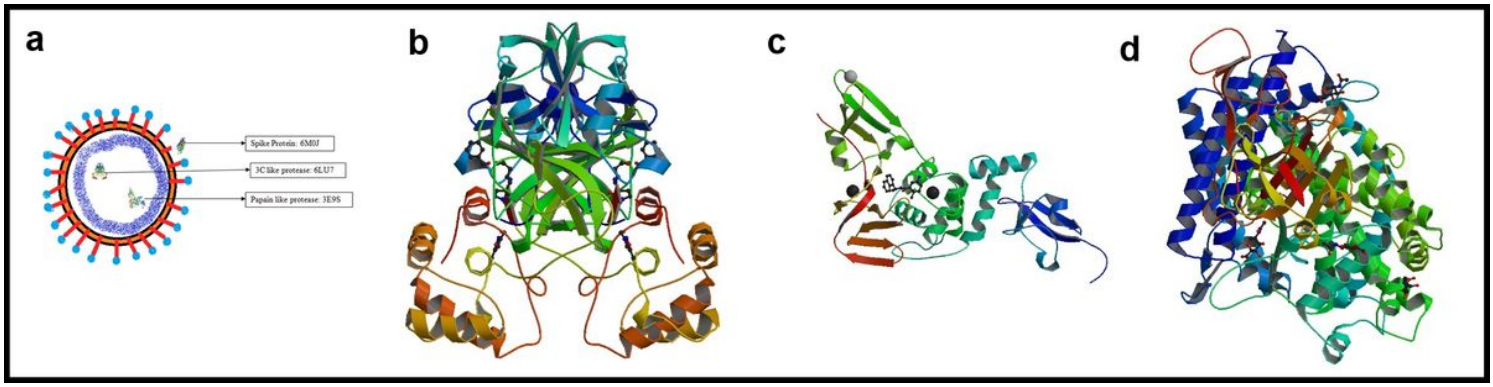

Figure 1

Protein structure of the targets selected for the study (a) SARS CoV-2 virus (b) 3CLpro: 3C-like main protease (c) PLpro: Papain-like protease d.SPIKE protein

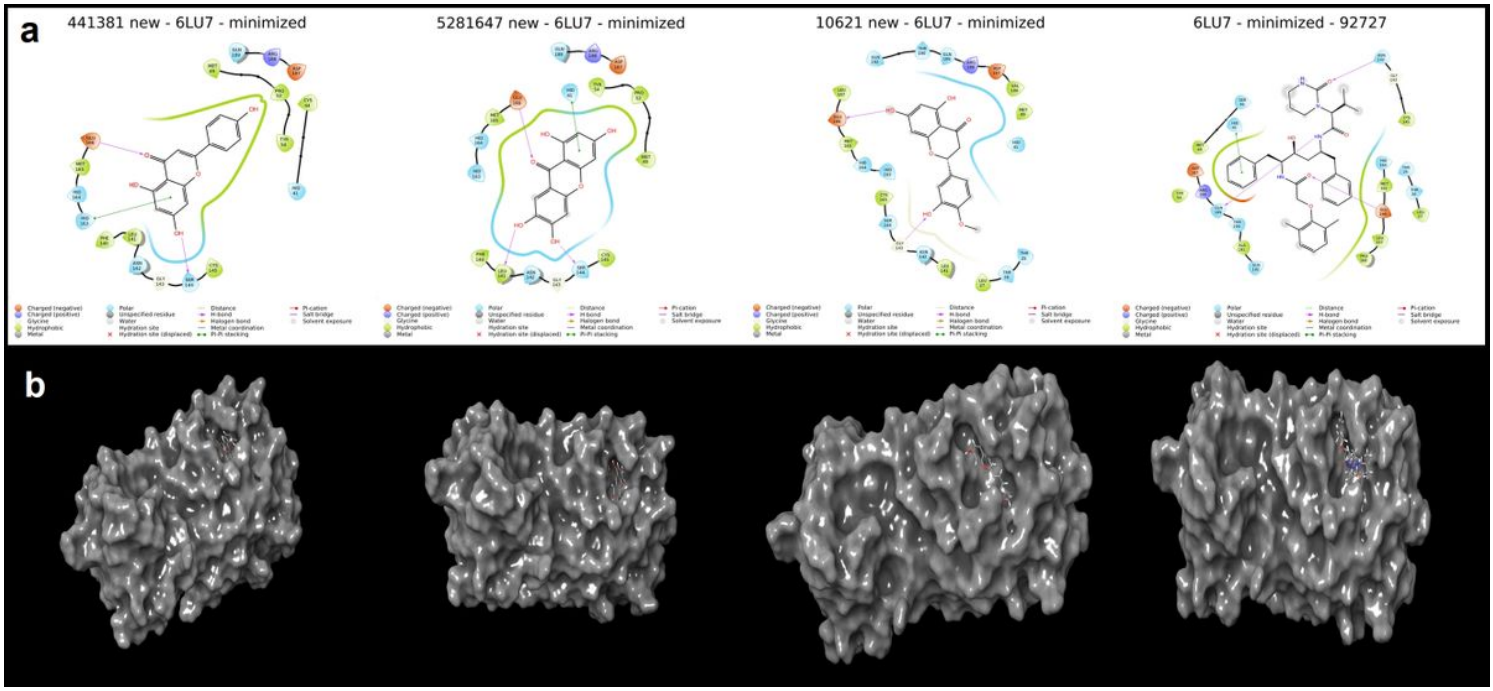

Figure 2

3CLpro protease enzyme of SARS-CoV-2 (a) Ligand-Protein interactions indicating separate amino acids (b) Full protease protein with ligand

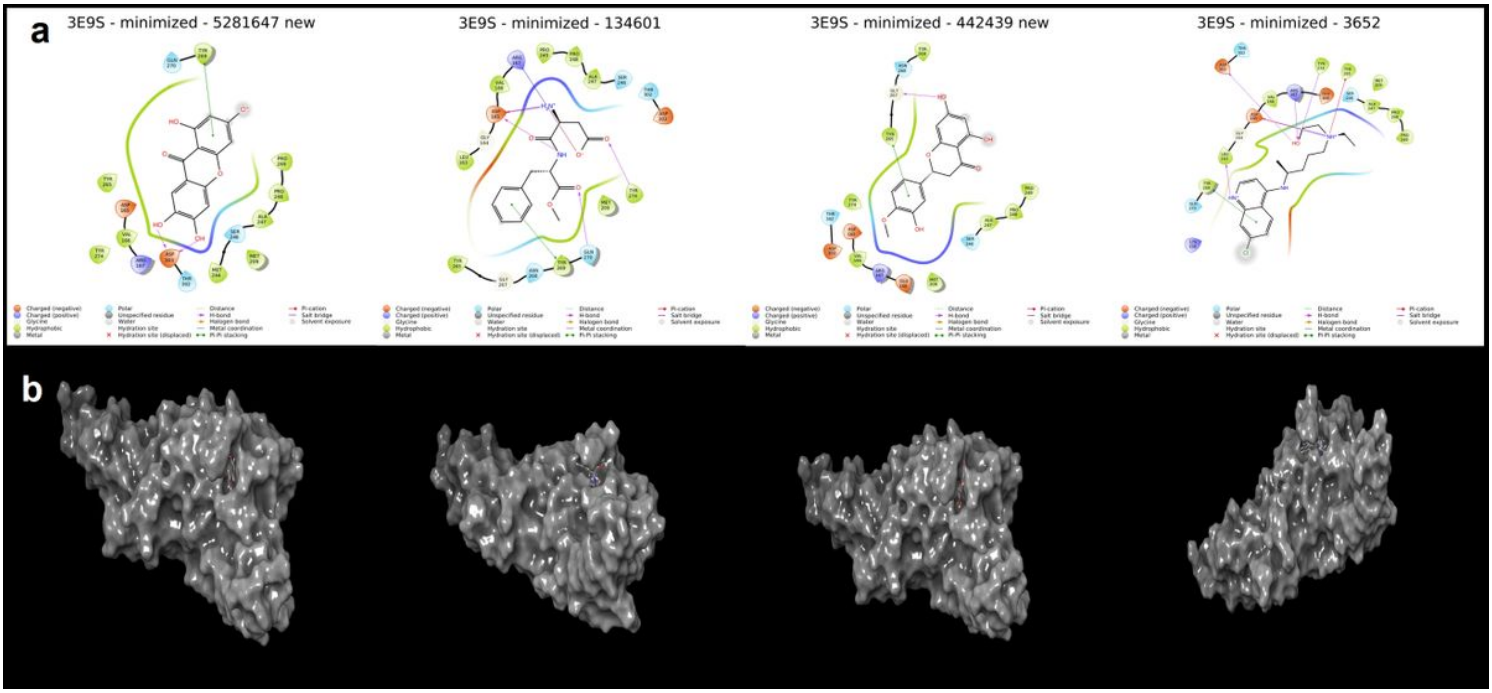

Figure 3

PLpro protease enzyme of SARS-CoV (a) Ligand –Protein interactions indicating separate amino acids (b) Full protease protein with ligand

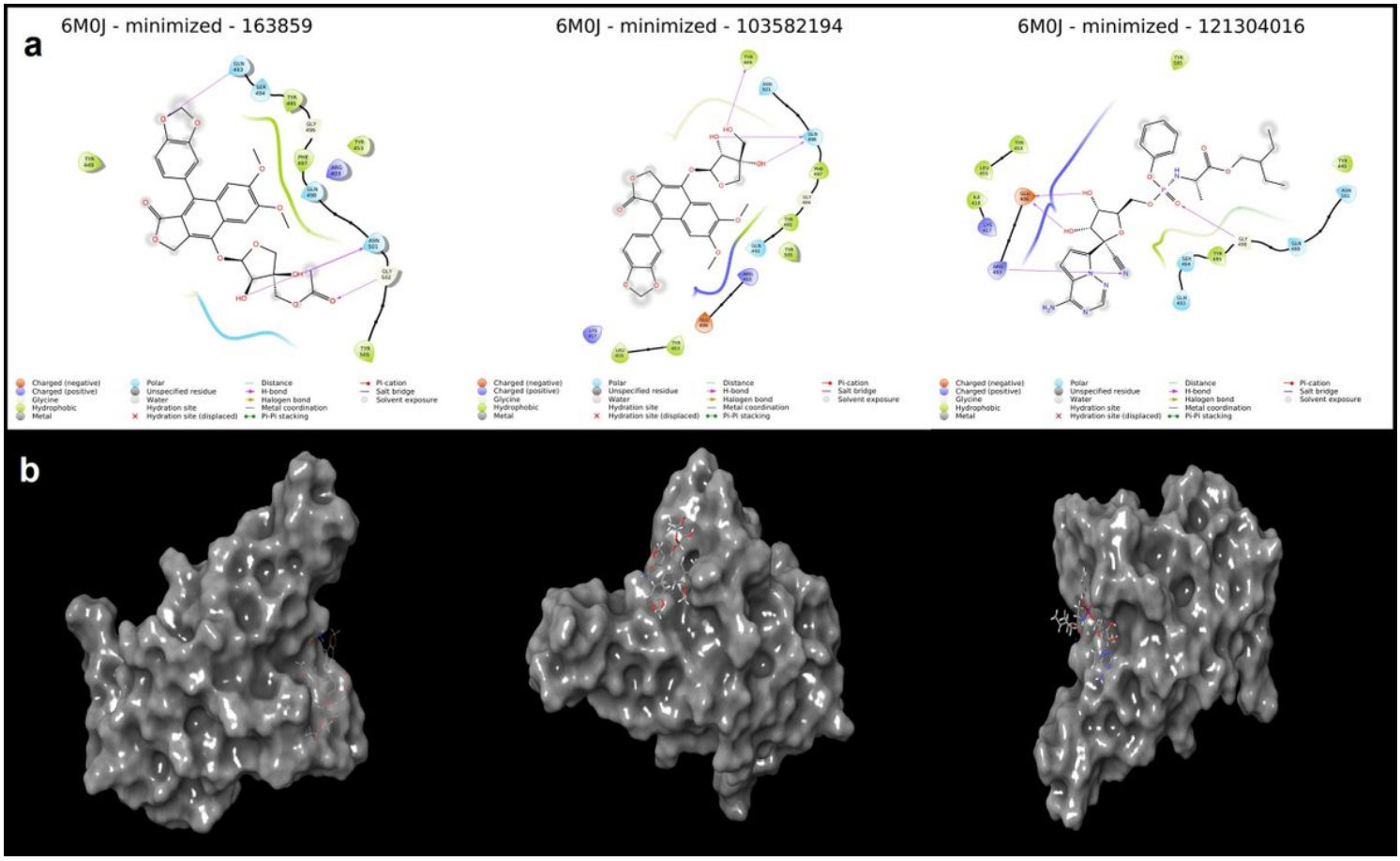

Figure 4

SPIKE protein of SARS-CoV-2 (a) Ligand –Protein interactions indicating separate amino acids (b) Full SPIKE protein with ligand

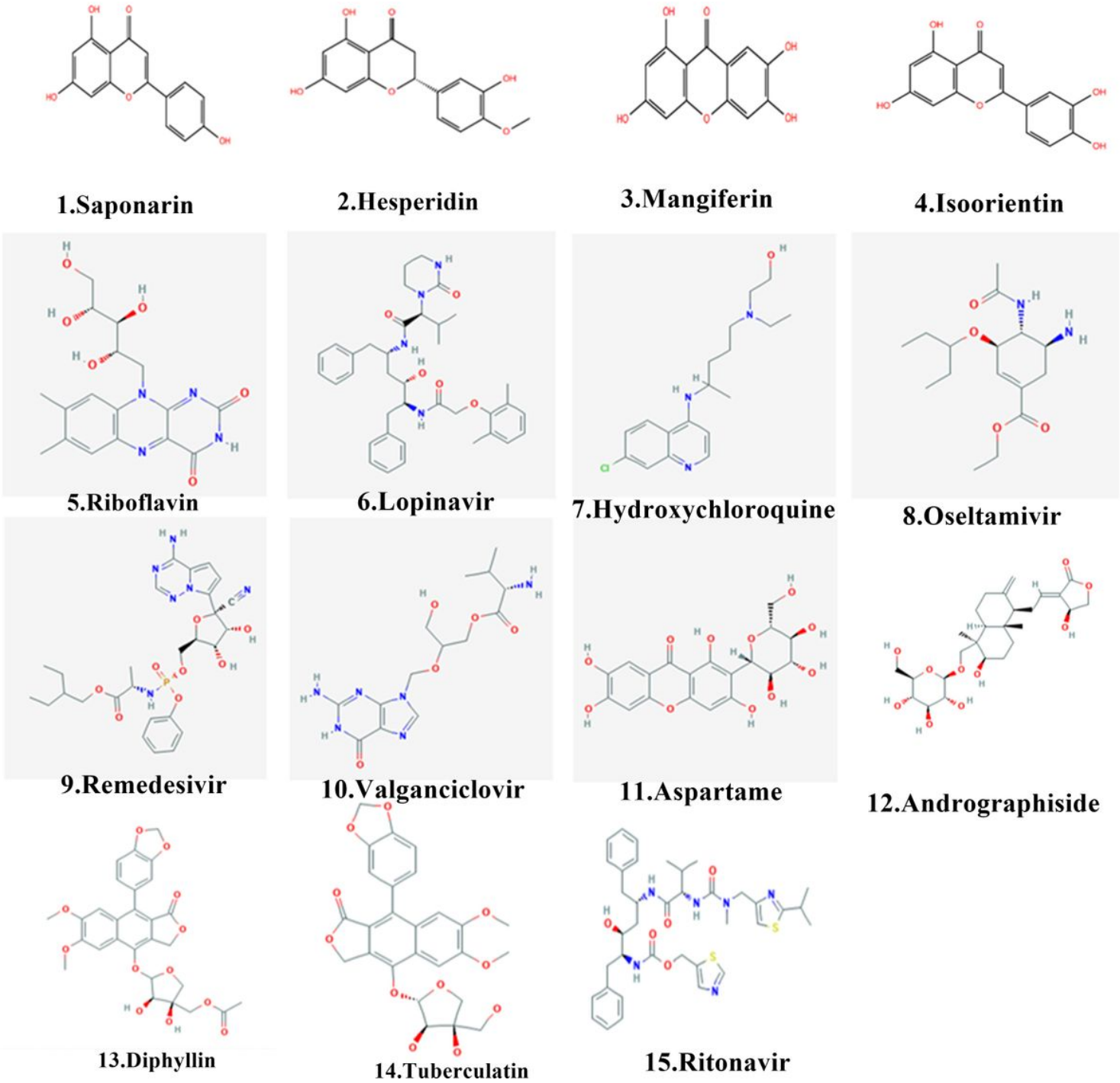

Figure 5

Chemical structures of important selected molecules for binding studies and identification of HITS against the target proteins of SARS-CoV-2.