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Review Article

Potential therapeutic drug candidates against SARS-CoV-2 (COVID-19) through molecular docking: A review

Aynaz Nourani[1], Vahid Rahimkhoei[2], Ali Akbari[2*]

[1] *Department of Health Information Technology, School of Allied Medical Sciences, Urmia University of Medical Sciences, Urmia, Iran*

[2] *Solid Tumor Research Center, Research Institute for Cellular and Molecular Medicine, Urmia University of Medical Sciences, Urmia, Iran*

***Corresponding author:** Ali Akbari, **Address**: Solid Tumor Research Center, Research Institute for Cellular and Molecular Medicine, Urmia University of Medical Sciences, Urmia, Iran, **Email**: akbari.a@umsu.ac.ir, **Tel**: +984433486165

Abstract

The severe acute respiratory syndrome coronavirus 2 (known as COVID-19), initially appeared in the Wuhan city of China in December 2019, has become a current medical issue around the world. Due to its highly contagious nature, COVID-19 has spread widely to all countries. As no effective treatment or vaccine is developed for this infectious disease, preventive measures are the only mandatory strategy to stop its human-to-human transmission. In the present spread of COVID-19, the discovery of antiviral drugs is crucially important as the development of these drugs often takes time. However, no specific drug has yet been approved for COVID-19. In this review, we focus on the available drug candidates used for the treatment of infections caused by COVID-19 to identify potential inhibitors through molecular docking.

Keywords: Antiviral drug, COVID-19, Inhibitors, Molecular docking, SARS COV-2

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Introduction

In December 2019, a series of acute atypical respiratory diseases occurred in the Wuhan city of China and rapidly spread to other regions of the world. The outbreak was declared a public health emergency of international concern on 30 January 2020 (1).

Coronaviruses are known for the crown-like (corona in Latin) spikes with a diameter of 70 to 160 nm, as detected by electron microscopy. Structurally, 2019-novel coronavirus (nCoV) possesses the enveloped positive-sense single-stranded RNA genome. The virus has glycoprotein spikes on its surface, giving it a crown-like appearance (2, 3). With the spread of 2019-nCoV, many efforts are being made to reveal detailed information about the epidemiology and pathogenesis of COVID-19, and more importantly, to develop methods to reduce its consequences (4-6). In virtue of obligatory isolation/quarantine, this virus has had many adverse and far-reaching effects not only on the global economy but also on the lives of millions of people (7).

Development of new drug is a time-consuming process due to expensive clinical trials, potential errors, and other difficulties. Therefore, today's bioinformatics tools, such as molecular docking, simulation, chemical stability research, and target determination, play an indispensable innovative role in the design of new drugs (8). In the absence of special drugs or vaccines during the SARS-CoV-2 pandemic, drug repositioning or drug repurposing acts a fascinating role; however, such drugs require clinical trials to prove their effectiveness against the disease (9).

Molecular docking is a tool in drug discovery and a computer-aided drug design technology. This method, uses computer technology to simulate the geometric structure of molecules and the interaction between molecules through stoichiometric calculation methods (10, 11). During molecular modeling approaches of finding potential inhibitors, special emphasis is placed on the significance of binding affinity of ligand-protein complexes and their drug-likeness features (12). In molecular docking, which is very much like lock-key model, the molecule binds to different parts of the receptor and explains the binding affinity in the form of energy. This approach is able to generate possible conformation, directions, or positions in which molecules or compounds bind to the receptors (13, 14). However, it should be pointed out that the biological activity of these molecules is also highly important. Computational tools provide new testable hypotheses for the discovery of conventional drugs involving 2019-nCoV (15, 16).

Computational techniques like molecular docking, drug-likeness screening, simulations, and others can help the exploration of COVID-19 (17, 18). Recently, virtual screening technology has been carried out through molecular docking and cell-based analysis to identify the active sites on viral proteases that bind to many natural compounds (19-21). Clinical trials to evaluate the efficacy of antiviral drugs available for COVID-19 are still ongoing, and there are various types of antiviral drugs used globally.

Coronaviruses are enveloped structures. Their RNA nucleic acid is positive and single-stranded, meaning that they can infect humans and animals. SARS-CoV-2 is composed of structural proteins, such as membrane, envelope, and spike protein. Among these proteins, the club-shaped spike glycoprotein (SGp) interacts with the angiotensin-converting enzyme 2 (ACE2) of human cells and cause the SARS-CoV-2 virus to enter the cell (22, 23). The sequence of SARS-CoV-2 genome revealed that it encodes 16–17 nonstructural proteins. Two proteases, papain-like protease (PL^{pro}) and 3-chymotrypsin-like protease (3CLpro), also known as M^{pro}, are essential for virus maturation and infectivity (24-27). After releasing the structure of SARS-CoV-2 proteins (such as M^{pro}, RdRp [RNA-dependent RNA polymerase], SGp, etc.) and genome sequence (28-31), a structure-based molecular docking study and simulation were conducted to identify the most effective inhibitors. This information was obtained from the RCSB protein data bank (https://www.rcsb.org/), which houses approved medications and phytochemicals with medical significance (32, 33). Molecular docking method assist researchers in designing effective drugs or potential drug candidates using the principles of drug design. This method also helps repurpose already existing drugs showing inhibitory activity based on the rationale of structure-based drug designing, which focuses on the key structural features of a protein and identifies the potent inhibitors based on the concept of estimated free energy of binding and the formation of various intermolecular interactions, e.g. hydrogen bonds, hydrophobic interactions, and van der Waals interactions (34-36). Herein, we summarize the antiviral drugs and compounds that may be used for SARS-CoV-2 infection. We hope this review could help scientists, clinicians, and the pharmaceutical industry to find new treatments for COVID-19.

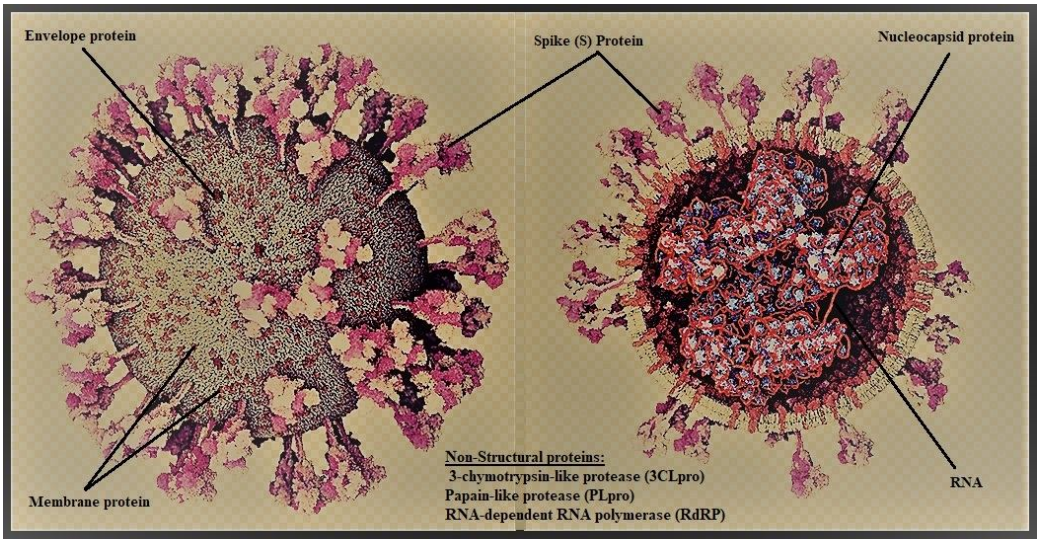


Fig. 1. Scheme of SARS-CoV-2 and some of its molecular protein targets.

SARS-CoV-2 Mpro/3CLpro:

COVID-19 is the source of 3CLpro, also known as Mpro. As Mpro/3CLpro plays a key role in the growth and spread of the virus, it represents a potential target for inhibiting CoV replication (37). The genome of the coronavirus encodes two proteins, ppla and pplb, which are involved in spike, membrane, envelope, nucleoprotein, replication, and polymerase activities. Protease activity can be neutralized by antiviral drugs called protease inhibitors, which selectively bind to the catalytic site of the enzyme and inhibit the production of infectious virus particles (2, 38). It has been also shown that SARS-3CLpro is a cysteine protease essential to the virus life cycle (39). The lack of effective 3CLpro inhibitors and the availability of x-ray crystal structure of 3CLpro persuaded researchers to conduct computational studies to identify potential commercially available inhibitors (40). Mpro/3CLpro has been successfully crystallized from COVID-19, and its structure has been mechanically adjusted and repositioned in the protein database (PDB) of the imported chimera to visualize the binding domain of the complex and identify the amino acids in the binding pocket. It is now accessible to the general public and can be used to understand binding domains of complexes (41, 42).

Researchers tried different treatments to determine potential inhibitors against the SARS-CoV-2 Mpro protein using computational methods. For instance, Hosseini et al. relied on the efficiency of the repurposing concept, combined with molecular docking and molecular dynamics simulation methods (43). They concluded that simeprevir and pyrrolidine could be potential drug candidates for the treatment of COVID-19. Simeprevir docked with 3CLpro (PDB Id: 6LU7) with a binding affinity of -252.54 kcal/mol and a docking score of 11.33 via strong hydrogen bonding (3 bonds) residues Asn 119, His 163, and Thr 26 and three sigma and pi interactions with other key substrate residues. Another study identified flavonoids (eleven known compounds isolated from the aqueous extract of *Salvadora persica* aerial parts) as an inhibitor with an estimated binding free energy of -7.76 kcal/mol. As shown in Figure 2, flavonoids are stabilized at the N3 binding site of Mpro through several variable electrostatic bonds (44). In a similar study, by using computational modeling strategies, the biological activities of selected heterocyclic drugs (favipiravir, amodiaquine, 2'-Fluoro-2'-deoxycytidine, and ribavirin) were evaluated as an inhibitor of COVID-19 agents and nucleotide analogs. Compared to favipiravir, 20-fluoro-20-deoxycytidine, ribavirin, and amodiaquine showed

the lowest binding energy (-7.77 kcal/mol). The drug and the receptor's amino acid residues interact hydrophobically in three different ways and through three hydrogen bonds (45).

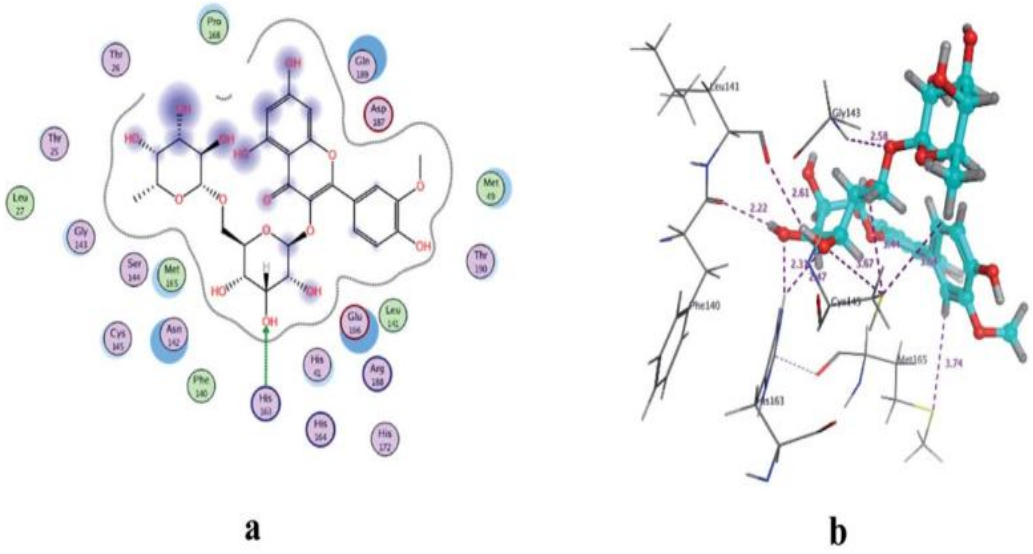
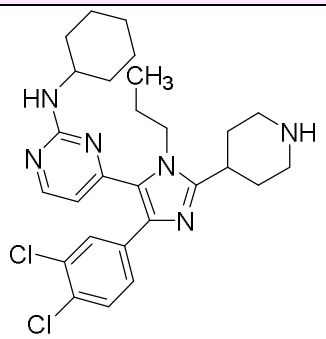
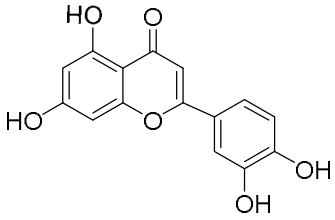
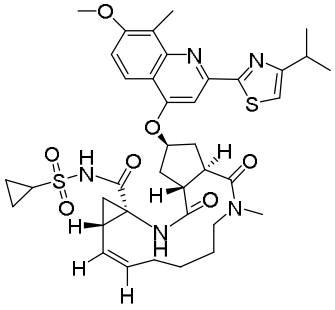
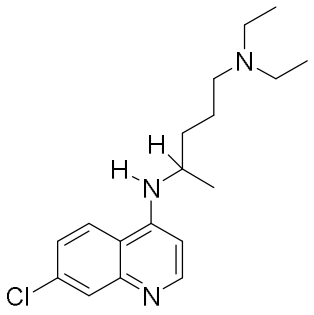
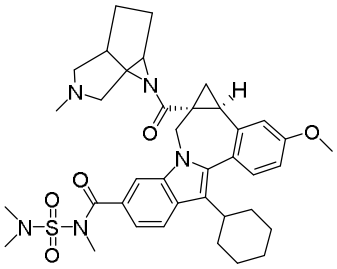
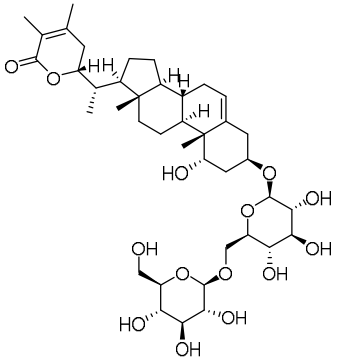
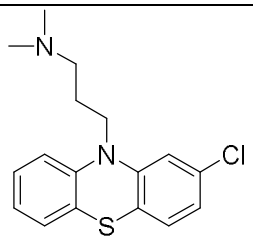


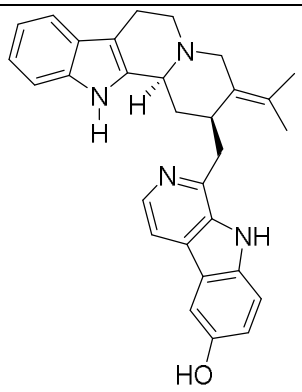
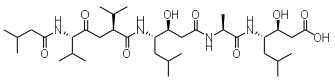
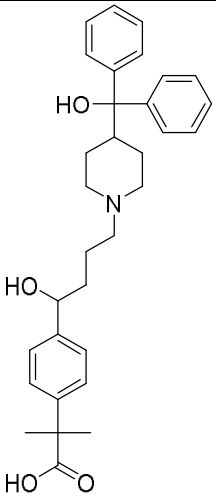
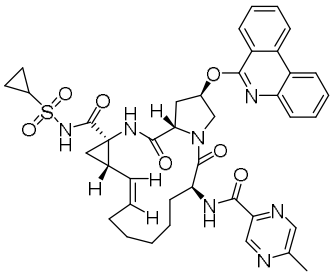
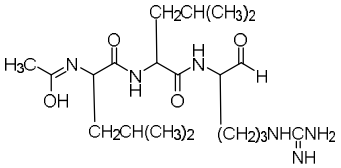
Fig. 2. (a) 2D and (b) 3D representation of docking of flavonoid into the N3 binding site of the COVID-19 Mpro (44).

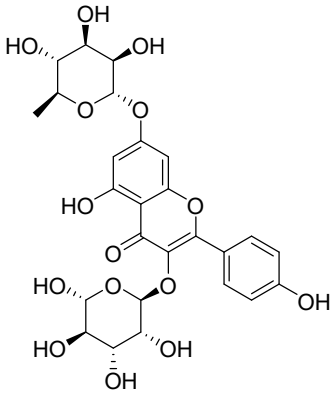
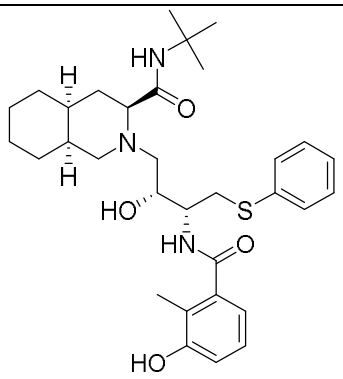
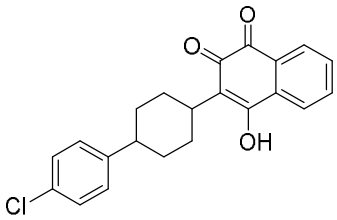
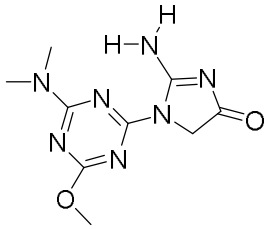
In a drug repurposing study, ribavirin, telbivudine, vitamin B12, and nicotinamide were suggested as COVID-19 inhibitors with docking scores of 2.00, 2.01, 1.99, and 1.92, respectively. Theoretical calculations illustrated that ribavirin and telbivudine formed two hydrogen bonds with the backbone of THR25 and SER49 and the side chain of GLN189 and GLV189, respectively (46). Das et al. studied small-molecule inhibitors that may bind to the active site of SARS-CoV-2 protease (PDB: 6Y84) (47). Rutin, a natural compound known as vitamin P, showed the highest inhibitory activity by blind molecular docking analysis (six hydrogen bonding) and displayed an estimated binding free energy of -9.55 kcal/mol. Catalytic residues such as His41 and Cys145 interact with the π-alkyl and π-sulfur bonds of the aromatic backbone of the ligand. It indicates six hydrogen bonds and additional van der Waals interactions to stabilize the interaction between protein and ligand (48). Another similar study explored the combination score of ritonavir (antiviral drug) and 3CLpro (PDB ID: 6Y84), which was shown to be -8.12. The hydroxyl group of the ligand forms an arene-H bond with Met165 residues (49). Furthermore, Ryu et al. corroborated that quercetin demonstrated a promising inhibitory effect on SARS-CoV 3CLpro expressed in *Pichia pastoris*, with an inhibitory rate of 82% (50). In another interesting study, saquinavir, aclarubicin, TMC-310911, and faldaprevir were suggested as potential 3CLpro inhibitors with binding energies of -125, -150, -151, and -123 kJ/mol, respectively (51). Through virtual screening of synthetic and natural compound libraries, some computational studies have been conducted to identify anti-3CLpro inhibitors from SARS-CoV-2 (Table 1).

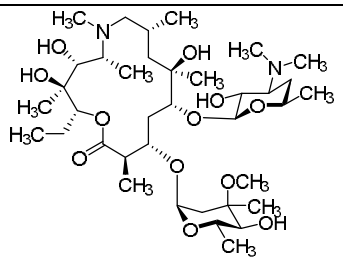
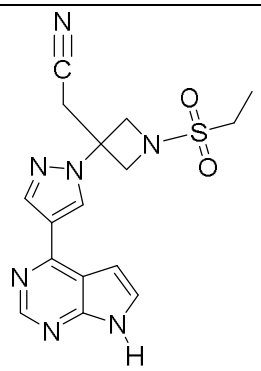
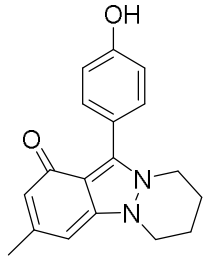
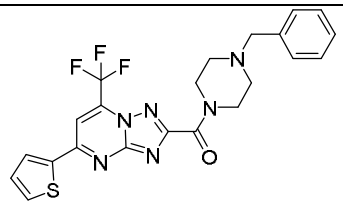
Table 1. Existing promising and potential molecules against 3CLpro/Mpro from SARS CoV-2

	Drug candidate	Structure	indication	Binding free energy (kcal/mol)	Interacting residues	References
1	DB02388		Not available	-49.67	GLU166, TYR54, and ASP187 (hydrogen bonds)	(52)
2	Luteolin		Antioxidant, anti-inflammatory	-28.88	———	(53)
3	Simeprevir		Treatment of HCV	-11.33	Asn119, His163, and Cys145 (hydrogen bonds) His41 (Sigma and Pi interactions)	(54)

4	Chloroquine		Antimalarial, anti-inflammatory	-10.8	HIS164, ASN142, CYS145, ARG188, and GLU166 (hydrogen bonds) PRO168 (Pi interactions)	(55)
5	Beclabuvir		Treatment of HCV	-10.4		(56)
6	Withanoside V		Phytochemicals of ayurvedic medicinal plants	10.32	ASN84, ARG40, and MET82 (hydrogen bonds) CYS85, ARG105, and PHE134 (Pi interactions)	(57, 58)
7	Chlorpromazine		Antipsychotic drug	−10.1	His163 (hydrogen bonds)	(59)

8	10-Hydroxyusambarensine		Antimalarial	−10.1	GLN189 and TYR54 (hydrogen bonds) PHE294, and PRO293 (Pi interactions)	(60)
9	Pepstatin A		Inhibitor of acid proteases	-9.9	———	(61)
10	Allegra		Anti-histamine	-9.6	Thr111, Asn151, and Asp153 (hydrogen bonds)	(62)
11	Paritaprevir		Treatment of HCV	-9.5	Cys145 and MET49 (Pi-Sigma) HIS41, GLN189, THR26, ASN119, and GLY143 (hydrogen bonds)	(63)
12	Leupeptin hemisulfate		Inhibitor of serine and cysteine proteases	-9.3	———	(61)

13	Kaempferitrin		An immunomodulator, an anti-inflammatory agent	-8.63	Thr190, Thr26, Gly143, and Gln192 amino acids (hydrogen bonds)	(64)
14	Nelfinavir		Antiretroviral drug	-8.4	LEU282, PHE291, GLN127, GLY283, LYS137, GLY138 and TYR126	(58, 65)
15	Atovaquone		For treating Pneumocystis carinii pneumonia and malaria	-8.2	Thr199 (hydrogen bonds)	(62)
16	Imidazolidin-4-one, 2-imino-1-(4-methoxy-6-dimethylamino-1,3,5-triazin-2-yl)		Not available	−7.013	Glu166 and Gln192 (hydrogen bonds)	(66)

17	Azithromycin		Antibiotic	-6.3	Leu272 (hydrogen bonds)	(67)
18	Baricitinib		Anti-inflammatory, immunomodulating and antineoplastic	-6.3	Asp197, Leu287, and Lys137 (hydrogen bonds)	(67)
19	Nigellidine		Not available	-6.3	HIS 163 (hydrogen bonds)	(68)
20	ZINC00793735		Not available	-6.20	GLN189 (hydrogen bonds) LEU141 and HIE41 (Pi interactions)	(69)

Angiotensin-converting enzyme2:

ACE2, a protein on the surface of many cell types, can produce small proteins by chopping up the larger protein angiotensin, and then continuing to regulate cell functions (70). It is known that ACE2 is expressed in various human organs, and its organ and cell-specific expression indicate that it may play a role in regulating cardiovascular, renal functions, and fertility (71). In addition, the encoded protein is the functional receptor for the spike glycoprotein of human coronavirus and human severe acute respiratory syndrome coronavirus SARS-CoV and SARS-CoV-2, which the latter is the cause of coronavirus disease factor (COVID-19). The SARS-CoV-2 virus uses spike-like proteins on its surface to bind to ACE2 before entering and infecting cells, just like inserting a key into a lock (72, 73). Therefore, ACE2 acts as a gate receptor for the virus that causes COVID-19. In addition, ACE2 is a vital element in the biochemical pathway and essential for the regulation of blood pressure, wound healing, and

inflammation (74). The pathway is known as the renin-angiotensin-aldosterone system. ACE2 helps regulate many activities of a protein called angiotensin II (ANG II), which increases blood pressure and inflammation, enhances damage to the vascular intima and causes various types of tissue damage (75, 76). ACE2 converts ANG II into other molecules that can counteract the effects of ANG II. When the SARS-CoV-2 virus binds to ACE2, it prevents ACE2 from performing its normal function to regulate ANG II signaling. Therefore, the effect of ACE2 is "suppressed", eliminating the brakes from the ANG II signal, allowing more ANG II to be used to damage tissues. This reduced immobilization may cause injuries to COVID-19 patients, especially lung and heart injuries (77). The traditional Chinese medicine ingredient Huoxiang zhengqi oral solution can be combined with ACE2 through network pharmacology and molecular docking, targeting PTGS2, CAMSAP2, and other targets, thereby preventing and controlling COVID-19 (78).

An investigation by Lestari et al. exhibited the connection of three quinoline-based antimalarial drugs (chloroquine, hydroxychloroquine, and quinine) with the peptidase space of the ACE2 receptor (79). Among these three compounds, quinine had the strongest affinity (-4.89 kcal/mol) for the ACE2 receptor (PDB ID: 6VW1). It interacts with Lys353 via hydrogen bonding and forms positive ionizable bonds with His34 and Glu. Dithymoquinone, the main component of *Nigella sativa*, through absorption, distribution, metabolism, and excretion analysis (ADME) showed high solubility and intestinal absorption and indicated an estimated binding free energy of -8.6 kcal/mol through Autodock/vina (three hydrogen bonds and one ionic interaction with LYS31 residues) (80). In a similar study, nigellidine indicated a binding affinity of -6.11 kcal/mol when docked with ACE2 through hydrogen bonding residue, namely GLU166 (81). Another study revealed the active ingredients and potential molecular mechanisms through which Cold–Damp Plague Formula treatment can effectively fight COVID-19. Han et al. identified L-tyrosine as an inhibitor with an estimated binding free energy of -6.5 kcal/mol using Autodock Vina, where ACE2 was mainly connected through amino acid residues Ala413, Phe438, Thr434, Asn437, Ile291, Asn290, and Pro289 (82). In a drug repurposing study, quercetin showed a minimum binding free energy of -8.4 kcal/mol, which was almost equal to the control drug (ritonavir = -8.5 kcal/mol). It manifested four hydrogen bonds with the amino acid residues Lys745, Tyr613, His493, and Asp609 (74). In a study of chemical compounds from traditional Mongolian medicine, Phillyrin and chlorogenic acid showed stable estimated binding affinity and ADME properties. When docked against ACE2 (PDB ID: 2AJF), both compounds exhibited interactions with the active site residues, strong hydrogen bonding interactions, and potent stability of the protein-ligand complex (83). Another virtual screening study using molecular docking identified two antimalarial compounds, chloroquine and hydroxychloroquine, as likely inhibitors of ACE2 with a binding affinity of -7.1 and -6.8 kcal/mol, respectively (84).

RNA-dependent RNA polymerase:

RdRp is involved in the replication and transcription of all RNA-containing viruses with no DNA stage such as the SARS-CoV-2 genome (85). RdRp is a vital enzyme in the life cycle of RNA viruses. As a result, it has become a target for many viral infections, including hepatitis C virus, Zika virus, and coronavirus. The active site of RdRp is highly conserved, and there are two continuous and surface-accessible aspartic acids in the β-turn structure (86, 87). By targeting the virus-specific RdRp, several antiviral drugs have been developed against the Zika virus, hepatitis C, and other coronaviruses. A recent study explored that the antiviral drugs remdesivir and favilavir can be used to treat several RNA virus diseases. These drugs effectively inhibit RdRp and RNA polymerase and play an important role in the replication of SARS-CoV-2 *in vitro* (42, 88-91).

Recently, Elfiky conducted an investigation on approved antiviral drugs for different viral RdRps, such as galidesivir, remdesivir, tenofovir, YAK, sofosbuvir, IDX-184, etc. (89). Among these drugs, setrobuvir,

IDX-184, and YAK compounds showed excellent results in binding to SARS-CoV-2 RdRp, with binding energies of -9.3, -9.0 and -8.4 kcal/mol, respectively. Figure 3 depicts established interactions after docking with setrobuvir forming 3H-bonds (R444 (2) and K689), three hydrophobic contacts (D509, K689, and E702), and a cation interaction with R444.

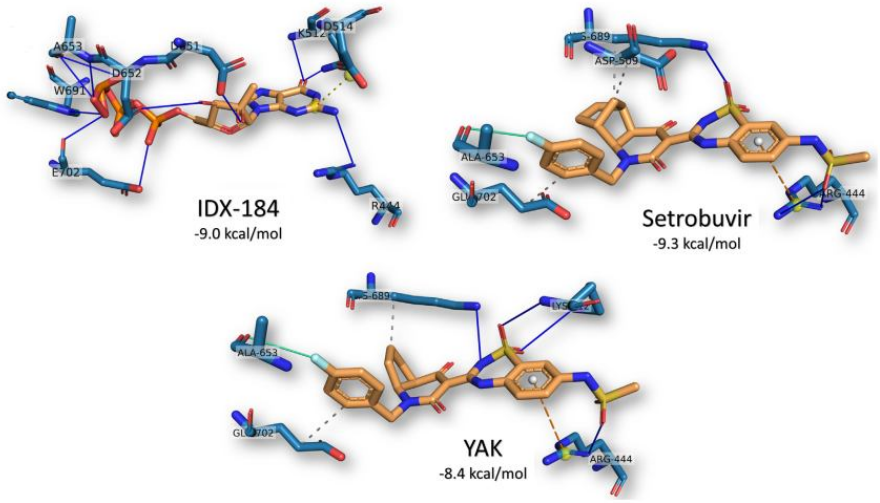


Fig. 3. Interactions established after docking the IDX-184, setrobuvir, and YAK against SARS-CoV-2 RdRp (89).

In Yu et al.'s study, luteolin displayed an estimated binding affinity of -7.5 kcal/mol using Autodock Vina when docked against RdRp (PDB ID: 6NUS) of SARS-CoV-2 with three hydrogen bonds (92). In another study, favipiravir analog CID89869520 indicated stable binding free energy of -5.1 kcal/mol by Autodock and ADME properties, which were more negative than favipiravir binding affinity (-4.9 kcal/ mol). It forms three hydrogen bonds with Lys798, Trp800, and Asp761 residues (93). Chang et al. used computational methodologies to repurpose HIV protease inhibitors and nucleotide analogs for COVID-19 (94). Through two independent MD simulations (Autodock Vina and RosettaCommons), it was observed that remdesivir has the highest docking score (-7.8). Comparison of docking sites between remdesivir and other drug candidates showed that the overlap area of remdesivir was almost perfect for docking protein pockets. Another virtual screening study identified diosgenin, a natural product found in Dioscorea (wild yam) species, as a potential inhibitors of RdRp binding affinity of -9.1 kcal/mol (95). In a drug repurposing study, the limonin molecule, a crystalline substance found in citrus and other plants, exhibited minimum binding free energy (-9.0 kcal/mol). It formed three hydrogen bonds with the residues of THR556, SER682, and LYS621 that maintain a strong affinity with the target protein, 3 π-alkyl interactions, and several other stabilizing vans der Waals interactions (96).

Papain-like protease:

PLpro is an essential COVID-19 enzyme, which is required to process virus polyproteins to produce functional replicase complexes and enable the virus to spread (97). PLpro is also involved in the post-translational modification of the cleavage of the host protein as an evasion mechanism against the host's antiviral immune response (98, 99). Sahoo and Vardhan studied the molecular docking of influenza antiviral drugs baloxavir acid (BXA) and baloxavir marboxil (BXM), and PLpro protein (PDB ID: 4MM3). The drugs BXA and BXM bound to the protein PLpro, and their dock scores were -8.9 to -7.2 kcal/mol and -7.0 to -6.5 kcal/mol, respectively, but computer-based protein-

ligand interaction studies showed that there was no binding posture as the active site, composed of three catalytic triads of PLpro (CYS112, HIS273, and ASP287) (100). In another study, the effectiveness of ivermectin (antiparasitic agent) and doxycycline (antibiotic) in COVID-19 was explored (101). The predicted binding energies of ivermectin and doxycycline to PLpro (PDB ID: 6w9c) were -8.5 and -7.1 kcal/mol, respectively. Figure 4 shows the active binding site and 2D interaction of ivermectin and doxycycline with SARS-CoV-2 PLpro.

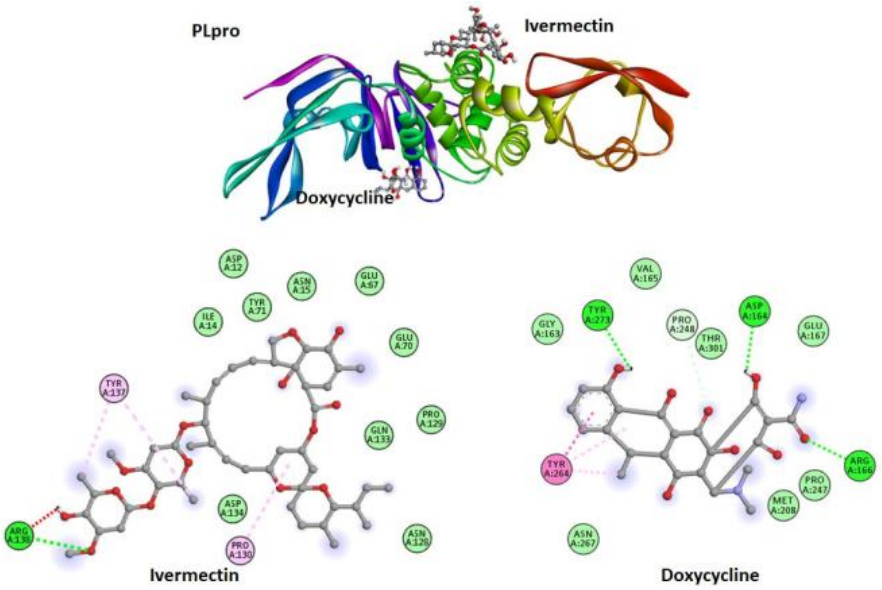


Fig 4. The binding site of ivermectin and doxycycline with SARS-CoV-2 PLpro and their interactions (101).

Spike protein:

Spike protein is a crucial recognition factor for virus attachment and entry into host cells. It exists on the outer surface of the virion in a homotrimeric state. The CoV spike protein binds to the host cell membrane through receptor-mediated interactions that allow entry into the host cell (71). Although there are structural similarities between the SARS-CoV-2 spike protein and the SARS spike protein, the conservation is only 73% and most of the mutations are in the host cell interaction region of the protein (102). In one specific study, the binding free energy prediction in interaction with spike proteins for eriodictyol was found to be approximate -7.5 kcal/mol (103). Hall and Ji studied several drugs to target the SARS-CoV-2 spike protein. They identified that coenzyme A has the highest binding affinity (-11.5 kcal/mol) among the candidate drugs (104).

Conclusion

The high transmission rate of SARS-CoV-2 has led to the current COVID-19 pandemic, with infections all over the world, and more than 1 million deaths worldwide. While clinical trials of the ideal vaccine continue, it is essential to find alternative antiviral candidates to prevent the further spread of the virus. Due to virus rapid development, timely drug development for the treatment of 2019-nCoV is important. At present, it is important to control the source of infection, cut off the route of transmission, and use existing drugs and methods to actively control the progression of the disease. In this review, we focus on using potential drug candidates to treat infections caused by 2019-nCoV to identify potential inhibitors through molecular docking. Although these drugs are expected to become special for the treatment of COVID-19, care must be taken when

using these drugs when there is insufficient evidence to prove their effectiveness and safety.

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Ethical considerations

Nil

Conflict of interest

The authors have no conflict of interest in this study.

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