Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Review article

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

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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, Lomibuvir, Asunaprevir, Ribavirin, and Simeprevir), HBV (Entecavir), HSV (Penciclovir), CMV (Ganciclovir), and Ebola (Remdesivir), anticoagulant drug (Dabigatran), and an antifungal 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

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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 health care 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-19drug 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.

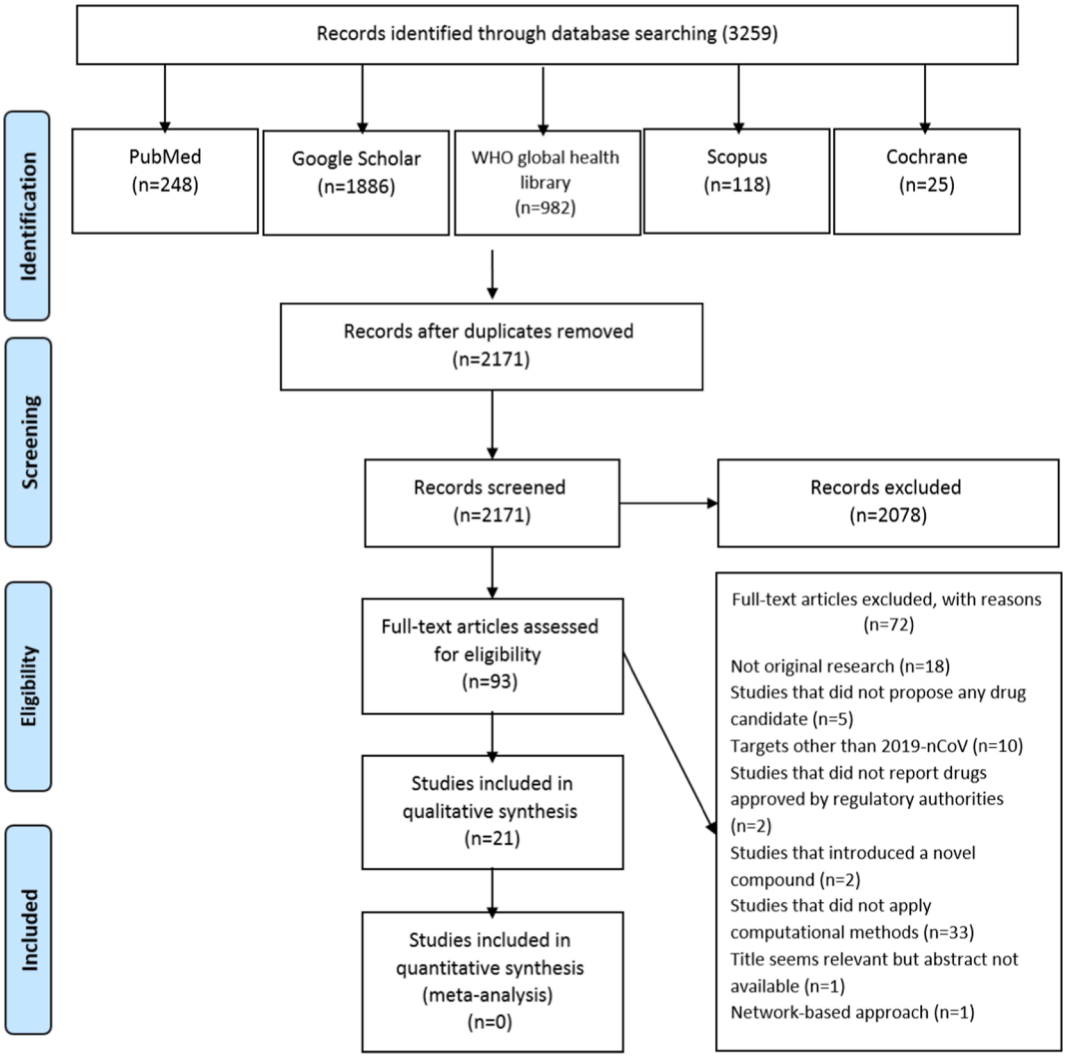

Fig. 1. Flow diagram of the literature search process.

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)	Beclabuvir, Saquinavir, Ledipasvir, Elbasvir, Raltegravir, Indinavir, Nelfinavir, Amprenavir, Tipranavir, Darunavir, Ritonavir, Lopinavir, Fosamprenavir, Atazanavir, Nilotinib, Tadalafil, Lifitegrast, Digitoxin, Digoxin, and Tirilazad
Elfiky 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: IDX-184, Sofosbuvir, Ribavirin, and Remidisvir
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, Paritaprevir and Simeprevir
Chang 2020, Taiwan	Ligand-based virtual screening, molecular docking, and molecular dynamic simulation		Swiss-model, CASTp tool, AutoDock Vina and RosettaCommons	SARS-CoV 3CL Protease	Indinavir, Lopinavir, Atazanavir, Saquinavir, Ritonavir, Nelfinavir, Darunavir, Tipranavir, Amprenavir, Fosamprenavir
				SARS-CoV RdRp	RdRp: Remdesivir, Galidesivir, Ribavirin, Favipiravir
Arya 2020, India	Homology modeling, virtual screening, and molecular docking		SWISS-MODEL workspace, SEESAR suite of programs from BioSolveIT	PLpro	Biltricide, Cinacalcet, Procainamide, Terbinafine, Pethidine, Labetalol, Tetrahydrozoline, Ticlopidine, Ethoheptazine, Levamisole, Amitriptyline, Nephazoline, Formoterol, Benzylpenicillin, Chloroquine, Chlorothiazide
Beck 2020, Korea	Molecule Transformer-Drug Target Interaction (MT-DTI)		Molecule transformer-drug target interaction (MT-DTI), BERT framework, SMILES	3CL pro	Atazanavir, Efavirenz, Ritonavir, Dolutegravir, Asunaprevir, Simeprevir
				RdRp	Grazoprevir, Ganciclovir, Atazanavir, Daclatasvir, Acyclovir, Etravirine, Entecavir, Efavirenz, Asunaprevir, Abacavir Dolutegravir, Lomibuvir, Penciclovir, Trifluridine, Danoprevir, Ritonavir,, Saquinavir,
					Raltegravir, Lamivudine
				Helicase	Simeprevir, Atazanavir, Grazoprevir, Asunaprevir, Telaprevir, Ritonavir, Lopinavir, Darunavir, Ganciclovir, Penciclovir, Etravirine, Raltegravir, Dolutegravir, Nelfinavir, Indinavir, Efavirenz, Entecavir, Boceprevir, Lomibuvir, Acyclovir
				3'-to-5' exonuclease	Simeprevir, Efavirenz, Danoprevir, Ganciclovir, Penciclovir, Atazanavir, Entecavir, Daclatasvir, Grazoprevir, Asunaprevir, Ritonavir, Lomibuvir, Darunavir, Raltegravir, Dolutegravir, Lopinavir
				endoRNAse	Efavirenz, Atazanavir, Ritonavir, Danoprevir, Grazoprevir, Dolutegravir, Lomibuvir, Lopinavir, Darunavir, Nelfinavir, Telaprevir, Abacavir, Raltegravir, Boceprevir
				2'-O-ribose methyltransferase	Atazanavir, Efavirenz, Boceprevir
Chen 2020, Hong Kong	Preparation of structural model, Virtual screening and molecular docking		BLASTp, PyMOL (version 1.7.X), AutoDock Vina5, MTiOpenScreen	3CL protease	Diosmin, Hesperidin, MK-3207, Venetoclax, Dihydroergocristine, Bolazine, R428, Ditercalinium, Etoposide, Teniposide, UK-432097, Irinotecan, Lumacaftor, Velpatasvir, Eluxadoline, Ledipasvir
Contini 2020, Italy	homology modeling, virtual screening, molecular docking, molecular dynamic simulation		MOE2019 software, PLANTS	Mpro	Angiotensin II human acetate, GHRP-2, Indinavir, Cobicistat(GS-9350), Montelukast, Octenidine dihydrochloride, Tyloxapol, Salvianolic acid B, Travoprost, Monomethyl auristatin E (MMAE), Nafarelin acetate, Leuprorelin acetate, Somatostatin acetate, Icatibant acetate, Nystatin, Goserelin acetate, Alarelin acetate, Gonadorelin acetate, Amphotericin B, Carfilzumib, Thymopentin, Lentinan, Ritonavir, NAD+, Octreotide acetate, Colistin sulfate, Cangrelor tetrasodium, Oxytocin, Flucytosine, Echinacoside
				3Cl protease	Caspofungin acetate, Lopinavir(ABT-378), Atazanavir, GHRP-2, Indinavir, Angiotensin II human acetate, Ritonavir, Salvianolic acid B, Elbasvir, Montelukast sodium, Cobicistat(GS-9350), Tyloxapol, Salmeterol xinafoate, Penfluridol, Gonadorelin acetate, Leuprorelin acetate, Nafarelin acetate, Goserelin acetate, Bacitracin

(continued on next page)

Table 1 (*continued*)

					zink, Amphotericin B, Alarelin acetate, Deferoxamine mesylate, Nystatin, Octreotide acetate, Carfilzumib, Terlipressin acetate, Somatostatin acetate, Flucytosine, Lypressin acetate, Sennoside A
Elfiky 2020, India	Sequence analysis, homology modeling, and docking		ExPASy translate tool, Swiss Model, Basic Local Alignment Tool(BLAST), PyMOL software, AutoDock Vina software	PLpro	anti-SARS Plpro: GRL-0667, GRL-0617, and Mycophenolic acid anti-HCV NS3 Telaprevir, Boceprevir, and Grazoprevir
Hosseini 2020, Iran	Virtual screening procedure, molecular docking simulation		Discovery Studio visualizer version 17.2 and Pymol version 1.1evel, AutoDockTools AutoDock 4.2.	Mpro	Piclitaxel, Simeprevir, Docetaxel, Palbociclib, Cabazitaxel, Alectinib, Imatinib, Plerixafor, Azelastine, Dasabuvir, Lopinavir, Ritonavir, Chloroquine, Hydroxychloroquine, Captopril, Enalapril, Remdesivir
Jin 2020, China	Structure-based *ab initio* drug design, virtual drug screening, and high-throughput screening		Program Xia2, Phaser module in CCP4, Phenix, ligPrep module of Maestro, Glide (version8.2) of Schrödinger 2019-1, iFitDock	Mpro	PX-12, Shikonin, TDZD-8, Tideglusib, Carmofur, Ebselen, Disulfiram
Khan 2020, India	Homology modeling, molecular docking and molecular dynamics simulation		SWISS-MODEL, Protein BLAST, Structure Analysis and Verification Server (SAVES) v5.0 meta server which includes ERRAT Verify-3D and PROCHECK programs, AutoDockVina docking wizard inbuilt in PyRx	3Cl protease	Paritaprevir (DB09297) and Raltegravir (DB06817)
				2'-OMTase	Dolutegravir (DB08930) and Bictegravir (DB11799)
Li 2020, China	high-throughput screening, molecular docking, Homologous targets screening		PyMOL v2.3, SeeSAR (version 9.2; BioSolveIT GmbH), online software AutoDock Vina, Perl program (developed by them)	Mpro	Prulifloxacin, Bictegravir, Nelfinavir, Tegobuvir
Lin 2020, China	Homology modeling, molecular docking, molecular simulating		SWISS-MODEL, SAVES, Discovery Studio software (version 2.5, Accelrys Software Inc.)	3CL protease	Ritonavir, Lopinavir (*continued on next page*)
				PLVP	Darunavir
Nguyen 2020, USA	structural-based drug repositioning (SBDR): Sequence identity analysis, homology modeling, Structure similarity analysis, molecular docking, Binding analysis		The SWISS model, CNN Mathpose model, MathDL deep convolutional neural networks (CNNs)	3CL protease	Bortezomib, Flurazepam, Ponatinib, Sorafenib, Dasatinib, Paramethasone, Clocortolone, Flucloxacillin, Sertinadole, Clevidipine, Aprepitant, Atorvastatin, Cinolazepam, Clofazimine, Fosaprepitant
Nguyen 2020, USA	Machine intelligence-based GNC, Sequence identity analysis, Sequence similarity analysis, homology modeling		SMILES string, MathPose model, MathDL, 2DFP-DNN	The 2019-nCoV protease (PDB ID 6lu7) and SARS-CoV 3CL protease (PDB ID: 2gx4)	Lopinavir, Ritonavir, Kaletra (or Aluvia), 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 POWER9 build of Autodock Vina34 for SUMMIT	S-protein-ACE2 interface	Pemirolast, Isoniazid pyruvate, Nitrofurantin, Eriodictyol
Ton 2020, Canada	A novel deep learning platform – DD		Omega pose routine, Glide SP module	Mpro	CMK, AG7088 (Rupintrivir), Lopinavir, Remdesivir
Wang 2020, USA	Virtual docking screening, molecular dynamics simulations, HVS		Schrodinger software, Promals3D web server, Glide flexible docking program	COVID-19 main protease	Carfilzomib, Eravacycline, Valrubicin, Lopinavir, and Elbasvir Charged molecules: Streptomycin, Flavin adenine dinucleotide, Oftasceine
Wu 2020, China	Sequence alignment and analysis, homology modeling, target-based virtual		BLASTn, pymol structure alignment tool, ICM 3.7.3 software	Helicase	Lymecycline, Cefsulodine, Rolitetracycline, Itraconazole, Saquinavir, Dabigatran, Canrenoic acid
				Plpro	Ribavirin, Valaganciclovir, beta-Thymidine, Aspartame, Oxprenolol, Doxycycline, Acetophenazine, Ipromide,

Table 1 (*continued*)

	ligand screening, molecular doking				Riboflavin, Reproterol, 2,2′-Cyclocytidine, Chloramphenicol, Chlorphenesin carbamate, Levodropropizine, Cefamandole, Floxuridine, Tigecycline, Pemetrexed, L(+)-Ascorbic acid, Glutathione, Hesperetin, Ademetionine, Masoprocol, Isotretinoin, Dantrolene, Sulfasalazine, Silybin, Nicardipine, Sildenafil
				3CLpro	Lymecycline, Chlorhexidine, Alfuzosin, Cilastatin, Famotidine, Almitrine, Progabide, Nepafenac, Carvedilol, Amprenavir, Tigecycline, Demeclocycline, Montelukast, Carminic acid, Mimosine, Flavin mononucleotide, Lutein, Cefpiramide, Phenethicillin, Candoxatril, Nicardipine, Estradiol valerate, Pioglitazone, Conivaptan, Telmisartan, Doxycycline, Oxytetracycline
				RdRp	Valganciclovir, Chlorhexidine, Ceftibuten, Fenoterol, Fludarabine, Itraconazole, Cefuroxime, Atovaquone, Chenodeoxycholic acid, Cromolyn, Pancuronium bromide, Cortisone, Tibolone, Novobiocin, Silybin, Idarubicin, Bromocriptine, Diphenoxylate, Benzylpenicilloyl G, Dabigatran etexilate
				Spike protein	Rescinnamine, Iloprost, Prazocin, Posaconazole, Itraconazole, Sulfasalazine, Azlocillin, Penicillin, Cefsulodin, Dabigatran etexilate
Xu 2020, China	Homolgy modeling, molecular docking, molecular dynamics simulations, Binding free energy calculation		SWISS-MODEL, MolShaCS, MGLToos version 1.5.6, PyMOL, SMINA which is a fork of AutoDock Vina	Mpro	Nelfinavir, Pitavastatin, Perampanel, Praziquantel, eszopiclone, and zopiclone

Table 2
Quality of studies included in the systematic review.

The first author, year	Targets		The target template modeling			Docking tools		Molecular dynamics simulation		Approved drug database	
	Mono	Multi	Crystal structure	Homology modeling	Co-crystal-ligand	Auto dock vina	Others	Yes	No	Mono	Multi
Sekhar 2020 (141)						SMINA	Python and shell scripts			SuperDRUG2 database	
Elfiky 2020 (131)										ND	
Alamri 2020 (125)											AFCL library and PubChem database
Chang 2020 (128)							RosettaCommons				Literature survey and PubChem database
Arya 2020 (126)							SEESAR				DrugBank database, the Zinc15 library
Beck 2020 (127)							MT-DTI				Drug Target Common (DTC) database and BindingDB database
Chen 2020 (129)							MTiOpenScreen			MTiOpenScreen	
Contini 2020 (130)							PLANTS				FDA-approved drug database (Selleckchem and TargetMol)
Elfiky 2020 (132)										PubChem database	
Hosseini 2020 (133)											Zinc database, Drug Bank Database
Jin 2020 (134)							Glide (version8.2) of Schrödinger 2019-1, iFitDock				Approved Drug Library (TargetMol, USA), Clinic Compound Library (TargetMol, USA), FDA-approved Drug Library (Selleck, USA), Natural Product Library (Selleck, USA), and Anti-virus drug, library (Shanghai Institute for Advanced Immunochemical Studies, SIAIS)
Khan 2020 (135)										DrugBank database	
Li 2020 (136)							SeeSAR and Perl program			DrugBank database	
Lin 2020 (137)							Discovery Studio software (version 2.5, Accelrys Software Inc.)				
Nguyen 2020 (138)							Deep CNNs and MathDL				DrugBank + ChEMBL database
Nguyen 2020 (139)							Deep CNNs, MathDL, and 2DFP-DNN				ChEMBL database
Smith 2020 (140)										SWEETLEAD molecular library	
Ton 2020 (142)							Glide SP module			ZINC15 library	
Wang 2020 (143)							Glide flexible docking program				DrugBank database (approved drugs, investigational drugs, and experimental drugs) and PubChem
Wu 2020 (144)							ICM 3.7.3 software				ZINC drug database, the database of natural products, and the database of commonly used antiviral drugs (78 compounds)
Xu 2020 (145)						SMINA				DrugBank release version 5.1.5	

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. 3CLPa

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

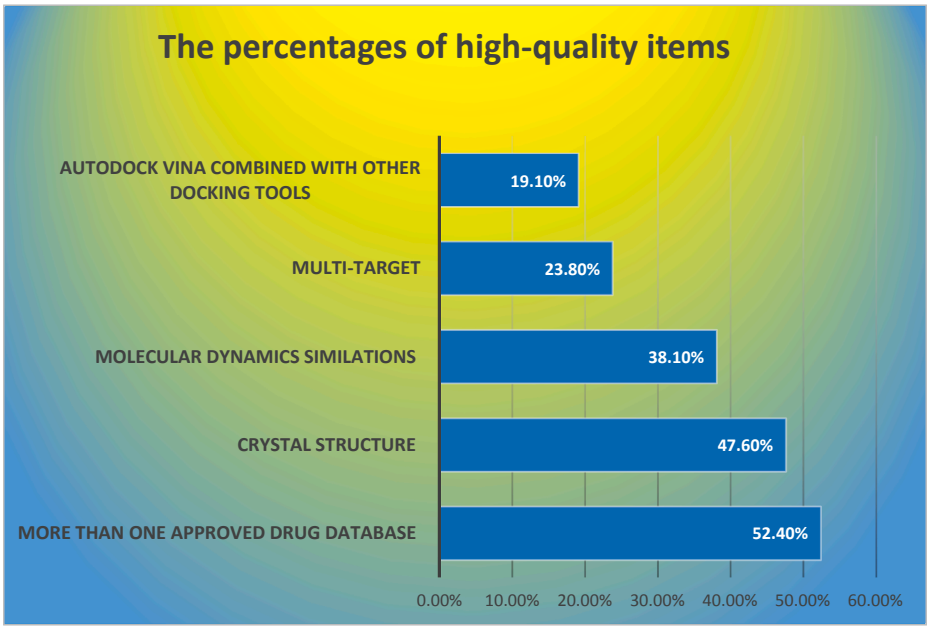

Fig. 2. The percentage of studies reported high-quality items.

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 Atanzavir 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, Clocortolone, 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-CoV2 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 mono-target 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 Lomibuvir 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. Lomibuvir and Boceprevir commonly target helicase and endoRNAse, while RdRp and 3′-to-5′ exonuclease are merely targeted by Lomibuvir 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)		11
Lopinavir	8 (128, 130, 133, 137, 139, 141, 142, 158)			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 (137)		1 (127)	1 (127)		1 (127)		6
Raltegravir	2 (135, 141)		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)		6
Efavirenz	1 (127)		1 (127)	1 (127)	1 (127)	1 (127)	1 (127)		6
Simeprevir	3 (125, 127, 133)			1 (127)	1 (127)				5
Indinavir	3 (128, 130, 141)			1 (127)					4
Grazoprevir		1 (132)	1 (127)	1 (127)	1 (127)		1 (127)		5
Asunaprevir	1 (127)		1 (127)	1 (127)	1 (127)				4
Saquinavir	2 (128, 141)		1 (127)	1 (144)					4
Remdesivir	2 (133, 142)		2 (128, 131)						4
Lomibuvir			1 (127)	1 (127)	1 (127)		1 (127)		4
Entecavir			1 (127)	1 (127)	1 (127)				3
Boceprevir		1 (132)		1 (127)		1 (127)	1 (127)		4
Dabigatran			1 (144)	1 (144)				1 (144)	3
Ribavirin		1 (144)	2 (128, 131)						3
Penciclovir			1 (127)	1 (127)	1 (127)				3
Itraconazole			1 (144)	1 (144)				1 (144)	3
Danoprevir			1 (127)		1 (127)		1 (127)		3
Telaprevir		1 (132)		1 (139, 144, 161)			1 (127)		3
Ganciclovir			1 (6)	1 (6)	1 (127)				3
Chloroquine	2 (144 ,133)	1 (126)							3
Valganciclovir		1 (144)	1 (144)						2
Daclatasvir			1 (127)		1 (127)				2
Acyclovir			1 (127)	1 (127)					2
Etravirine			1 (127)	1 (127)					2
Abacavir			1 (127)				1 (127)		2
Bictegravir	1 (136)					1 (10)			2
Hesperidin	1 (129)							1 (144)	2
Chlorhexidine	1 (144)		1 (144)						2
Silybin		1 (144)	1 (144)						2
Tigecycline	1 (144)	1 (144)							2
Sulfasalazine	1 (144)							1 (144)	2
Lymecycline	1 (144)			1 (144)					2
Cefsulodin				1 (144)				1 (144)	2
Etexilate			1 (144)					1 (144)	2

Table 4
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 as 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.
Alamri 2020	- Three top 3CLpro inhibitor candidates in this study were compound 621, 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 DTI model, the viral proteinase-targeting drugs were predicted to act better on the viral replication process than viral proteinase. - An antiviral drug, such as guanosine analogs (e.g., acyclovir, ganciclovir, and penciclovir), reverse transcriptase inhibitors, and integrase inhibitors, were more than proteinase 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 (K_d 21.83 nM), helicase (K_d 25.92 nM), 3′-to-5′ exonuclease (K_d 82.36 nM), 2′-O-ribose methyltransferase (K_d of 390 nM), and endoRNAse (K_d 50.32 nM). - Ganciclovir was predicted to bind to RNA-dependent RNA polymerase (K_d 11.91 nM), 3′-to-5′ exonuclease (K_d 56.29 nM), and RNA helicase (K_d 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 K_d of 90.38 nM against 2019-nCoV's helicase.
Chen 2020	- Dual-component HCV drugs, Epclusa (velpatasvir/sofosbuvir), and Harvoni (ledipasvir/sofosbuvir) act on two viral proteins, 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.
Contini 2020	- Indinavir was selected by both COVID-19 main protease (PDB code 6LU7) and COVID-19 3CL-PRO proteinase. - Lopinavir and Atazanavir were best selected for 3CL-PRO - Cobicistat was chosen as a potential COVID-19 primary protease inhibitor. - Angiotensin II and GHRP-2 were selected too. Although these might bind the target, they are cleaved by the target too because these are peptides, and they are just served as substrates. - Caspofungin identification is unexpected and doubtful. - Further parameterization schemes and calculations are required to confirm these compounds' effectiveness.
Elfiky 2020	- Although both the anti-SARS PLpro (GRL-0667, GRL-0617, and Mycophenolic acid) and the anti-HCV NS3 (Telaprevir, Boceprevir, and Grazoprevir) binding energies for 2019-CoV PLpro are a bit less than that calculated for SARS PLpro and HCV, they can still bind to the active site (C112, H273, and D287) of 2019-nCoV PLpr.
Hosseini 2020	- The FDA approved anti HCV NS3/4A protease, Simeprevir, demonstrated better affinity than Lopinavir and Ritonavir, in binding with COVID-19 main protease.
Jin 2020	- The virtual screening revealed that cinanserin is a well-known serotonin antagonist that fits firmly into the substrate-binding pocket, with having an IC50 value of 124.93 μM for Mpro. - High-throughput screening results - Ebselen, a drug that is currently in the clinical trial, has the most robust inhibition of Mpro activity with an IC50 of 0.48 μM.
Khan 2020	- Four drugs were found that act as potential inhibitors against 2019nCoV; they are as follow: Raltegravir and Paritaprevir are against 3CLproBictegravir and Dolutegravir are against 2′-OMTase
Li 2020	- All of the following molecules, Prulifloxacin, Bictegravir, Nelfinavir, and Tegobuvir, showed stable binding conformations with the main viral protease. - Affinity and physical–chemical properties analysis using SeeSAR suggests that Prulifloxacin, Tegobuvir, and Bictegravir are better than Nelfinavir.
Lin 2020	- Due to the unknown catalytic mechanisms of CEP_C30 and PLVP domains, we cannot accurately define whether ritonavir, Lopinavir, and darunavir are competitive or non-competitive inhibitors. However, it can be predicted that both ritonavir and Lopinavir have an inhibitory effect on CEP_C30, and acclaim that ritonavir has a better effect. - In addition to the ability of darunavir to bind PLVP by changing its conformation with little conformation changes and that might make it a competitive inhibitor.
Nguyen 2020	- Three top suggested drugs are: Bortezomib, Flurazepam, 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.
Nguyen 2020	- 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	- Nitrofurantoin, 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-spike protein interface. Therefore, it is expected that these affinities and interactions may restrict the binding of nCoV-2019 spike protein with the ACE2 receptor 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 Mpro. - Compound 80″ is a non-peptide small molecule inhibitor of SARS Mpro, with a reported IC50 of 0.95 μM. - ZINC000541677852 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 Elbasvir, have inhibitory activities against COVID-19 protease. - Streptomycin, a charged molecule, might be an inhibitor of COVID-19 protease.
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–Spike complex. Thus, these compounds could merely inhibit ACE2 enzyme activities rather than the inhibition of the viral infections caused by ACE2. - 2-PROTAC technology might be the right choice for the proteins that finding their inhibitor is quite hard. In this technology, the proteins are first degraded, then this leads the inhibition if the viral infection, e.g., natural hesperidin was selected for Spike protein. In this condition, the viral infection process could be inhibited by any small molecule that interferes with the re-folding of the spike when it is bound to it.

(*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.Ritonavir's possible target is Nsp3c or E-channel. - Lopinavir's possible target is Nsp3b, Nsp3c, helicase, NRBD, or E-channel. - For both Lopinavir and Ritonavir, no evident bonding to the main proteases (aka 3CLpro, PLpro, RdRp) was seen. - 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 human TMPRSS2, a protein that boosts the virus infection.
Xu 2020	- 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.

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 distinctively 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 pyruvate, Eriodictyol, are the top three candidates that bind to the ACE2 part of the ACE2 receptor-spike 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 druggable compounds through the docking process of their structural model of helicase. The authors predicted that anti-bacterial drugs (Lymecycline, Cefsulodine, and Rolitetracycline), anti-fungal drug Itraconazole, anti-human immunodeficiency virus-1 (HIV-1) drug Saquinavir, anti-coagulant drug Dabigatran, and diuretic drug Canrenoic acid could act as potential coronavirus helicase inhibitors with high mfScores. 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 K_d (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′-O-MTase, 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 Efavirenze 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, Lomibuvir, Asunaprevir, Ribavirin, and Simeprevir), HBV (Entecavir), HSV (Penciclovir), CMV (Ganciclovir), and Ebola (Remdesivir), anticoagulant drug (Dabigatran), and an antifungal 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 (EC_{50}) 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 EC_{50} (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 C_{trough}/EC_{50} 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 EC_{50} and the highest SI as well as the C_{trough}/EC_{50} ratio higher than one.

Because of the absence of any effect of Darunavir on SARS-CoV cultured 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 (EC_{50} = 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	Mpro	PLVP	RdRp	Helicase	3'to5'exonuclease (127)	2'-OMTase	EndoRNAse (127)	Spike	Total
Elbasvir	(130, 141)								3
Amprenavir	(128, 141)								3
Ledipasvir	(129, 141)								2
fosamprenavir	(128, 141)								2
Tipranavir	(128, 141)								2
Sofosbuvir		(129, 131)							2
Paritaprevir	(125, 135)								2
Favipiravir Reported by (144), without a specific target.			(128)						2
Beclabuvir, Nilotinib, Tadalafil, Lifitegrast, Digitoxin, Tirilazad, Digoxin	(141)								1
Galidesivir			(128)						1
Hydroxychloroquine	(133)								1
Trifluridine, Lamivudine			(127)						1
Prulifloxacin Tegobuvir	(136)								1
Norvir	(139)								1
Rolitetracycline, Canrenoic acid				(144)					1
Rescinnamine, Iloprost, Prazocin, Posaconazole, Azlocillin, Penicillin,								(144)	1
Fludarabine, Cefuroxime, Atovaquone, Chenodeoxycholic acid, Cromolyn, Pancuronium bromide, Cortisone, Tibolone, Novobiocin, Idarubicin, Bromocriptine, Diphenoxylate, Benzylpenicilloyl G,			(144)						1
, Alfuzosin, Cilastatin, Famotidine, Almitrine, Progabide, Nepafenac, Carvedilol, Demeclocycline, Montelukast, Carminic acid, Mimosine, Flavin mononucleotide, Lutein, Cefpiramide, Phenethicillin, Candoxatril, Nicardipine, Estradiol valerate, Pioglitazone, Conivaptan, Telmisartan, Doxycycline, Oxytetracycline	(144)								1
beta-Thymidine, Aspartame, Oxprenolol, Doxycycline, Acetophenazine, Ipromide, Riboflavin, Reproterol, 2,2′-Cyclocytidine, Chloramphenicol, Chlorphenesin carbamate, Levodropropizine, Cefamandole, Floxuridine, Pemetrexed, L(+)-Ascorbic acid, Glutathione, Hesperetin, Ademetionine, Masoprocol, Isotretinoin, Dantrolene, Nicardipine, Sildenafil		(144)							1
Pitavastatin, Perampanel, Praziquantel, eszopiclone, and zopiclone	(159)								1
Carfilzomib, Eravacycline, Valrubicin, Charged molecules: Streptomycin, Flavin adenine dinucleotide, Oftasceine	(161)								1
CMK, AG7088 (Rupintrivir	(142)								1
Pemirolast, Isoniazid pyruvate, Nitrofurantin, Eriodictyol								(140)	1
Bortezomib, Flurazepam, Ponatinib, Sorafenib, Dasatinib, Paramethasone, Clocortolone, Flucloxacillin, Sertinadole, Clevidipine, Aprepitant, Atorvastatin, Cinolazepam, Clofazimine, Fosaprepitant	(138)								1
PX-12, Shikonin, TDZD-8, Tideglusib, Carmofur, Ebselen, Disulfiram	(134)								1
Piclitaxel, Docetaxel, Palbociclib, Cabazitaxel, Alectinib, Imatinib, Plerixafor, Azelastine, Dasabuvir, , Captopril, Enalapril,	(133)								1
GRL-0667, GRL-0617, and Mycophenolic acid		(132)							1
Caspofungin acetate, Salmeterol xinafoate,	(130)								1

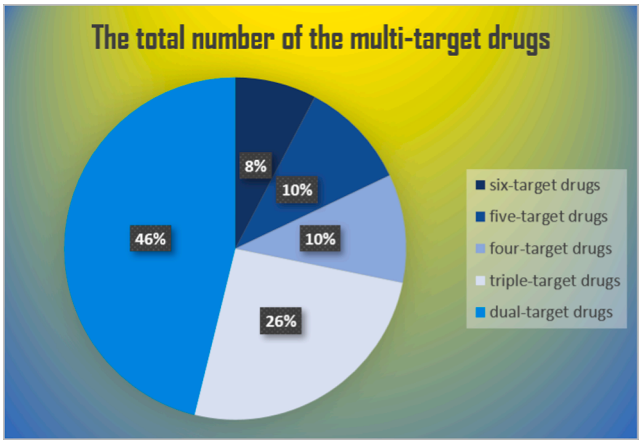

Fig. 3. The distribution of multi-target drugs for COVID-19.

respectively. It was reduced to 22.50 μM for Nafamostat and 2.12 for Nitazoxanide. Two drugs could have a powerful effect on SARS-CoV2 replication at low doses: Remdesivir and Chloroquine associated with EC_{50} (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 system, and if we consider the matter of time, computational methods are our best shots. Since the incidence of this outbreak, many investigations have been conducted to present an appropriate therapeutic agent for COVID-19 utilizing computation drug repurposing approaches. Therefore, the review intended to cover all these studies to help build a concise framework for future research into COVID-19 therapy.

All methods have inherent limitations, and computational methods are not exceptional in this field. Thus, the use of models –which are illustrations of the real world- in running computational research, might be an inherent limitation. Besides, the results reported by docking score, binding energy, binding affinity, and other numerical variants were immensely divergent across twenty-one studies included in the review. Having the fact in mind that there is not any specific tool for quality assessment and comparison of computational repurposing methods; it would not be possible to evaluate the potential candidates from different studies to declare which is more significant.

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

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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. N.R. supervised the project and critically appraised the manuscript.

Declaration of Competing Interest

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

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