Molecular Docking as a Potential Approach in Repurposing Drugs Against COVID-19: a Systematic Review and Novel Pharmacophore Models

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Abstract

Purpose of Review This article provides a review of the recent literature related to the FDA-approved drugs that had been repurposed as potential drug candidates against COVID-19. Moreover, we performed a quality pharmacophore study for frequently studied targets, namely, the main protease, RNA-dependent RNA polymerase, and spike protein.

Recent Findings Ever since the COVID-19 pandemic, the whole spectrum of scientific community is still unable to invent an absolute therapeutic agent for COVID-19. Considering such a fact, drug repurposing strategies seem a truly viable approach to develop novel therapeutic interventions.

Summary Drug repurposing explores previously approved drugs of known safety and pharmacokinetics profile for possible new effects, reducing the cost, time, and predicting prospective side effects and drug interactions. COVID-19 virulent machinery appeared similar to other viruses, making antiviral agents widely repurposed in pursuit for curative candidates. Our main protease pharmacophoric study revealed multiple features and could be a probable starting point for upcoming research.

Keywords COVID-19 · Drug repurposing · Pharmacophore analysis · Main protease · Spike proteins · RNA-dependent RNA polymerase

Introduction

Towards the end of 2019, a novel beta coronavirus was identified as the causative agent of huge cases of unprecedented pneumonia, reported for the first time in Wuhan city, China. Soon after, the WHO labeled the severe acute respiratory syndrome as COVID-19 and the virus as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1, 2]. Starting on March 2020, the WHO announced that COVID-19 has become a global pandemic [3]. The pandemic affected the whole world, [1, 4], and due to its airborne infectivity, social distancing measures have been imposed by international authorities [5].

As a response to the sudden outbreak of COVID-19, an intensive global research efforts have been devoted to investigate potential therapeutic approaches. Looking at the fast return and the low cost of drug repurposing strategies, it has been implemented as immediate drug discovery pipeline [6•]. Many clinically useful drugs including aspirin and sildenafil which were originally used as inflammation and hypertension have been successfully repurposed for cardiovascular diseases and erectile dysfunction, respectively [7, 8]. Nowadays, molecular docking as an in silico method is very popular in drug discovery researches, because of its ability to illustrate the interactions between the ligand and its biological targets [8, 9]. Pharmacophore modeling — defined as a set of molecular features that enable biologically active ligands to exert a pharmacological effect — practice is
widely used in the drug discovery process [10]. Herein, we reviewed and summarized research of FDA-approved drugs repurposed against SARS-CoV-2 virus.

**Methods**

**Workflow**

**Search Strategy**

During the period of COVID-19, the scientific community had published an immense number of studies about repurposing drugs for COVID-19. These studies are scattered on the internet, and no one database will be inclusive enough to all of these studies, aside from Google Scholar. All studies have been collected by the end of 2020/12/30. In order to achieve an efficient search strategy, the following combinations of keywords were applied during the research in the Google Scholar database: (COVID19 OR SARS-CoV-2) AND (Drug repurposing OR Drug repositioning OR Drug re-profiling OR Drug rediscovery) AND (Docking AND Molecular dynamic).

**Data Selection and Extraction**

Titles and abstracts were first checked for eligibility using specific inclusion and exclusion criteria (Table 1). Selected paper were then completely reviewed as a second stage, while articles that met the exclusion criteria were eliminated.

Primarily, searching revealed a total of 405 articles, after applying the above mentioned criteria above, we ended up with 92 research articles, as presented in the flow diagram (Fig. 1). We further classified them according to SARS-CoV-2 targets: 73 for the main protease, 11 for spike protein, and 8 for replicase complex.

**Pharmacophore Analysis**

To perform the pharmacophore study, we had to ensure that all the drugs analyzed bind to the same site on the target. Thus, we classified the drug within the same target according to the binding site. There are various approaches used in literature to define the binding site or the docking site. Nevertheless, we obtained one binding site for each target except the main protease; it gave us two binding sites. Phase from Schrodinger suits was used to generate the pharmacophore hypothesis [11]. As the quality of the pharmacophore was our biggest concern, we used the number of features and the Hyposcore as a measure of quality. The following criteria were implemented: a maximum of 7 features, a minimum of 6 features, and minimum coverage of 50% of the compounds at the question.

**Data Description**

In silico work on COVID-19, drug discovery started even before the PDB structure of SARS-CoV-2 targets was released; during that time, homology modeling was used to generate the protein structure in question. The generated targets that have been investigated are spike protein, RNA-dependent RNA polymerase (RdRp), main protease, helicase, and papain-like protease. However, from them, we reviewed only the most studied targets (main protease, spike protein, and RdRp) [1, 2].

All papers follow a similar protocol, as shown in Fig. 2a either docking alone or docking and molecular dynamics simulation.

As illustrated in Fig. 2b, the most used software for molecular docking was Autodock vina, followed by Glide and preceded by Autodock 4. The open source feature of Autodock rationalizes its greatest usage frequency. Autodock vina is the most used because it is easier to use compare to Autodock4, and it has have been implemented in many software packages like PyRx. In addition, Autodock vina is faster and more accurate depending on the system and the parameter setting [12].

While docking studies consider the flexibility of the ligand as a rigid structure, molecular dynamic (MD) simulation takes the ligand–protein complex as a dynamic module. It searches the conformational space for the most stable conformation, giving more accurate results. Moreover, due to the cost of running MD simulation, only 48 studies out of 89 confirmed docking results with MD (Fig. 2a).

| Table 1 | Inclusion and exclusion criteria for the included articles |
|---------|---------------------------------------------------------|
| Parameter | Inclusion criteria | Exclusion criteria |
| Type of publication | Original article | Preprint, review article, letters, conference abstracts |
| Kind of the study | Studies that evaluated antiviral activities against COVID-19 | Studies that evaluated antiviral activities against other viruses |
| Method of study | Docking, molecular dynamic | Homology modeling |
| Type of molecule | Drugs | Phytochemicals, non-drug molecules |
| Language | English | Language other than English |
and AMBER were the most used free MD software. On the other hand, Desmond was the most used commercial software (Fig. 2c).

Results and Discussion

Main Protease

The fact that no human protease mimics the cleavage activity of the viral main protease; it has been a well-positioned drug target [13••]. The sequence identity shows that 96% of SARS-CoV-2 main protease is identical with other SARS-CoV viruses [14]. This high conservation encourages researchers to study inhibitors and other drugs for repurposing them against SARS-COV-2 main protease. Yang’s group was the first group to release the crystal structure of the main protease (PDB ID: 6LU7) [15]. In this paper, we classified the drugs according to the anatomical therapeutic chemical classification system (Table 2).

Anti-infective agents were the most frequent class, with antivirals and tetracycline being the predominant subclasses; thus, they have been considered in the discussion. The following most frequent classes are the antineoplastic and immunomodulating agents (Table 2). However, we did not find any similarity between the original mechanism during our analysis, and they had failed pharmacophore analysis.

Antivirals

Of the 29 antiviral drugs that were reported to bind with the viral main protease, 16 drugs are already protease inhibitors; hence, the hypothesis here is whether they are SARS-COV-2 protease inhibitors too. These drugs are indinavir, ritonavir, lopinavir, nelfinavir, saquinavir, simeprevir, paritaprevir, darunavir, atazanavir, glecaprevir, telaprevir, tipranavir, brecanavir, grazoprevir, tipranavir, and amprenavir. Furthermore, they work on only two proteases, human immunodeficiency virus type 1 protease and NS3/4A protein. Of these compounds, indinavir was reported eight times with seven different docking software, ritonavir was repeated twelve times with seven different docking software, and finally, lopinavir was repeated eleven times with seven different docking software. All these evidences support their potential as drugs for COVID-19. On the other hand, asunaprevir, ciluprevir, and pleconaril work on “Genome polyprotein,” a complex protein with many functions including protease activity, and they could be considered for further analysis.
Lastly, the other ten drugs have diverse targets, and they failed pharmacophore analysis, so we excluded them in pharmacophore analysis.

### Tetracyclines

Another class of compounds that peaked our interest is the tetracyclines; we found that five tetracyclines in the literature claim to have inhibitory activities against the main protease. These compounds are oxytetracycline, lymecycline, tetracycline, minocycline, and doxycycline. Tetracyclines are broad-spectrum antibiotics, and they have the general structure of four fused rings. They work by inhibiting protein synthesis; notably, they inhibit the binding of aminoacyl-tRNA to the mRNA translation complex [89].

### Pharmacophore Analysis of the Main Protease

Most studies on the main protease have been conducted on the 6LU7 structure, and all of those studies performed their docking analysis on two binding sites. One has cysteine-type endopeptidase activity (CYS145), and the other is a larger protein cavity. It is worth noting that our pharmacophore studies only conducted on the cysteine type, as replicating such analysis has failed on the second one.

The CYS145 was the most studied binding site in 85% of all the studies that used the PDB 6LU7. The number of drugs for this binding site was huge, putting pressure on the phase alignment algorithm. We had to create pharmacophore modules for the predominant classes of drugs, including antivirals, tetracyclines, antineoplastics, immunomodulating, and all combined drugs. As described in the workflow, we used strict parameters, and only tetracyclines and antivirals had survived. For comparison purposes, we included the N3 complexed inhibitor and the binding site hypothesis. We studied quality, type of features, and features alignment for these pharmacophores (Table 3, Fig. 3a).

N3 is a co-crystallized inhibitor with 6LU7; its pharmacophore is rich in hydrogen donor features, which is expected because it is a polypeptide, subsequently containing alternating hydrogen bond donor and hydrogen bond acceptor. Tetracycline is also rich in hydrogen donor features, and the antivirals pharmacophore is rich in hydrogen acceptors. The pharmacophore search of antivirals having an anti-protease activity — as its original mechanism of action — was successful with 6 features and a Hyposcore of 1.09 (Table 3). On the other hand, the search for pharmacophores of the other antivirals, where-the original mechanism of action is not anti-protease, had failed due to our strict parameters. These hypotheses contain at least one aromatic ring, and the negative charge feature is only present on the binding site.

Notably, the best scores were obtained with tetracycline pharmacophores; it had seven features and a Hyposcore of 1.35; their structural similarity supported this result (Table 3, Fig. 3a).
| PDB ID | Drug space | Drugs | References |
|--------|------------|-------|------------|
| 6LU7   | Ivermectin | Ivermectin | [16] |
| 6LU7   | Anti-HIV drug | Darunavir | [17] |
| 6NU1   | FDA-Approved Drugs | Asinex BioDesign Library | [19] |
| 6M03   | Penicillins | Penicillins | [22] |
| 6LU7, 6M2N | Approved protease inhibitors | 2949 protease inhibitors | [21] |
| 6LU7, 6M2N | DrugBank | 10,000 compounds | [27] |
| 6LU7 | Approved anti-viral drugs | 6660 compounds | [28] |
| 6LU7 | Metocurine compounds | 110 molecules | [24•, 25] |
| 6LU7 | Approved anti-viral drugs | 10,000 compounds | [26] |
| 6LU7 | 10,000 compounds | 2949 protease inhibitors | [29, 30•] |
| 6W63 | 23 drugs | 2949 protease inhibitors | [31] |
| 6LU7 | Eight approved drugs | 35 molecules | [32] |
| 6W63 | 292 protease inhibitor | 31 FDA-approved anti-HIV drugs, and traditional Chinese medicines | [38•] |
| 6LU7 | SuperDRUG2 database | 23 drugs | [41] |
| 6LU7 | FDA Approved and SWEETLEAD database | 60 molecules | [42] |
| 6LU7 | Remdesivir, chloroquine, and lutein | 33 molecules | [43] |
| 6LU7 | Remdesivir, chloroquine, and lutein | 2949 protease inhibitors | [46] |
| 6LU7 | Remdesivir, chloroquine, and lutein | 2949 protease inhibitors | [47] |
| 6LU7 | Remdesivir, chloroquine, and lutein | 2949 protease inhibitors | [48] |
Table 2 (continued)

| PDB ID | Drug space                                                                 | Drugs                                                                 | References |
|--------|----------------------------------------------------------------------------|----------------------------------------------------------------------|------------|
| 6Y2F   | FDA approved antivirals and our in-house database of natural and drug-like compounds of synthetic origin | Remdesivir, saquinavir, darunavir                                      | [48]       |
| 6LU7   | FDA approved in ZINC database and Specs database                           | Cobicistat, ipromide, cangrelor, fortovase                          | [49]       |
| 6Y84   | FDA approved antiviral compounds, and active phytochemicals               | Nelfinavir                                                            | [49, 50]   |
| 6Y2F   | FDA approved                                                               | Tetracycline, dihydroergotamine, ergotamine, dutasteride, nelfinavir, paliperidone | [49–51]    |
| 6LU7   | 8000 known drugs                                                          | NAD, NAD-like derivatives                                            | [52]       |
| 6LU7   | Ritonavir, lopinavir, remdesivir, oseltamivir, ribavirin, chloroquine, mycophenolic acid, pemirolast, hydroxychloroquine, isoniazid, eriodictyol | Eriodictyol                                                          | [53]       |
| 6Y2F   | 13 approved antimalarial drugs                                             | Halofantrine, mefloquine                                            | [53, 54]   |
| 5R7Y, 5R7Z, 5R80, 5R81, 5R82 | FDA-approved antiviral drugs                                               | Lopinavir, ritonavir, tipranavir, raltegravir | [55]       |
| 6Y2E   | 61 clinically used antivirals                                              | Lopinavir, asunaprevir, indinavir, ritonavir, paritaprevir           | [56]       |
| 6LU7   | Azithromycin, chloroquine, hydroxychloroquine                             | Azithromycin                                                         | [57]       |
| 6LU7   | 88 conventional drugs                                                     | Bedaquiline, glibenclamide, miconazole                              | [58]       |
| 6Y2E   | DrugBank database                                                         | DB02388, cobicistat                                                  | [59]       |
| 6LU7   | α ketoamide group and pyridone ring based drugs                           | Telaprevir, temsirolimus, pimecrolimus, aminoglutethimide, apixaban, buspirone, lenalidomide, pomalidomide | [60]       |
| 6W63   | Amodiaquine, 20-fluoro-20-deoxycytidine, ribavirin                        | Amodiaquine, ribavirin                                               | [61]       |
| 6LU7   | 3981 approved drugs                                                       | Bedaquiline, plecanaril, adefovir dipivoxil, stavudine               | [58]       |
| 6LU7   | Pyrazoline derivatives                                                    | Pyrazoline                                                           | [63]       |
| 6LU7   | Noscapine                                                                | Noscapine                                                            | [64]       |
| 6Y2F, 6W63 | FDA-approved antiviral from Selleckchem Inc. and DrugBank database         | Mitoxantrone, leucovorin, birinapant, dynasore                       | [65]       |
| 6LU7   | CHEMBL database, ZINC database, FDA-approved drugs and molecules under clinical trials | Cobicistat, ritonavir, lopinavir, darunavir                          | [66]       |
| 6LU7   | Asinex Focused Covalent (AFCL) library                                    | Paritaprevir, simeprevir                                            | [66, 67]   |
| 6LU7   | TMB607 and TMC310911                                                      | TMB607, TMC310911                                                    | [66, 67, 68•] |
| 6LU7   | Chloroquine, hydroxychloroquine, remdesivir, ritonavir, beclabuvir, indinavir, favipiravir, α-ketoamide inhibitor (13b) | Chloroquine, hydroxychloroquine, remdesivir, ritonavir, beclabuvir, indinavir, favipiravir | [66, 67, 68•, 69] |
| 6LU7   | eDrug3D and Reaxys-marketed                                               | Carprofen, celecoxib                                                | [70]       |
| 5r82   | selleckchem FDA-approved, ZINC15                                           | Oxycrtyccline, doxorubicin, kanamycin, celpiramide, teniposide, proanthocyanid, salvianolic | [71]       |
| 6LU7   | 51 phytochemicals of J. procera                                          | Rutin                                                                | [72]       |
| 6LU7, 6M03, 6W63 | PubChem database                                                        | Lopinavir, ritonavir, α-ketoamide 13b, ebselel                      | [72, 73]   |
| 6LU7   | Melatonin                                                                | Melatonin                                                            | [74]       |
| 6W63   | Hydroxychloroquine                                                       | Hydroxychloroquine                                                   | [75]       |
| PDB ID | Drug space                                                                 | Drugs                                           | References |
|--------|-----------------------------------------------------------------------------|-------------------------------------------------|------------|
| 6M03   | (Natural products, coronaviruses main protease inhibitors, and FDA-approved drugs) | Rutin, acarbose, saquinavir, octreotide, colistin | [76]       |
| 6LU7   | Dexamethasone/umifenovir                                                   | Dexamethasone/umifenovir                         | [77]       |
| 6Y2G   | US-FDA approved drug from DrugBank                                          | arbutin, terbutaline, barnidipine, tipiracil, aprepitant | [78]       |
| 6LU7   | ~33,000 conformers library                                                  | Pentagastrin, isavuconazonium                    | [79]       |
| 6LU7   | FDA-approved drugs                                                          | saquinavir, ritonavir, remdesivir                | [80]       |
| 6LU7   | SARS-CoV-2-target, with 1017 compounds and SARS-CoV-2-ML, with 1577 both from OTAVA | Apixaban                                        | [81]       |
| 6W63   | 1615 FDA-approved drug                                                      | Simeprevir, ergotamine, bromocriptine, tadafalaf | [82•]      |
| 6LU7   | Drug Bank database                                                         | Ritonavir, nelfinavir, leuprolide, valrubicin, teniposide | [82•, 83] |
| 6LU7   | ZINC database                                                              | Nelfinavir, tipreanavir                          | [82•, 83, 84] |
| 6M03, 6LU7 | ZINC database                                                      | Nelfinavir, baloxavir marboxil, oseltamivir, lopinavir, ritonavir, Indinavir | [14]       |
| 6LU7   | Anti-protease molecules                                                     | Leupeptin, hemisulphate, pepstatin A, nelfinavir, birinapant, lypression, octreotide | [85]       |
| 6LU7   | 10,755 compounds                                                           | Walrycin B, hydroxocobalamin, Z-DEVD-FMK, suramin sodium, LLL-12, Z-FA-FMK | [86]       |
| 6LU7   | Drug Bank database                                                         | Nafarelin, icatibant                             | [87]       |
| 6LU7   | 3000 drug                                                                  | Caspofungin, lopinavir, atazanavir, GHRP-2, indinavir, angiotensin II, dehydroandrographolide succinate | [88]       |
Analyzing the table, it seems that tetracycline and N3 are the most similar pair of hypotheses, but that is not enough. Pharmacophores have to agree on the location of the features concerning each other, so how do these hypotheses align to each other? They align with at least 3 matches, except N3 inhibitor and tetracycline aligned with 4 matched features. Considering this, we concluded our search for pharmacophores with four hypotheses, and we emphasized the overlapping features of N3 and tetracycline; 2 hydrogen bond donors, 1 hydrogen bond acceptor, and 1 aromatic ring (Fig. 3a).

**RNA-Dependent RNA Polymerase**

RNA-dependent RNA polymerase (RdRp) is a replicase that operates the synthesis of a complementary RNA strand using RNA [18••, 90]. SARS-CoV-2 RdRp is composed of 932 amino acids forming a framework of SARS-CoV RdRp linked to the Nsp7 and Nsp8 cofactors. Structurally, the RdRp protein is divided into the N-terminal and polymerase domains, which extend from amino acid residues 1 to 397. The polymerase domain is subdivided into three structurally different subunits: the finger, palm, and thumb [18••, 90].

The active site of Nsp12 is situated in the middle of the substrate domain, where the synthesis of RNA takes place when an RNA template is accessed from the template input channel and nucleoside triphosphate (NTP) from NTP input channel [91••]. RdRp has been proposed to be an important target for developing drugs against coronavirus as detailed in Table 4.

**Drug Affecting RNA-Dependent RNA Polymerase**

In accordance with the inclusion criteria of literature, results showed a handful papers concerning Nsp12. Data reported five antiviral agents targeting the polymerase (remdesivir, tipranavir, tegobuvir, simeprevir, and filibuvir). The second common drugs were binimetinib, palbociclib, lonaferribin, and pegamotecan, which are antineoplastic agents. Other drugs seemed to have miscellaneous pharmacological classes.

Antiviral agents have diverse mechanisms of action and viral targets. Despite this fact, our analysis suggested that antiviral drugs can inhibit the catalytic activity of the Nsp12. Notably, remdesivir is a known nucleoside analog that has been globally well-studied, both in silico and in vitro. Mechanistically, remdesivir is incorporated into the growing viral RNA leading to the termination of the RNA replication. The high affinity of the compound for the active site of RdRp indicates that remdesivir would compete with the natural substrates ribonucleotides and get incorporated into the growing RNA chain. It has been investigated in multiple COVID-19 clinical trials (available at [https://clinicaltrials.gov](https://clinicaltrials.gov)), and granted the FDA Emergency Use Authorization in COVID-19 treatment. While other reported drugs share no similarity in their original clinical use, in silico docking data revealed that definitive interaction with Nsp12 active site is therefore predicted to be a promising inhibitors. Despite the low available data, we performed a pharmacophore analysis based on drugs and the common binding site.

**Pharmacophore Analysis of the RNA-Dependent RNA Polymerase**

Drug-based analysis was performed on eight FDA-approved drugs of miscellaneous pharmacological classes. The same settings of the main protease pharmacophore were followed, and six-feature pharmacophore was obtained. Among those features, the hydrogen-bond donor was observed only once, while the hydrogen-bond acceptor appeared three times. The remaining two features are reported under the name of the aromatic ring as per Maestro Phase software (Table 3).

The PDB ID 6M71 was the most frequent target observed. The results revealed seven features with a unique feature of negative ionic that was not observed under drug-based hypothesis analysis. Those seven features have 3 hydrogen-bond donors, 1 hydrogen-bond acceptor, and 2 aromatic rings. Comparing the two analyses, they disagree on the
hydrogen bond donor and hydrogen bond accepter, but they agree on the aromatic ring, with the unique negative ionic feature reported only for the binding-site based hypothesis study (Table 3, Fig. 3b).

**Fig. 3** The pharmacophore analysis for targeting SARS-CoV-2 enzymes. 

**a** Main protease. 

**b** RNA-dependent RNA polymerase

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**Spike Protein**

Spike proteins are a class fusion glycoprotein localized in the surface of SARS-CoV-2. It has a crucial role in viral
infection by recognizing the host angiotensin-converting enzyme-2 receptor (ACE2) [98]. It contains two subunits, S1 and S2. The S1 subunit contains a receptor-binding domain (RBD) with a size of 180–200 KD that binds and recognizes the ACE2 receptor, while the S2 subunit mediates viral cell membrane fusion [99••]. The S protein uses the ACE-2 receptor for entry to the host cell. The spike protein is coated with polysaccharide molecules to evade the surveillance of the host immune system during entry; targeting this molecule can potentially decrease the chance of infection owing to the prevention of the viral invasion to the host cells [100]. Much research was conducted computationally to identify the role of repurposed drugs on spike proteins and ACE2 (Table 5).

First study that investigate drugs that bind spike protein showed that these drugs such as troxerutin could not be able to recognize ACE2, example of such drug is troxerutin [102••]; second study that investigate drugs that bind ACE2 thus compete with spike protein on ACE2 binding site, example of such a drug is lopinavir [106]; third study that investigate drug binding to the complex of spike and ACE2 (6M0J) and prevent the transition to active state, example of such a drug is polymyxin B [88]. According to the ATC classification system, most of the drugs affecting the spike protein, ACE2, and the complex fall in the anti-infective category (Table 5).

### Drug Affecting Spike Protein

As demonstrated in Table 5, thirty-four drugs have been reported to target the spike protein, 6 of them are antivirals (lamivudine, nelfinavir, Dolutegravir, vidarabine, Remdesivir, Daclatasvir), and 3 of them (lamivudine, vidarabine, remdesivir) are nucleoside analogs that originally target the DNA synthesis in viruses with the same exact mechanism of action, and therefore a similar binding mode.

Ivermectin is reported 2 times in the spike docking analysis and is investigated in clinical trials, but its frequency of appearance here does not indicate a potential for being a lead compound, because some in silico trials targeted the ivermectin from the beginning and not as the end result of an exhaustive virtual screening [16].

### Drug Affecting the ACE2/Spike Complex

A number of studies investigate the binding of drugs to the ACE2/spike complex after the binding of spike to ACE2 has already been achieved; they seek a drug that can disrupt the interaction of ACE2 with RBD after the binding; 8 drugs were reported targeting ACE2/spike complex, and these drugs are (naltrexone, ivermectin, lopinavir, chloroquine, polymyxin B, colistin, daptomycin, oritavancin). Excluding naltrexone and chloroquine, a common trend in these drugs is that they have a molecular weight above 500 and most of them are above 1000. We run a pharmacophore analysis of

### Table 4 Drugs that target RNA-dependent RNA polymerase

| PDB ID | Drug space | Drugs                                      | References    |
|--------|------------|--------------------------------------------|---------------|
| 6M71   | DrugBank database | Bedoradrine, and Palbociclib               | [92]          |
| 6M71   | Miscellaneous compound from literature | Chlorhexidine and Remidivir             | [93]          |
| 6NUR   | ZINC database | Etilmbronpop, Tipranavir, Ergotamine and Convaptan | [51]          |
| 6M71   | NA         | Montelukast                                | [94]          |
| 7W84   | ZINC database | Lonafarnib, Tegobuvir, Simeprevir and Flibuvir | [95]          |
| 6M71   | FDA database | Nacartocin, Cisatracurium and Pegamotecan  | [96]          |
| 6M71   | FDA database | Nebivolol                                  | [97]          |
| 7BV2   | FDA database | Pitavastatin, Ridogrel and Rosoxacin       | [91••]        |

### Table 5 Drugs that target the spike protein

| PDB ID | Drug space | Drugs                                      | References    |
|--------|------------|--------------------------------------------|---------------|
| 6M17   | FDA Database | Ivermectin                                | [16]          |
| 6LVG   | FDA Database | Hydroxychloroquine, chloroquine            | [101]         |
| 6VV1   | FDA Database | Troxerutin                                 | [102••]       |
| 6VSB   | FDA Database | Dolutegravir                               | [102••, 103]  |
| 6M17   | FDA Database | Cangrelor                                  | [102••, 103, 104••] |
| 6M17   | FDA Database | Kanamycin                                  | [104••]       |
| 6VSB   | FDA Database | Nelfinavir                                 | [104••, 105]  |
| 2AJF   | FDA Database | Lopinavir                                  | [106]         |
| 6LVG   | FDA Database | Hydroxychloroquine                         | [101]         |
| 6VSB   | FDA Database | Daclatasvir                                | [42, 102••]   |
| 6M0J   | FDA Database | Polymyxin B                                | [88]          |
| 6M17   | FDA Database | Pralatrexate                               | [107]         |
| 6VXX   | FDA Database | Imipenem                                   | [107, 108••]  |
| 6VSB   | FDA Database | Streptomycin                               | [53]          |
these drugs and it had failed due to their complexities and variability.

Two studies targeting the ACE2 receptor only have been investigated. They seek a compound that can prevent the recognition of the spike to ACE2 [101, 103]. Herein, 10 drugs were reported (lividomycin, burixafor, quisinostat, fluoprofylline, pemetrexed, spirofylline, edotecarin, dinoprofylline, hydroxychloroquine, chloroquine). Obviously, a drug targeting ACE2 would not be much useful, but those studies were originally part of a bigger investigation and concluded that these compounds bind well to many targets, one of which is ACE2 [103].

Pharmacophore Analysis of the Spike Protein

During pharmacophore analysis, we did not find any consistency in the use of a common PDB structure from the paper that studied the spike protein like what we achieved in the main protease. However, we proceeded with choosing only one PDB (the one with the highest resolution) for binding site pharmacophore with the argument that they all have the similar sequence and thus a similar PDB structure. In the end, the pharmacophore analysis failed due to the diversity of the drugs.

Conclusion

Herein, we reviewed the current research concerning drug repurposing using molecular docking and other in silico drug discovery approaches in the battle against COVID-19. Antiviral drugs were the most studied drugs. The main protease represented a potential target looking at its central role in viral replication and huge availability per our standards. Moreover, studies indicated that the best results of pharmacophore investigation were obtained with tetrazycines and antivirals, which were originally protease inhibitors. We recommend using the models in further research, including virtual screening, which could help the overall efforts in finding effective therapeutic agents against COVID-19.

Author Contribution All authors listed have significantly contributed to the development and the writing of this article.

Declarations

Conflict of Interest The authors declare no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

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