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Review article

Computational drug discovery and repurposing for the treatment of COVID-19: A systematic review

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Keywords: Drug discovery, Drug repurposing, Computational methods, SARS-CoV-2, COVID-2019

Abstract

Background: Since the beginning of the novel coronavirus (SARS-CoV-2) disease outbreak, there has been an increasing interest in finding a potential therapeutic agent for the disease. Considering the matter of time, the computational methods of drug repurposing offer the best chance of selecting one drug from a list of approved drugs for the life-threatening condition of COVID-19. The present systematic review aims to provide an overview of studies that have used computational methods for drug repurposing in COVID-19.

Methods: We undertook a systematic search in five databases and included original articles in English that applied computational methods for drug repurposing in COVID-19.

Results: Twenty-one original articles utilizing computational drug methods for COVID-19 drug repurposing were included in the systematic review. Regarding the quality of eligible studies, high-quality items including the use of two or more approved drug databases, analysis of molecular dynamic simulation, multi-target assessment, the use of crystal structure for the generation of the target sequence, and the use of AutoDock Vina combined with other docking tools occurred in about 52%, 38%, 24%, 48%, and 19% of included studies. Studies included repurposed drugs mainly against non-structural proteins of SARS-CoV2: the main 3C-like protease (Lopinavir, Ritonavir, Indinavir, Atazanavir, Nelfinavir, and Clocortolone), RNA-dependent RNA polymerase (Remdesivir and Ribavirin), and the papain-like protease (Mycophenolic acid, Telaprevir, Boceprevir, Grazoprevir, Darunavir, Chloroquine, and Formoterol). The review revealed the best-documented multi-target drugs repurposed by computational methods for COVID-19 therapy as follows: antiviral drugs commonly used to treat AIDS/HIV (Atazanavir, Efavirenz, and Dolutegravir Ritonavir, Raltegravir, and Darunavir, Lopinavir, Saquinavir, Nelfinavir, and Indinavir), HCV (Grazoprevir, Lomitaprevir, Asunaprevir, Ribavirin, and Simeprevir), HBV (Entecavir), HSV (Penciclovir), HSV (Penciclovir), CMV (Ganciclovir), and Ebola (Remdesivir), anticoagulant drug (Dabigatran), and an anti-fungal drug (Itraconazole).

Conclusions: The present systematic review provides a list of existing drugs that have the potential to influence SARS-CoV2 through different mechanisms of action. For the majority of these drugs, direct clinical evidence on their efficacy for the treatment of COVID-19 is lacking. Future clinical studies examining these drugs might come to conclude, which can be more useful to inhibit COVID-19 progression.

1. Introduction

The 21st century has allowed for coronaviruses to become well perfected and higher pathogenic to humans. In 2003 the world experienced severe acute respiratory syndrome of coronavirus (SARS-CoV) outbreak. It started from China and spread to five continents, with the calculated fatality rate of 9.6% during the outbreak period [1]. In 2012, the second outbreak of the Middle East respiratory syndrome-related coronavirus (MERS-CoV) occurred in the Arabian Peninsula, with the fatality rate of about 34.4% [2]. An outbreak of the novel coronavirus disease (COVID-19) has emerged in Wuhan, Hubei Province, China, in December 2019. It is expanding at a remarkable pace so that on March 11th, 2020, the World Health Organization (WHO) declared COVID-19 as a pandemic [3]. As of writing this, there are more than one million
people infected with, and more than 80,000 people died from COVID-19.

Having multiple routes of transmission and lack of full adherence to social distancing guidelines are important barriers making its prevention difficult [4–7]. Also, despite widespread efforts, finding the origin, diagnosis, treatment, and management of COVID-19 has been a challenge for the healthcare system [8–11]. Such efforts have so far occurred separately in different biomedical disciplines, particularly immunology, genetics, medical biotechnology, molecular engineering, nutrition, picotechnology, and regenerative medicine [12–32], highlighting the need for an integrated view of COVID-19 [33–35] aimed at doing science of high-quality [36]. With respect to the absence of specific treatment for COVID-19, we can provide only the combination of symptomatic treatment and supportive measures [37,38], that for a significant proportion of cases, will not suffice. The fact is given as the disease can cause hyper inflammation affecting multiple systems and organs making it difficult to treat [26,39–45].

The process of de novo drug design is hugely time-consuming. Drug repurposing, also known as drug repositioning or drug re-profiling, works as an alternate, systematic method in drug discovery that can aid in determining the new indications for the existing drugs. It is of high importance that this method repurposes drugs which their safety and pharmacokinetics have been recognized so far. Hence, it would confidently reduce the risk of adverse side effects, drug interactions, and drug development time and expenditure. The fastness of the computational or in silico techniques has made them an exciting approach to the drug repurposing world [46]. There are two main approaches to the computational drug repurposing process: target-based and disease-based [47]. The former allows the drug and the target to interact with each other leading to the establishment of drug-target interactions. The latter utilizes datasets to determine new indications for already approved drugs from comparisons of characteristics of diseases. Computational drug repurposing approaches differ from each other in some points, such as target modeling, algorithms, and the drug bank or data sets [48].

Since the beginning of the COVID-19 outbreak, there has been an increasing interest in finding a potential therapeutic agent for COVID-19. Considering the matter of time that this pandemic is not the time of trial and error [49] and also the possibility of re-infection [50], the computational methods of drug repurposing offer the best chance of selecting one drug from a list of approved drugs for the life-threatening condition of COVID-19. The present systematic review aims to provide an overview of studies that have used computational methods for COVID-19 drug repurposing.

2. Methods

We prepared this review according to the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) statement [51]. Before beginning the database search, the protocol of the present systematic review was developed and submitted to PROSPERO.

2.1. Search strategy

We undertook a systematic search in five databases, including PubMed, Scopus, Google Scholar, Cochrane, and the WHO global health library. The search terms and keywords included but not limited to the following terms for the disease: “Novel coronavirus”, “2019 nCoV”, “COVID-19”, “Wuhan coronavirus”, “Wuhan pneumonia”, “SARS-CoV-2”, and for the drug repurposing: “Antiviral Agents”, “Drug Therapy”, “therapeutic use”, “therapeutic agents”, “Drug Repositioning”, “virtual screening”, “docking”, and “computational”. We imported search results into EndNote Version X9, Clarivate Analytics, USA.

2.2. Study selection

The present systematic review included original articles in English that applied computational methods for COVID-19 drug repurposing. Eligible studies should repurpose drugs that are already approved by at least one of the following authorities: the European Medicines Agency (EMA), the Japan Pharmaceuticals and Medical Devices Agency (PMDA), or the U.S. Food and Drug Administration (FDA). Studies that either investigated biologic agents (such as interleukins, vaccines, and miRNA), nutritional supplements, and traditional medicines or focused on protein structure prediction or determination rather than having a drug discovery project were not eligible to be included in this review. Also, studies examining a wet lab approach were excluded.

By considering the above criteria, two authors (K.M. and N.Y.) independently performed title/abstract screening and detailed review. In the case of disagreement, the two authors discussed the reasons to reach a consensus. When they were unable to reach a consensus, the third author (A.S.) was consulted.

2.3. Data extraction

The first two reviewers (K.M. and N.Y.) extracted the following data from each included publication: the first author, year of publication, country of origin, drug repurposing method, sequence alignment, target preparation, the resource for approved drugs, the visualization tool, molecular docking tool, coronavirus strain, target structures, candidate therapeutic agents, and the authors’ conclusions. A consensus discussion between the two authors was made on items of discrepancies. The third author (A.S.) was involved in the points on which consensus did not happen.

2.4. Quality assessment

The idea of bias in computational drug research studies is not well established. However, few statements can aid in assessing bias systematically. Cleves et al. [4] argue about a bias that is produced by two dimensional (2D) descriptors in compound screening. The use of the method would reduce the probability of finding novel compounds. Also, Hert et al. [5] have introduced a bias that occurs when screening drug libraries, and therefore the result of screening would be restricted to the compounds with known biological effects. It is a threat to novelty, and a possible solution to this bias is the development of useful decoys (DUD), which use a standard set of ligands to make comparisons of different docking methods simultaneously [6]. Recently, Scannell et al. [7] have presented a bias that occurs when targeting a single molecule with a single compound and can be avoided with a multi-target approach. Eventually, it is crucial to point out the molecular flexibility of the targets. This point is usually missed out when one docking method is applied. The best way of putting this bias into account is to use the molecular dynamics simulations, a robust method with many functions that can predict the drug-target interaction in a better way. The most crucial function of molecular dynamics simulations is to provide multiple receptor conformations, in addition to many other sophisticated analyses that can accurately differentiate between a proper docking and an inadequate docking [52].

According to the potential issues of bias, a tool was designed for the assessment of five main aspects of quality of studies included in the present systematic review: design (mono-target vs. multi-target), target template modeling (crystal structure, homology modeling, and co-crystal ligand), docking tools, molecular dynamics simulation (yes vs. no), and the resource for approved drugs. The quality of each eligible article was independently appraised by two authors (K.M. and N.Y.) and then was double-checked by the third author (A.S.).
3. Results

3.1. Study selection

There were 3256 studies retrieved from the database search, of which 2171 papers remained after the removal of duplicates (Fig. 1). We conducted title and abstract screening on these 2171 studies and nominated 93 of them for detailed review. Considering the inclusion and exclusion criteria, we excluded 72 studies for different reasons as follows. There were studies not regarded as original research \((n=18)\) \([53–70]\), studies proposed a novel drug, an unapproved drug, or no drug at all \((n=9)\) \([71–79]\), studies reporting drugs against targets other than the novel coronavirus (also known as 2019-nCoV or SARS-CoV2) \((n=10)\) \([80–89]\), studies applying any methods other than computational methods for drug repurposing \((n=33)\) \([90–122]\), studies not published in full-text articles \((n=1)\) \([123]\), and one study using network-based approach \([124]\). Finally, we included 21 original articles utilizing computational drug methods for COVID-19 drug repurposing \([125–145]\).

3.2. Study characteristics

As summarized in Table 1, there were variations across studies in methods/techniques, software, targets, and modeling. AutoDock Vina \((45.45\%)\), the SWISS Model Web Server \((41.9\%)\), and PyMOL software \((36.36\%)\) were the most commonly used tools for docking, homology modeling, and visualization, respectively. Various targets were utilized in the computational drug repurposing approaches. Most of them were obtained from the RCSB Protein Bank Database and NCBI GenBank. Studies used the following components of the novel coronavirus as targets: main protease \([146]\), endopeptidase, 3C-like protease \((3CLP)\) \([125,127–130,133–139,141–145]\), RNA dependent RNA polymerase \((RdRp)\) \([127,128,131,144]\), papain-like protease \((PLP)\) \([126,132,137,144]\), helicase \([127,144]\), 3′-to-5′ exonuclease \([127]\), 2′-O-ribose methyltransferase \([127,135]\), endorNAse \([127]\), and spike \((S)\) protein \([140,144]\). There was only one study combined with in vitro experiments \([134]\).

3.3. Study quality

Table 2 represents the details of the appraisal of study quality. Regarding the number of approved drug databases, more than 50% of studies used two or more databases. About 38% of the studies analyzed the molecular dynamics simulations. For the item target, more than 70% of studies investigated only one viral structure as the target. Also, more than 50% of the studies used homology modeling for the generation of the target sequence. AutoDock Vina was the only docking tool in more than 80% of studies. Fig. 2 displays the percentages of studies reporting high-quality items.
| Table 1 | Characteristics of studies included in the systematic review [158-161]. |
|-----------------------------------------------|---------------------------------------------------------------|
| **The first author, year, country** | **Method, protocol** | **Software** | **Target** | **Candidate drugs** |
| Sekhar 2020, India | Ligand-based virtual screening and molecular docking | Avogadro, PyMOL, and Rasmol, AutoDock Vina, SMINA, and customized Python and shell scripts | Residues 41 and 145 (main protease) | Becaplermin, Saquinavir, Ledipasvir, Libavir, Raltegravir, Indinavir, Nefaviramid, Amprenavir, Darunavir, Ritonavir, Lopinavir, Fusamprenavir, Atazanavir, Nelfinavir, Tadalafil, Lifitegrast, Diflucan, Dovigrin, and Tinilazid. |
| Lifiky 2020, Egypt | Sequence alignment and modeling and molecular docking | Swiss Model web server, PROCHECK, AutoDock tools | COVID-19 and SARS (PDB ID: 6NUR, chain A) RdRps | GTP and UTP and the four drugs: IDA 184, Sofosbuvir, Ribavirin, and Remdesivir. |
| Alamri 2020, Saudi Arabia | Sequence and structural alignment analysis, structure-based virtual screening, molecular docking, and molecular dynamic simulation | PyMOL tool and Discovery studio Visualizer, AutoDock vina, and PyRx | SARS-CoV-2 3CL protease (PDB ID: 6LU7) | 621, Pantaprazole and Simpeprevir |
| Chung 2020, Taiwan | Ligand-based virtual screening, molecular docking, and molecular dynamic simulation | Swiss-model, CASTp tool, AutoDock Vina and RosettaCommons | SARS-CoV 3CL pro | Indinavir, Lopinavir, Atazanavir, Saquinavir, Ritonavir, Nefaviramid, Darunavir, Tipranavir, Amprenavir, Fusamprenavir |
| Arya 2020, India | Homology modeling, virtual screening, and molecular docking | SWISS-MODEL workspace, SEESAR suite of programs from BioSolveIT | PIpro | 621, Pantaprazole and Simpeprevir |
| Beck 2020, Korea | Molecule Transformer Drug Target Interaction (MT-TDI) | Molecular transformer drug target interaction (MT-TDI), ISET framework, SMILES | 3CL pro | Atazanavir, Efavirenz, Ritonavir, Dolutegravir, Asunpravir, Simpepreviral |
| 621, Pantaprazole and Simpepreviral | Raltegravir, Lamivudine | Helicase | Simeprevir, Atazanavir, Grazoprevir, Asunpravir, Telaprevir, Ritonavir, Lopinavir, Penciclovir, Efavirenz, Raltegravir, Dolutegravir, Fendiclovir, Indinavir, Efavirenz, Entecavir, Boceprevir, Lomivir, Aconavir |
| 3′-5′ exonuclease | 621, Pantaprazole and Simpepreviral | Efavirenz, Atazanavir, Ritonavir, Dolutegravir, Grazoprevir, Asunpravir, Telaprevir, Lomivir, Penciclovir, Ritonavir, Raltegravir, Dolutegravir, Lopinavir |
| 621, Pantaprazole and Simpepreviral | 621, Pantaprazole and Simpepreviral | Efavirenz, Atazanavir, Ritonavir, Dolutegravir, Grazoprevir, Dolutegravir, Lomivir, Penciclovir, Ritonavir, Raltegravir, Dolutegravir |
| 2′-O-methyltransferase | 621, Pantaprazole and Simpepreviral | Atazanavir, Efavirenz, Bocepreviral |
| Chen 2020, Hong Kong | Preparation of structural model: Virtual screening and molecular docking | BLASTp, PyMOL (version 1.7.4), AutoDock Vina, MT/OpenScreen | 3CL pro | Dostinum, Hesperidin, MK-3307, Venetocox, Dihydroergocistamine, Bolocine, M2B2, Ditracareum, Topiside, Tensiposite, UK-435097, nitrican, Lumacaftor, Velbafusin, Eluxadoline, Ledipasvir |
| Contini 2020, Italy | Homology modeling, virtual screening, molecular docking, molecular dynamic simulation | MOL2/2019 software, PLANETS | Mpro | Angiotensin II human peptide, GHRP-2, Indinavir, Cobocstat(GS-9350), Montelukast, Cetuximide dihydrochondrine, Tylopal, Salvanolonic acid B, Trasprovid, Monomethyl auristatin E (MMAE), Nafarelin acetae, Leuprolin acetate, Somatostatin acetate, icatibant acetate, Nystatin, Goserelin acetate, Arelin acetate, Gonadorelin acetate, Ampotericin B, Carfilzomib, Thymopentin, Lentim, Ritonavir, NAD+, Octreotide acetate, Colistin sulfate, Cangreol tetrasodium, Oxycrin, Flunoxysine, Etinicoside |
| 3CL pro | Caspofungin acetate, Lopinavir(AST-378), Atazanavir, GHRP-2, Indinavir, Angiotensin II human peptide, Ritonavir, Salvanolonic acid B, Ebasir, Montelukast sodium, Cobocstat(GS-9350), Tylopal, Salmetorol erinafoste, Peunfluclid, Gonadorelin acetate, Leuprolin acetate, Nafarelin acetate, Goserelin acetate, Betamethasone |
| Reference | Technique | Tools/Software | Notes/Comments |
|-----------|-----------|----------------|---------------|
| Lin 2020, China | Homology modeling, molecular docking, molecular simulating | SWISS-MODEL, SAVES, Discovery Studio software (version 2.5, Accelrys Software Inc.) | 3C1 protease | Pitolisatin, Lopinavir (continued on next page) |
| Nguyen 2020, USA | Structural-based drug repositioning (SDoR), Sequence identity analysis, homology modeling, Structure similarity analysis, homology modeling | SMILES string, MathPose model, MathDL, ZDFP-DNN | The 2019-nCoV protease (PDB ID 6U7I) and SARS-CoV-3C1 protease (PDB ID 2gq4) | Lopinavir, Ritonavir, Kaletra (or Alavita), and Norvir |
| Smith 2020, USA | Structural modeling, molecular simulations, structural clustering (ensemble building), and small-molecule docking (in silico ligand screening) | SWISS-MODEL, MOE2016, a special POWER2 build of Autodock Vina4 for SLIMMT | S-protein-ACE2 interface | Pemrolast, Isoniazid pyruvate, Nitrofurantoin, Eridoidycol |
| Ton 2020, Canada | Virtual deep learning platform – DD | Omega pose routine, Glide SP module | Pyro | CMK, ACG0888 (Ruxonivir), Lopinavir, Remdesivir |
| Wang 2020, USA | Virtual docking screening, molecular dynamics simulations, NVE | Schrodinger software, Fronals3D web server, Glide flexible docking program | COVID-19 main protease | Carfizomib, Ibravacycline, Valubicin, Lopinavir, and Elbasivir |
| Wu 2020, China | Sequence alignment and analysis, homology modeling, target-based virtual | BLASTn, pymol structure alignment tool, ICM 3.7.3 software | Pyro | Ribavirin, Valganciclovir, Iba-Thymine, Asparagine, Oxyrenolol, Doxycycline, Acetophenazine, Ibropride, |
3.4. Data synthesis

Conserved structures in the viral genome represent a high potential to be target candidates. While the phylogenetic tree inevitably undergoes evolutionary changes, a highly conserved structure can maintain its sequence among strains. Targeting such a highly conserved site will provide cross-reactive protection in different strains. Highly conserved elements of the 2019-nCoV (SARS-CoV2) include non-structural proteins such as 3CLP, RdRp, and PLP, and structural proteins, such as the S protein [78,124]. Below is a target-based synthesis of data for COVID-19 drug repurposing as summarized in Table 4.

3.5. 3CLP

The main protease of the 2019-nCoV, also known as 3CLP or the C30 endopeptidase, is a highly conserved element that shares 96.1% similarity with the main protease of SARS-CoV. This protease is a member of the coronavirus polyproteins. When translation takes place, it is the first one that is auto-cleaved from the polyprotein. Then, it, in turn, would mediate the cleavage of the other 11 non-structural proteins that are vital for viral replication and transcription. Thus, 3CLP might serve as a marvelous target for COVID-19 therapy [78].

Lopinavir and Ritonavir are the most documented candidate drugs that target 3CLP (Table 3). However, Wu et al. claimed that Lopinavir and Ritonavir have not an excellent binding score in docking compared to other drugs. Therefore, it is crucial to find other drugs that can be effective against 3CLP.
to other drugs [144]. Moreover, Contini et al. developed molecular dynamics simulations, which are known to be more potent than docking in the prediction of the drug-target binding [147]. The authors showed that Ritonavir failed to form the interaction with the 3CLP [130]. The good binding energy and docking score for each one of Elbasvir, Simeprevir, Indinavir, and Atazanavir might nominate these drugs as candidates for the inhibition of 3CLP of SARS-CoV2. Interestingly, both Indinavir and Remdesivir might be effective against SARS-CoV2 infection due to their excellent docking scores and limited toxicity, as confirmed by Chang et al. [128]. Nelfinavir was also mentioned as one of the best drugs binding to the 3CLP. However, it appeared less efficient than Tegobuvir and Bictegravir when the affinity and the physical-chemical analysis parameters were calculated using SeeSAR [136,145]. Nguyen et al. suggested an unusual inhibitor of 3CLP, Clorcortolone, a medium-strength steroid that is used for dermatitis and has good binding scores making it a promising cleanser against SARS-CoV2 contaminated surfaces [139].

3.6. RdRp

Viral RdRp is an enzyme that accelerates the replication of RNA from a template RNA and shares around 97.08% of its sequence with SARS-CoV [131]. Among the drugs that target this protein, Remdesivir is a bold one which, by a triphosphate nucleotide, would act as an ATP-competitive inhibitor of RdRp and intervene with the viral RNA synthesis. Also, Remdesivir can bind to the human TMPRSS2, a protein that mediates the cleavage of the viral S protein and promotes the entry of SARS-CoV into the host cells [144]. Ribavirin is another drug reported in two studies to interact with RdRp. It appeared not to be a very effective drug compared to other drugs [128,131].

3.7. PLPa

PLP plays a crucial part in the initiation of infection through its ability to antagonize interferon (IFN) activity and deubiquitinate viral and cellular proteins [148].

Eight different structures attached to SARS-CoV PLP comprise sequences that are at least 82.17% identical to that of SARS-CoV2 PLP [132]. Two studies mainly focused on PLP drug candidates. Elfiky et al. pointed out drugs against SARS (GRL-0667, GRL-0617, and Mycophenolic acid) and HCV NS3 (Telaprevir, Boceprevir, and Grazoprevir) that have acceptable binding energy for SARS-CoV2 PLP but lack an excellent binding score [132]. Lin et al. demonstrated conformational changes of PLP upon binding to Darunavir and suggested Darunavir as a competitive inhibitor of PLP [137]. Arya et al. also reported two drugs that affect the SARS-CoV2 PLP: Chloroquine, an anti-malarial agent, and Formoterol, a drug that mainly works as a bronchodilator [126].

4. Discussion

Multi-target therapeutic (Table 3) agents are more useful than monotarget drugs (Table 5) in terms of better predictive pharmacokinetics, better patient compliance, and reduced risk of drug interactions [149]. Simultaneously impacting different targets is, in particular, advantageous to approach individuals that express intrinsic or induced variability in drug response due to modifications in key disease-relevant biological pathways and activation of compensatory mechanisms [150,151]. Below is a discussion of drugs repurposed for COVID-19 that target multiple viral elements (see Fig. 3).

This review revealed Atazanavir, Efavirenz, and Dolutegravir as the top-ranked drugs as arranged by the number of drugs. These drugs can similarly hit 3CLP, RdRp, helicase, 3′-to-5′ exonuclease, 2′-O-ribose methyltransferase, and endoRNAse proteins [127,135]. Subsequently, each one of Ritonavir, Raltegravir, Darunavir, and Grazoprevir can target five viral replication proteins. Helicase, 3′-to-5′ exonuclease, and endoRNAse are common between them while Darunavir can exclusively target PLP and 3CLP, Grazoprevir can target PLP and RdRp, and both Ritonavir and Raltegravir are related to RdRp and 3CLP. Lopinavir-Asunaprevir Lomitabuvir and Boceprevir can target four viral replication proteins. Lopinavir and Asunaprevir commonly target 3CLP, helicase, and 3′-to-5′ exonuclease, while they exclusively target endoRNAse and RdRp, respectively. Lomitubuvir and Boceprevir commonly target helicase and endoRNAse, while RdRp and 3′-to-5′ exonuclease are merely targeted by Lomitabuvir and PLP and 2′-O-ribose methyltransferase are only targeted by Boceprevir.

It is worth mentioning that this category contains the highest number of repetitions among the multi-target drugs repurposed for COVID-19 therapy. Initially, each one of Entecavir, Penciclovir, and Ganciclovir similarly hit RdRp, helicase, and 3′-to-5′ exonuclease proteins.
Table 3
Multi-target drugs repurposed for COVID-19.

| Drug         | 3CLP       | PLP  | RdRp  | Helicase | 3’to5’exonuclease | 2’-O-ribose methyltransferase | EndoRNase | Spike | Total |
|--------------|------------|------|-------|----------|-------------------|-------------------------------|------------|-------|-------|
| Ritonavir    | 7 (127, 128, 130, 133, 137, 139, 141) | 1 (127) | 1 (127) | 1 (127) | 1 (127) | 1 (127) | 11       |
| Lopinavir    | 8 (128, 130, 133, 137, 139, 141, 142, 158) | 1 (127) | 1 (127) | 1 (127) | 1 (127) | 1 (127) | 11       |
| Atazanavir   | 4 (127, 128, 130, 141) | 1 (127) | 1 (127) | 1 (127) | 1 (127) | 1 (127) | 9        |
| Darunavir    | 2 (128, 141) | 1 (132) | 1 (127) | 1 (127) | 1 (127) | 1 (127) | 6        |
| Raltegravir  | 2 (135, 141) | 1 (127) | 1 (127) | 1 (127) | 1 (127) | 1 (127) | 6        |
| Dolutegravir | 1 (127) | 1 (127) | 1 (127) | 1 (127) | 1 (135) | 1 (127) | 6        |
| Nelfinavir   | 4 (128, 141, 159, 160) | 1 (127) | 1 (127) | 1 (127) | 1 (127) | 1 (127) | 6        |
| Elvirent     | 1 (127) | 1 (127) | 1 (127) | 1 (127) | 1 (127) | 1 (127) | 6        |
| Simprevir    | 3 (125, 127, 133) | 1 (127) | 1 (127) | 1 (127) | 1 (127) | 1 (127) | 5        |
| Indinavir    | 3 (128, 130, 141) | 1 (127) | 1 (127) | 1 (127) | 1 (127) | 1 (127) | 4        |
| Darunavir    | 1 (127) | 1 (127) | 1 (127) | 1 (127) | 1 (127) | 1 (127) | 5        |
| Asunaprevir  | 1 (127) | 1 (127) | 1 (127) | 1 (127) | 1 (127) | 1 (127) | 4        |
| Saquinavir   | 2 (128, 141) | 1 (127) | 1 (144) | 1 (127) | 1 (127) | 1 (127) | 4        |
| Remdesivir   | 2 (133, 142) | 2 (128, 131) | 1 (127) | 1 (127) | 1 (127) | 1 (127) | 4        |
| Lomitabir    | 1 (127) | 1 (127) | 1 (127) | 1 (127) | 1 (127) | 1 (127) | 4        |
| Enteviravir  | 1 (127) | 1 (127) | 1 (127) | 1 (127) | 1 (127) | 1 (127) | 4        |
| Boceprevir   | 1 (132) | 1 (127) | 1 (127) | 1 (127) | 1 (127) | 1 (127) | 4        |
| Dabigatan    | 1 (144) | 1 (144) | 1 (144) | 1 (144) | 1 (144) | 1 (144) | 3        |
| Ribavirin    | 1 (144) | 2 (128, 131) | 1 (144) | 1 (144) | 1 (144) | 1 (144) | 3        |
| Penciclovir  | 1 (127) | 1 (127) | 1 (127) | 1 (127) | 1 (127) | 1 (127) | 3        |
| Itraconazole | 1 (144) | 1 (144) | 1 (144) | 1 (144) | 1 (144) | 1 (144) | 3        |
| Danoprevir   | 1 (127) | 1 (127) | 1 (127) | 1 (127) | 1 (127) | 1 (127) | 3        |
| Telaprevir   | 1 (132) | 1 (139, 146, 161) | 1 (127) | 1 (127) | 1 (127) | 1 (127) | 3        |
| Ganciclovir  | 1 (6) | 1 (6) | 1 (127) | 1 (127) | 1 (127) | 1 (127) | 3        |
| Chloroquine  | 2 (144, 133) | 1 (126) | 1 (144) | 1 (144) | 1 (144) | 1 (144) | 3        |
| Valganclovir | 1 (144) | 1 (144) | 1 (144) | 1 (144) | 1 (144) | 1 (144) | 2        |
| Daclatasvir  | 1 (127) | 1 (127) | 1 (127) | 1 (127) | 1 (127) | 1 (127) | 2        |
| Aclovir      | 1 (127) | 1 (127) | 1 (127) | 1 (127) | 1 (127) | 1 (127) | 2        |
| Etraflavin   | 1 (127) | 1 (127) | 1 (127) | 1 (127) | 1 (127) | 1 (127) | 2        |
| Abacavir     | 1 (127) | 1 (127) | 1 (127) | 1 (127) | 1 (127) | 1 (127) | 2        |
| Bictegravir  | 1 (136) | 1 (110) | 1 (110) | 1 (110) | 1 (110) | 1 (110) | 2        |
| Hesperidin   | 1 (125) | 1 (125) | 1 (125) | 1 (125) | 1 (125) | 1 (125) | 2        |
| Chlorhexidine| 1 (144) | 1 (144) | 1 (144) | 1 (144) | 1 (144) | 1 (144) | 2        |
| Silybin      | 1 (144) | 1 (144) | 1 (144) | 1 (144) | 1 (144) | 1 (144) | 2        |
| Tigecycline  | 1 (144) | 1 (144) | 1 (144) | 1 (144) | 1 (144) | 1 (144) | 2        |
| Sulfasalazine| 1 (144) | 1 (144) | 1 (144) | 1 (144) | 1 (144) | 1 (144) | 2        |
| Lymecycline  | 1 (144) | 1 (144) | 1 (144) | 1 (144) | 1 (144) | 1 (144) | 2        |
| Cefixolin    | 1 (144) | 1 (144) | 1 (144) | 1 (144) | 1 (144) | 1 (144) | 2        |
| Steviolglycoside (Steviol)
The main findings of studies included in the systematic review.

| The first author, year | Findings |
|------------------------|----------|
| Sekhar 2020            | By performing virtual high throughput screening in the superDRUG2 database, Saquinavir and Beclabuvir turned out to be best probable candidates or the treatment of COVID-19. |
| Elfiky 2020            | IDX-184, Sofosbuvir, and Ribavirin can bind to COVID-19 RdRP with high affinity and change the viral protein function, which leads to its elimination. Among the mentioned drugs, better results were observed about IDX-184 and then about Sofosbuvir in inhibition of novel coronavirus 2019. |
| Almri 2020             | Three top 3Clpro inhibitor candidates in this study were compound 62I, Paritaprevir, and Simeprevir, which are potent inhibitors in low micromolar concentrations. |
| Chang 2020             | Indinavir and Remdesivir were identified as potential therapeutic agents, as they possess docking sites that have a significant overlap with the protein pockets. Due to their limited toxicity, they can be used in COVID-19 treatment. |
| Arya 2020              | Chloroquine was selected as a potential inhibitor of viral PLpro. This drug works against the viral infection in both entry-level and post-entry stages. The latter might be due to the inhibition of the main viral protein. Formoterol, a drug that mainly works as a bronchodilator, and it might be used to improve breathing, plus having an inhibitory effect on the viral PLpro. |
| Beck 2020              | Through the DFT model, the viral protease-targeting drugs were predicted to act better on the viral replication process than viral protease. An antiviral drug, such as guanosine analogs (e.g., acyclovir, ganciclovir, and penciclovir), reverse transcriptase inhibitors, and integrase inhibitors, were more than protease inhibitors in the results. All subunits of the 2019-nCoV replication complex might be inhibited by Atazanavir, due to its predictive potential binding affinity to bind to RNA-dependent RNA polymerase (Kd 21.83 nm), helicase (Kd 25.92 nm), 3′-to-5′ exonuclease (Kd 82.36 μM), 2′-O-ribonucleoside monophosphate (Kd of 390 μM), and endorNAse (Kd 50.32 μM). Ganciclovir was predicted to bind to RNA-dependent RNA polymerase (Kd 11.91 nm), 3′-to-5′ exonuclease (Kd 56.29 nM), and RNA helicase (Kd 108.21 nM). Lopinavir and ritonavir predicted to have a potential affinity to 2019-nCoV helicase and suggested as MERS therapeutics. Darunavir was predicted to have a Ka of 90.38 nM against 2019-nCoV’s helicase. Dual-component HCV drugs, Epclusa (velpatasvir/sofosbuvir), and Harvoni (ledipasvir/sofosbuvir) act on two viral proteases, thus reducing the viral resistance ability. In addition to their easy administration (orally) with minimal side effects. Diosmin and hesperidin, which are flavonoid glycosides from citrus fruits, fit amazingly into the substrate-binding site and block it. However, these chemotherapy drugs have many adverse effects and should be administered intravenously. Venetoclax, which is also a chemotherapy drug, is loaded with side effects, including upper respiratory tract infection. |
| Chung 2020             | The seventh suggested drug is Clocortolone, a topical medium-strength steroid that is used for dermatitis. Hence, Clocortolone can be applied as a cleanser for 2019-nCoV contaminated surfaces or materials. |
| Nguyen 2020            | Three top suggested drugs are: Bortezomib, Fluozepam, and Ponatinib. The seventh suggested drug is Clocortolone, a topical medium-strength steroid that is used for dermatitis. Hence, Clocortolone can be applied as a cleanser for 2019-nCoV contaminated surfaces or materials. Fifteen anti-2019-nCoV molecules were detected in this study, which is observed to have more druggable features than FDA approved HIV inhibitors such as Kaletra (or Aluvia) and Norvir. |
| Smith 2020             | Nitrofurantoïn, Isoniazid pyruvate, Eriodictyol, and Pemirolast are the four top candidates in which the first three were observed to have more affinity for the ACE2 receptor part of the ACE2 receptor-spark protein interface. Therefore, it is expected that these affinities and interactions may restrict the binding of nCoV-2019 spike protein with the ACE2 re- ceptor and hence, inhibit the spread of infection. |
| Ton 2020               | The top predicted inhibitors share a number of characteristics with two known protease inhibitors (aka Lopinavir and compound 80), which are also likely to bind to the SARS-COV-2 spike. Compound 80° is a non-peptide small molecule inhibitor of SARS Mpro, with a reported IC50 of 0.95 μM. ZINC00054177852 was selected as the top identified molecule that has a better binding effect than both Lopinavir and compound 80. |
| Wang 2020              | Carfilzomib, Eravacycline, Valrubicin, Lopinavir, and Bictegravir are better than Nelfinavir. SeeSAR suggests that Prulifloxacin, Tegobuvir, and Bictegravir are better than Nelfinavir. |
| Wu 2020                | Virtual screening introduced many compounds able to bind the ACE2 target. However, none of these drugs bind with the contact surface of the ACE2–Spikes complex. Thus, these compounds could merely inhibit ACE2 enzyme activities rather than the inhibition of the viral infections caused by ACE2. |

(continued on next page)
Table 4 (continued)

| The first author, year | Findings |
|------------------------|----------|
| - The drugs that do not have clear targets are not suggested, such as: Chloroquine phosphate, which might target Nsp3b and E-channel. |Further, Sempremivir and Nelfinavir commonly hit 3CLP and Danoprevir has the same targets as the drugs mentioned above, with an energy value of 23.34, 25.92, 26.28, and 28.20, respectively.|
| Xu 2020 |For both Lopinavir and Ritonavir, no evident bonding to the main proteases (aka 3Clpro, Plpro, RdRp) was seen.|
| - Lopinavir’s possible target is Nsp3b, Nsp3c, helicase, NRBD, or E-channel. |4-The triphosphate nucleotide product of Remdesivir, Remdesivir-TP has two effects: It is a competitive substrate ATP with RdRp. Hence it intervenes with viral RNA synthesis. It has good binding, a score of –112.8. It was predictive to bind the humanTMPRSS2, a protein that boosts the virus infection.|
| - For both Lopinavir and Ritonavir, no evident bonding to the main proteases (aka 3Clpro, Plpro, RdRp) was seen. |After two steps of docking performed, energy calculation was done on four final candidates, and these calculations voted for Nelfinavir as a potential inhibitor of COVID-19 main protease.|
| |After two steps of docking performed, energy calculation was done on four final candidates, and these calculations voted for Nelfinavir as a potential inhibitor of COVID-19 main protease.|
| - Pitavastatin, Perampanel, and Praziquantel were identified as potential Mpro inhibitors with moderate activities. |It is a competitive substrate ATP with RdRp. Hence it intervenes with viral RNA synthesis. It has good binding, a score of –112.8. It was predictive to bind the human TMPRSS2, a protein that boosts the virus infection.|

Danoprevir has the same targets as the drugs mentioned above, with an exception to helicase, which is replaced by endoRNase. Moreover, Dabigatran, Itraconazole, and Saquinavir hit RdRp, helicase, and spike proteins; however, the later one hits 3CLP instead of the spike protein. Furthermore, Sempremivir and Nelfinavir commonly hit 3CLP and helicase, and distinctly hit each one of the 3′-to-5′ exonuclease and endoRNase, respectively.

Indinavir and Remdesivir are the most documented drugs among dual-target drugs. These two drugs similarly target the 3CLP and desperately target each one of the helicase and RdRp, respectively. Also, Ribavirin is a drug with a dual effect; it targets RdRp and PLVP.

Smith et al. mentioned that Nitrofurantoin, Isoniazid prophylaxis, Eriodictyol, are the top three candidates that bind to the ACE2 part of the ACE2 receptor-splice protein interface. Therefore, it might be expected that these drugs might restrict the binding of SARS-CoV2 spike protein to the ACE2 receptor and hence, inhibit the spread of infection [140]. However, this might be quite controversial if we consider what Wu et al. have declared about the inability of these drugs to block the viral infection and their restricted effect on the ACE2 Enzyme activity [144].

Chloroquine is another doubtful drug. Three studies have suggested that this drug might inhibit the PLP and the E-channel [126,133,144]. In all of these studies, the binding energy of Chloroquine is acceptable, but it lacks an excellent value and as declared by Wu and colleagues who emphasize on not considering the drugs that do not have a specific target like Chloroquine [144].

Wu et al. [144] have claimed that they found probable druguable compounds through the docking process of their structural model of helicase. The authors predicted that anti-bacterial drugs (Lymecycline, Cefadoline, and Roterliocycline), anti-fungal drug Itraconazole, anti-human immunodeficiency virus-1 (HIV-1) drug Saquinavir, anti-coagulant drug Dabigatran, and diuretic drug Canrenon acid could act as potential coronavirus helicase inhibitors with high mScores. Beck et al. [127] have also applied helicase as the drug repurposing target. The five top potential inhibitors have turned out to be Simeprevir, Atazanavir, Grazoprevir, Asunaprevir, and Telaprevir; with K50 (nM): 23.34, 25.92, 26.28, and 28.20, respectively.

Drug-target interaction (DTI) prediction results of repurposing of approved drugs indicate a list of possible inhibitors of 3′ to 5′ exonuclease, and the four top candidates were Simeprevir, Efavirenz, Danoprevir, and Ganciclovir [127].

2′-OMTase methylates the ribose 2′-O position of the first and second nucleotide in viral mRNA structure to sequester it from the host immune system [135]. The reported docking results in two separate studies that have utilized 2′-OMTase as their target was different. These two studies were performed by applying two different methodologies. Khan et al. [135] have performed homology modeling, molecular docking, and molecular dynamics simulations and have reported Dolutegravir and Bictegravir as probable candidates against SARS-CoV2. While Beck et al. [127] have conducted molecule transformer-drug target Interaction (MT-DTI) and have introduced Atazanavir, Efavirenz, and Boceprevir as potential inhibitors of SARS-CoV2 2′-OMTase.

EndoRNase is an enzyme that can cleave both single-stranded and double-stranded RNA. In all 21 included studies, only Beck et al. [127] have used endoRNase as a target for computational drug repurposing and proposed a list of approved drugs as potential candidates among which the top-ranked ones are Efavirenz and Atazanavir.

The best-documented multi-target drugs repurposed by computational methods for COVID-19 therapy include antiviral drugs commonly used to treat AIDS/HIV (Atazanavir, Efavirenz, and Dolutegravir Ritonavir, Raltegravir, and Darunavir; Lopinavir, Saquinavir, Nelfinavir, and Indinavir), HCV (Grazoprevir, Lomitaprevir, Asunaprevir, Ribavirin, and Simeprevir), HBV (Entecavir), HSV (Penciclovir), CMV (Ganciclovir), and Ebola (Remdesivir), anticoagulant drug (Dabigatran), and an anti-fungal drug (Itraconazole). For the majority of these drugs, direct clinical evidence on their efficacy for the treatment of COVID-19 is lacking. There is, however, evidence from in vitro and clinical studies for the use of some drugs mentioned above in SARS-CoV2.

Atazanavir (ATV) is an antiretroviral protease inhibitor primarily introduced for the treatment of HIV. When it is administered intravenously, it can reach the lungs and help to cure pulmonary fibrosis. An in vitro study has shown that ATZ lessens SARS-CoV2 replication in both Vero cells and human epithelial pulmonary cells (A549). ATZ can particularly attenuate the unwanted inflammatory response to SARS-CoV2 in infected monocytes, as measured by the reduced levels of pro-inflammatory cytokines, including IL6 and TNFA [152].

In vitro studies indicate the anti-SARS activities of Lopinavir. Ritonavir is a potent inhibitor of cytochrome P450. When combined with Lopinavir, Ritonavir can help reduce cytochrome P450-mediated metabolism of Lopinavir in the liver that will increase plasma half-life of and biological effects of Lopinavir. As evidenced by a randomized controlled trial (RCT), no difference in clinical outcomes appeared following Lopinavir–Ritonavir treatment in adult patients with severe COVID-19 [153]. Moreover, patients receiving Lopinavir–Ritonavir treatment developed gastrointestinal adverse events more than those who underwent standard care.

An in vitro study [154] compared the safety and efficacy of nine HIV-1 protease inhibitors on SARS-CoV2 in VeroE6 cells. Amprenavir, darunavir, and indinavir could provide inhibition of SARS-CoV2 replication at a high 50% effective concentration (EC50) of 31.32, 46.41, and 59.14 μM. There was a lower dose required for Tipranavir to inhibit SARS-CoV2 replication. However, the selectivity index (SI) of Tipranavir was low. Ritonavir, Saquinavir, Atazanavir, Lopinavir, and Nelfinavir were the drugs that could at the lowest doses mitigate SARS-CoV2 replication while having a relatively high SI. They correspond to EC50(SI) of 8.63 (8.59), 8.83 (5.03), 9.36 (>8.65), 5.73 (12.99), and 1.13 (21.52). Also, the Grough/EC50 ratio higher than one, which indicates that the compound can reach a trough serum concentration of higher than 50% effective concentration, occurred in only three of nine drugs Nelfinavir, Lopinavir, and Tipranavir. Overall, Nelfinavir seems to be the best among different anti-protease inhibitors, with both the lowest EC50 and the highest SI as well as the Grough/EC50 Ratio higher than one. Because of the absence of any effect of Darunavir on SARS-CoV2 culturated in Caco-2 cells, there is no SI attached to Darunavir [155]. By contrast, Remdesivir could reduce the cytopathogenic effect (CPE) of SARS-CoV at low doses (EC50 = 0.11 μM) and represent a noticeable SI higher than 900.

The study [156] evaluated the efficacy of seven drugs against SARS-CoV2 in Vero E6 cells. The 50% effective concentration at which the inhibitory effects of Ribavirin, Penciclovir, and Favipiravir on SARS-CoV2 replication appeared was as high as 109.5, 95.96, and 61.88 μM,
Table 5
Mono-target drugs repurposed for COVID-19.

| Drug                | PLVP | RdRp | Helicase | 3’/5’ exonuclease (127) | 2’-OMTase | EndoRNAase (127) | Spike | Total |
|---------------------|------|------|----------|-------------------------|-----------|------------------|-------|-------|
| Elbasvir            | (130, 141) | 3    |          |                         |           |                  |       |       |
| Amprenavir          | (128, 143) | 3    |          |                         |           |                  |       |       |
| Ledipasvir          | (129, 143) | 2    |          |                         |           |                  |       |       |
| Ritonavir           | (128, 141) | 2    |          |                         |           |                  |       |       |
| Sofosbuvir          | (129, 131) | 2    |          |                         |           |                  |       |       |
| Paritaprevir        | (125, 125) | 2    |          |                         |           |                  |       |       |
| Favipiravir         | (128) |      |          | (144), without a specific target. |         |                  |       |       |
| Bedaquiline, Tadalafil, Leflunomide, Digoxin, Tinilazet, Digoxin | (141) | | | | | | | |
| Galidesvir          | (128) | | | | | | | |
| Hydroxychloroquine  | (133) | 1    |          |                         |           |                  |       |       |
| Trifluridine, Lamivudine | (127) | | | | | | | |
| Prulifloxacin       | (136) | 1    |          |                         |           |                  |       |       |
| Telbivudine         | (139) | 1    |          |                         |           |                  |       |       |
| Rolnetracetline, Carboxylic acid | (144) | | | | | | | |
| Resilidine, Iprofos, Prazosin, Propanolol, Atenolol, Pencillin | | | | | | | | |
| Willetaline, Celecoxibine, Avisapone, Chondroitinase, Cymolyn, Paracortisol, Cortisone, Tobilone, Nebuloxine, Iodobut, Bromocriptine, Ophthasylate, Benzylpenicilloyl, | (144) | | | | | | | |
| , Afluzosin, Olausine, Fatomidine, Almitrine, Propalbo, Napafenac, Conavidos, Demecoquin, Montesque, Canvamicin, Mimosine, Flavin mononucleotide, Lutein, Celipramide, Phenantecillin, Canosafir, Nicardpine, Estradiol valerate, Pleoglazione, Convistet, Telmsartan, Dazoxudine, Orizatracetline | (144) | | | | | | | |
| Beta-Thymidine, Apsaparte, Oprenolol, Dazoxudine, Andaphephazine, Ipromicin, Molfofain, Reprotin, 2,2-Cyclopropane, Chloramphenicol, Chlorophenoxis carbatate, Levedropriphosphate, Cefamandole, Floxuridine, Pemetrexed, 1,4-Ascorbic acid, Glutathione, Iesperinet, Ademetionone, Masropicol, Insolntranone, Dantrolene, Nicardpine, Sildenafil | (144) | | | | | | | |
| Pivastatol, Pestapin, Prozapantol, etoposide, and zopiclone | (159) | | | | | | | |
| Carfizomib, Erawacydine, Valbeacon, Charged molecules: Streptomycin, Flavin adenine dinucleotide, Oltasctine | (161) | | | | | | | |
| CVM, ACTD888 (Repivir) | (142) | | | | | | | |
| Pemfetol, sorinad pyranate, Nitrofurant, Emelitral | (140) | | | | | | | |
| Bortezomib, Fluarapeem, Pomatinib, Sorafenib, Daratinib, Paraphanthase, Chlorattide, Fluconaxidin, Seritodine, Clevidipine, Agreptin, Atoratstatin, Glitazoxepam, Glitazomine, Fosaproptin | (138) | | | | | | | |
| PK-12, Snipom, TID8-B, Tidigisto, Carmotol, Ebasalin, Dilirafins | (134) | | | | | | | |
| Plicaxel, Docetaxel, Pabalcosib, Carbazolase, Alectroin, Imatinib, Pianaxor, Aezotroline, Basabuvi, Carceptin, Glatipet | (133) | | | | | | | |
| GRL-0667, GRL-0617, and Myophenodic acid | (132) | | | | | | | |
| Caspofungin acetate, Sameterol xinafoate, | (130) | | | | | | | |

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Fig. 3. The distribution of multi-target drugs for COVID-19.

respectively. It was reduced to 22.50 μM for Nafamostat and 2.12 for Nitazoxanide. Two drugs could have a powerful effect on SARS-CoV-2 replication at low doses: Remdesivir and Chloroquine associated with EC50 (SI) of 0.77 (>129.87) and 1.13 (>88.5).

Like Chloroquine, hydroxychloroquine can have anti-malarial and immunomodulatory effects in a manner useful to patients with auto-immune diseases. Both Chloroquine and hydroxychloroquine have shown to help antiviral immunity through inhibition of the fusion between viral and host-cell membranes, virus replication, and viral glycosylation and assembly. However, hydroxychloroquine has become more important for fewer adverse effects and drug-drug interactions. In vitro investigation points out a lower 50% effective concentration required for Chloroquine compared to hydroxychloroquine to exert anti-SARS-CoV2 effects in Vero cells [157]. It would indicate the more potency of Chloroquine than its analog, hydroxychloroquine, in inhibiting SARS-CoV2 replication.

In conclusion, at this growing rate of COVID-19 pandemic and increasing mortality rate, it seems quite unachievable to design a novel specific drug for it. Therefore, it puts a spotlight on the drug repurposing investigation points out a lower 50% effective concentration required for Chloroquine compared to hydroxychloroquine to exert anti-SARS-CoV2 effects in Vero cells [157]. It would indicate the more potency of Chloroquine than its analog, hydroxychloroquine, in inhibiting SARS-CoV2 replication.

5. Conclusion

Despite its limitations, the present systematic review provides a list of existing drugs that have the potential to influence SARS-CoV2 through different mechanisms of action. And in the near future, clinical studies examining these drugs might come to conclude, which can be more useful to inhibit COVID-19 progression.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

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Authors’ contributions

K.M. conceptualized the study. K.M. and N.Y. conducted database search, search results screening, detailed review, data extraction, quality assessment, and prepared the initial draft. A.S. prepared the final draft.

Declaration of Competing Interest

The authors declare that they have no competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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