

Emerging role of artificial intelligence in therapeutics for COVID-19: a systematic review

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ABSTRACT

To elucidate the role of artificial intelligence (AI) in therapeutics for coronavirus disease 2019 (COVID-19). Five databases were searched (December 2019–May 2020). We included both published and pre-print original articles in English that applied AI, machine learning or deep learning in drug repurposing, novel drug discovery, vaccine and antibody development for COVID-19. Out of 31 studies included, 16 studies applied AI for drug repurposing, whereas 10 studies utilized AI for novel drug discovery. Only four studies used AI technology for vaccine development, whereas one study generated stable antibodies against SARS-CoV-2. Approx. 50% of studies exclusively targeted 3CLpro of SARS-CoV-2, and only two studies targeted ACE/TMPSS2 for inhibiting host viral interactions. Around 16% of the identified drugs are in different phases of clinical evaluation against COVID-19. AI has emerged as a promising solution of COVID-19 therapeutics. During this current pandemic, many of the researchers have used AI-based strategies to process large databases in a more customized manner leading to the faster identification of several potential targets, novel/repurposing of drugs and vaccine candidates. A number of these drugs are either approved or are in a late-stage clinical trial and are potentially effective against SARS-CoV2 indicating validity of the methodology. However, as the use of AI-based screening program is currently in budding stage, sole reliance on such algorithms is not advisable at this current point of time and an evidence based approach is warranted to confirm their usefulness against this life-threatening disease.

Abbreviations: ACE2: angiotensin-converting enzyme 2; AI: artificial intelligence; COVID-19: coronavirus disease 19; COBP2: β 2 subunit of the coatomer protein complex; DL: deep learning; IC50: half maximal inhibitory concentration; HCV: hepatitis C virus; HBV: hepatitis B virus; HIV/AIDS: human immunodeficiency virus/acquired immunodeficiency syndrome; HRCE: human renal cortical epithelial cells; HR1: heptad repeat 1; HSV: herpes simplex virus; LINC: Library of Integrated Network-Based Cellular Signatures; ML: machine learning; MT-DTI: molecule transformer-drug target interaction; nsp: non-structural protein; PBMC: peripheral blood mononuclear cells; PLP: papain like protease; RdRp: RNA dependent RNA polymerase; RBD: receptor-binding domain; SARS-CoV: severe acute respiratory syndrome coronavirus; SARS-CoV-2: severe acute respiratory syndrome coronavirus; SMILE: Simplified Molecular-Input Line-Entry System; TMPRSS2: transmembrane protease serine 2; PPIases: peptidylprolyl-cis-trans isomerase; μ M: micromolar; 2019-nCoV: 2019 novel coronavirus; 3CLpro: 3-chymotrypsin-like protease

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Introduction

As the COVID-19 pandemic unfolds, the numbers of infections and deaths are increasing at an alarming rate. According to Johns Hopkins Coronavirus map tracker, more than 25,558,059 people have been infected by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and as much as 860,311 people have been reported dead by September 1, 2020 (John Hopkins University and Medicine, 2020). While diagnostic capabilities for COVID-19 have escalated considerably, the therapeutic developments are still onerous. Scientists and clinicians are desperately looking for effective therapeutic measures by designing either direct-acting antiviral agents against the target proteins in SARS-CoV-2

or host-targeting antivirals that modulate host factors (Nitulescu et al., 2020). Ongoing novel drug discovery and vaccine development programs are time-taking as well as incredibly complex processes. Meanwhile, drug repurposing of antiviral drugs and other already approved drugs (or those in advance clinical trials) is also being investigated for dealing with COVID-19 (Harrison, 2020).

Computational methods like molecular docking and molecular dynamics are being increasingly utilized to identify synthetic and natural drug candidates against the target protein of SARS-CoV-2. Synthetic or natural compounds from vast chemical libraries can be scrutinized for their ability to bind to the appropriate pharmacophores/active sites of the

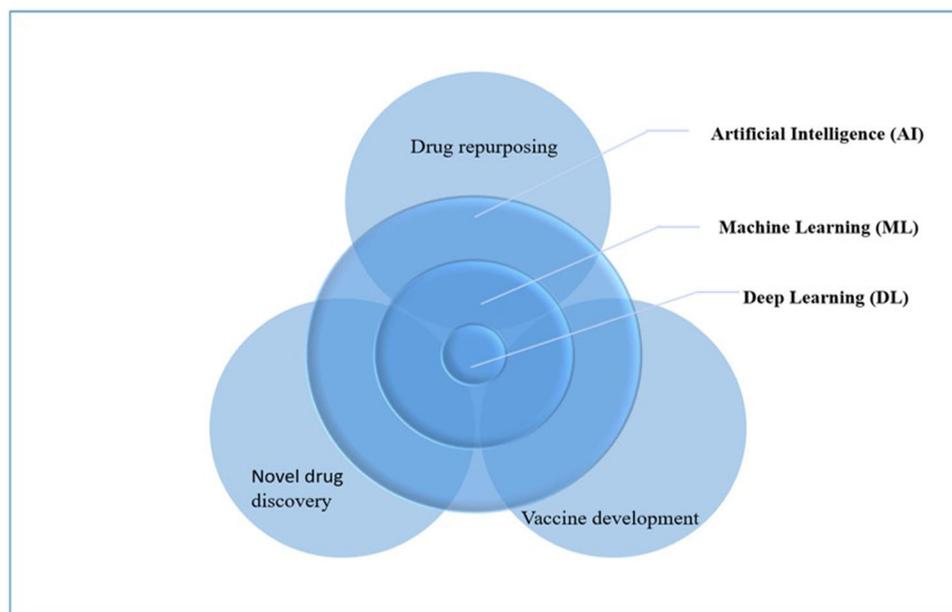


Figure 1. Artificial intelligence (AI) is the general ability of machines to perform tasks that generally require human intelligence such as to perceive, recognize, reason, plan, or to take action. ML is a subset of AI that involves the capabilities of machines to learn from data without explicit programming. Further, a subset of ML methods called DL, uses artificial neural networks to determine more complex structures and pattern data. These AI systems are employed for drug repurposing of already approved drugs, for novel drugs discovery and vaccine development for COVID-19 therapeutics.

targets (Pinzi & Rastelli, 2019). Binding poses are ranked by a mathematical predictive model making use of molecular docking and generating a score of binding free energy predicting stability of complex molecule (Bishop, 2013). Molecular dynamics simulations are applied to understand the properties of assemblies of molecules in terms of their 3D structure and the microscopic interactions between them (Nair & Miners, 2014). Recently, artificial intelligence (AI) has drawn substantial attention in the field of drug and vaccine development as it promises to accelerate these processes and reduce costs by facilitating the rapid identification of the compound (Zhavoronkov et al., 2019). It is being increasingly employed to explore virtually unlimited chemical space and develop novel small molecules with desired biological and physicochemical properties (Popova et al., 2018; Stokes et al., 2020). AI-based deep learning (DL) methods have shown promising results on protein–ligand binding prediction (Zhang et al., 2019). Advantages of AI-based approaches are that they can automatically learn to recognize intricate patterns from the input data and create predictive models even when our understanding of the underlying biological processes is limited (Bishop, 2013). Also, the learning algorithms can become more precise and accurate as they interact with training data, allowing us to get insights at an unprecedented rate (Mak & Pichika, 2019). A brief detail of AI system and its application in COVID-19 therapeutics is given in Figure 1. AI is the general ability of machines to perform tasks that generally require human intelligence such as to perceive, recognize, reason, plan or to take action. Machine learning (ML) is a subtype of AI focused on developing algorithms that can identify patterns within data without explicit specification. These algorithms can be classified into supervised and unsupervised learning. In supervised ML, the algorithm is trained on a human-labelled training data, then the algorithm provides classification or regression on unlabelled

data. In unsupervised ML, algorithms identify hidden patterns for unlabelled data (Réda et al., 2020). DL is a subtype of ML that uses neural network with many hidden layers (apart from the input and output layer) to extract features from raw data. DL permits machines to take care of complex issues in any event, when utilizing an informational index that is exceptionally differing and unstructured. The more DL calculations learn, the better they perform (Mohanty et al., 2020). For novel drug discovery or drug repurposing, various drug database provide input to the model. Different algorithms could be applied to the input and the required drug could be obtained. There has been a sudden recent surge in the number of studies on the therapeutic developments on COVID-19 through AI-based approaches. The scale and pace of data production is posing a challenge for organizations to effectively apprehend valuable insights from massive amounts of information and diverse sources. In this systematic review, we summarize the findings of all relevant individual studies that have applied AI & ML technology in therapeutics for COVID-19, thereby making the available evidence more accessible to decision-makers as a preliminary solution to the problem.

Methods

We prepared this review according to the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) statement (Moher et al., 2009).

Objective

To evaluate the role of AI in drug repurposing, novel drug discovery, vaccine and antibody development for the therapeutics of COVID-19.

Search strategy

We undertook a systematic search in five databases, including PubMed, Google Scholar, Embase, Oxford and Elsevier. The search terms and keywords included the following terms for the disease; 'Novel coronavirus' OR '2019-nCoV', OR 'COVID-19', OR 'SARS-CoV-2', AND 'Artificial intelligence' OR 'Machine learning', OR 'Deep learning' without any limitations on publication type. Additionally, to make the results more comprehensive, we also screened the reference list in each of the selected articles. Articles from search result were downloaded and imported into Mendeley reference management software.

Study selection

Inclusion criteria: The present systematic review included original articles in English that applied AI-based strategies for COVID-19 therapeutics. Eligible studies should discover novel drugs or repurpose EMA/FDA approved drugs or drugs from other public databases by utilizing AI-based methods. Studies that discovered candidate vaccine for COVID-19 and studies that found antibodies against SARS-CoV-2 by using AI-based strategies were also included in the study.

Exclusion criteria: Studies that discovered novel or approved drugs or vaccine by without using AI, ML or DL or those utilizing AI-based techniques only for structural prediction of SARS-CoV-2 proteins were excluded. Also, studies utilizing only molecular docking and molecular simulation techniques for drug discovery are not part of this review.

By considering the above criteria, two authors (KK and PS) 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 an agreement, they consulted third author (MN).

Data extraction

The first two reviewers (KK and PS) extracted the following data from each included publication: the first author, time of publication, country of origin, drug discovery method, drug repurposing method, the resource for approved drugs, the AI tool, coronavirus strain, target structures, candidate therapeutic agents and the authors' conclusions. Discrepancies were resolved through a consensus discussion.

Quality assessment

The idea of bias in AI-based drug research studies is slowly being established. Several recent studies claim that apart from helping overcome the inefficiencies and uncertainties of the traditional drug development methods, AI also minimizes bias and human intervention in the process (Hessler & Baringhaus, 2018; Seddon et al., 2012). Supervised models allow better control over data selection but are vulnerable to introduce human bias into the process. Whereas, unsupervised models are susceptible to learn bias from their data set

and are restricted by the quality of the inputs, that is, the data that it learns from (Nogrady, 2019). Apart from good quality data, high accuracy of identification also depends upon the amount of training data and higher amount of training data can lead to a good predictive model. With minimal data, the ML models cannot achieve an unbiased estimate of the generalization (Winkler & Le, 2017). These statements have helped us to learn that supervised and unsupervised learning models have their respective pros and cons. According to the potential issues of bias, a tool was designed for the assessment of four main aspects of quality of studies included in the present systematic review: model selection (is it unique for every target – yes/no), model optimization (does training data represents different groups – yes/no), model validation (performance monitoring using real data) (yes/no) and docking tools, molecular dynamics simulation (yes/no). The quality of each eligible article was independently appraised by two authors (KK and PS) and then was double-checked by the third author (MN).

Results

Study selection

There were 1078 studies retrieved from the database search, of which 901 papers remained after the removal of duplicates. We conducted title and abstract screening on these 901 articles and nominated 105 of them for detailed review. After full-text evaluation, we excluded 82 studies considering the inclusion and exclusion criteria. Excluded studies had diverse reasons like not regarded as original research ($n=42$), studies applying computational methods other than AI-based ($n=32$), studies reporting drugs against targets other than the SARS-CoV2 ($n=3$), studies not published in full-text articles ($n=1$), non-English articles ($n=2$). Eight studies were included after reviewing the cross-references. Finally, 31 articles which fulfilled the inclusion/exclusion criteria were included in the systematic review. The Prisma flow chart of the included studies is shown in Figure 2.

Details of the included studies

As summarized in Table 1, there were variations across studies in terms of AI tools, methods/techniques, software used and targets studied. The majority (52%) of the studies applied AI for drug repurposing ($n=16$), whereas 32% of studies utilized AI for novel drug discovery ($n=10$). Only four studies used AI technology for vaccine development, whereas one study generated stable antibodies against SARS-CoV-2 using AI (Figure 3). Among the drug repurposing category, six studies used AI for prediction of ligand binding affinities, five studies used AI in conjunction with molecular docking and molecular dynamics studies. Whereas six studies utilized AI for gene expression studies, knowledge graph studies and cell image analysis (two each). Almost all of the drug repurposing studies used either FDA/EMA approved drugs or drugs that are already in clinical trials. For approx. 50% of studies, 3CLpro has been a target of choice, wherein

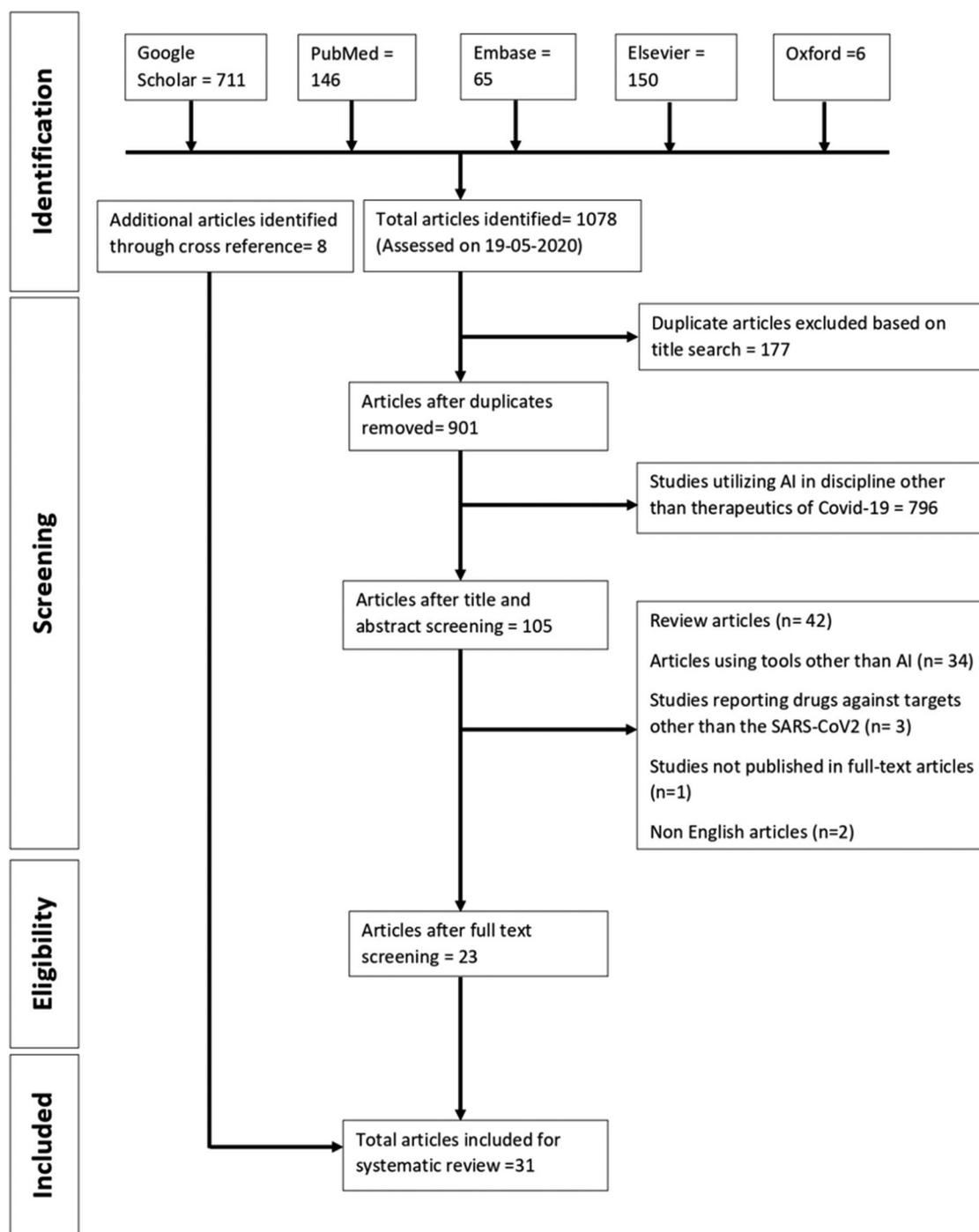


Figure 2. PRISMA flow diagram for the systematic review of role of artificial intelligence in therapeutics for COVID-19. The flow diagram template is adapted from the PRISMA statement.

nine studies solely targeted 3CLpro and four studies had 3CLpro in combination with other targets of SARS-CoV-2. Overall, only three studies aimed ACE/TMPSS2 receptor for inhibiting host viral interactions. Table 2 gives detail of a target-wise categorization of identified drugs for COVID-19. Only three out of 31 studies performed *in vivo* experiments using a human cell line, and one study has worked on the animal model. Five studies either screened natural compounds against SARS-CoV-2 proteins or compared novel potential drug candidates with natural compounds. Geographical distribution analysis of the research articles was

done by considering the country of origin of the first author. The study revealed that out of a total of 11 countries, more than 50% of the articles are published from only two countries: the USA, China (Table 3).

Discussion

Widespread research efforts are being made to address COVID-19 treatment. Figure 3 shows the time trend (from 01 December 2019 to 19 May 2020) of studies using AI for

Table 1. Summary of artificial intelligence-based studies for therapeutics of COVID-19.

Author Country	AI tool	Method/protocol	No. of drugs and database screened	Target(s)	Top-ranked promising candidate drug(s)/molecule(s)
Beck et al. (2020) Republic of Korea	Molecule transformer-drug target interaction (MT-DTI)	Binding affinity values prediction based on chemical sequences (SMILES) and amino acid sequences (FASTA) of target proteins	3410 binding DB, (FDA-approved drugs)	3CL pro, Helicase, EndoRNase, RdRp, 3'-exonuclease, EndoRNase 2'-O-ribose methyltransferase	Atazanavir, Remdesivir, Efavirenz, Ritonavir, Dolutegravir, Lopinavir, Darunavir, Asunaprevir, Tiotropium-bromide, Daclatasvir, Grazoprevir, Ganciclovir, Simeprevir, Dolutegravir
Hu et al. (2020) China	Multi-task neural network	Homology modelling, estimation of binding affinity (pKa) between drug and target	4895 commercial drugs, Global Health Drug Discovery Institute (GHDDI)	RdRp, 3CLpro, PLpro, helicase, S protein, E protein, 3'-exonuclease, EndoRNase, 2'-O-ribose methyltransferase	Abacavir Darunavir, Almitrine mesylate, Roflumilast, Itraconazole, Daclatasvir, Metoprolol tartrate, Fibroflapon sodium
Zhang et al. (2020) China	DFCNN (dense fully convolutional neural network)	Homology modelling Identification and ranking of protein-ligand interactions by virtual drug screening	Chimdiv, PDBbind, Targetmol-approved, natural compound & bioactive compound libraries	3CLpro	Meglumine, Ganciclovir, Vidarabine, Adenosine, Mannitol, Dulcitol, D-Sorbitol, D-Mannitol, Sodium gluconate, Vidarabine, 5'Deoxy-adenosine, IKP-Tri-amino acid peptide
Kim et al. (2020) USA	Fluency (AI platform), Disease Cancelling Technology platform	Binding prediction analysis Gene expression analysis	657 drugs, Selleckchem FDA approved drug library	ACE2, TMPRSS2	Fosamprenavir, Emricasan, Piperacillin, Glutathione, Glutamine, Brigatinib, Tirofiban Hydrochloride, Aleuritic acid, Ombitasvir, Elbasvir, Capecitabine, Cefotiam Hexetil hydrochloride, Bictegravir
Ke et al. (2020) Taiwan	Deep-neural network (DNN)	Generation of AI prediction models, Prediction of potential inhibitor, cell-based FIP virus replication assay	2684 drugs, DrugBank	3CL pro	Bedaquiline, Brequinar, Celecoxib, Clofazimine, Conivaptan, Gemcitabine, Tolcapone, Vismodegib
Batra et al. (2020) USA	ML-based models and high-fidelity ensemble docking simulations	Random forest algorithm on SMILES data to predict docking simulation scores	(1500) CureFFI, (4000) DrugCe-ntral (FDA approved drugs) Binding DB, (19,000)	S protein, S protein-ACE2 interface complex	Pemirolast, Sulfamethoxazole, Valaciclovir, Sulfanilamide, Tzaobactam, Nitrofurantoin, A rank-ordered list of 75 promising candidates
Mahapatra et al. (2020) India	ML model based on the Naïve Bayes algorithm	Ranking based on various binding energy function	4900 Drugs, DrugBank, (including FDA approved drugs)	3CLpro	Atazanavir, Paritaprevir, Saquinavir, Ritonavir, Amprenavir, Indinavir, Fosamprenavir, Lopinavir, Darunavir, Tipranavir
Kadioglu Mshjgte (2020) Germany	Supervised machine learning with neural network & Naïve Bayes algorithm	Homology modelling, compound databases construction, virtual drug screening, molecular docking, drug-likeness study	40,000 compounds, ZINC (including 1577 FDA-approved drugs and natural compounds)	S protein, N protein, 2'-o-ribose methyltransferase protein	Paritaprevir, Simeprevir, Grazoprevir, Velpatasvir, Teniposide, Ergotamine, Venetoclax, Rifapentine, Rifabutin, Nilotinib, Telithromycin, Lumacaftor, Venetoclax, Posaconazole, Ergotamine
Karki et al. (2020) USA	Deep-neural network-based machine learning algorithm	Prediction of drug binding with half maximal inhibitory concentrations, validation by drug docking algorithm	750,000 compounds from BindingDB, ZINC, SANC, NuBBE (including FDA approved drugs)	ACE2 receptor open, closed, and a closed conformation in complex with the S protein	Glecaprevir, Velpatasvir, Remdesivir, Rifamycin, Oritavancin, Vancomycin, Grazoprevir, Velpatasvir,
Avchaciov et al. (2020) Singapore	Deep-neural network	Mining of gene expression signatures for drugs with potential activity against coronavirus	27,870 unique molecular perturbation	Gene expression signatures similar to COBP2 gene knockdown	Niclosamide, Nitazoxanide, Brefeldin A, Afatinib, Ixazomib, Reserpine

(continued)

Table 1. Continued.

Author Country	AI tool	Method/protocol	No. of drugs and database screened	Target(s)	Top-ranked promising candidate drug(s)/molecule(s)
Zhu et al., (2020) China	Infinity Phenotype (deep-neural network)	Analysis of transcriptional changes induced by various compounds	3682 (FDA approved drugs and natural products library)	Negative regulation of viral genome	Liquiritin, (natural product) Procaterol, Pibrentasvir Carbocisteine
Richardson et al. (2020) United Kingdom	BenevolentAI	Medical knowledge graph	378 AAK1 inhibitors in BenevolentAI knowledge graph	AP2-associated protein kinase 1 (AAK1)	Baricitinib
Ge et al. (2020) China	Data-driven drug repositioning framework	Construction of the virus-related knowledge graph, network-based knowledge mining algorithm	6225 drugs (approved, investigational & experimental drugs) DrugBank, ChEMBL, BlindindDB, GHDDI	N-terminal domain of Nucleocapsid (NTD) protein	CVL218 (PARP1 inhibitor)
Heiseret al. (2019) USA	Artificial intelligence-enabled phenomic analysis	Chemical suppressor screening for phenomic profiling of perturbed cells	1670 compounds (FDA/EMA approved & late-stage clinical trials drugs)	Phenomic profiles of SARS-CoV-2 infected human cells	Remdesivir
Han et al. (2020) China	Information-theoretic metric learning (ITML) algorithm	Image data analysis of drugs acting on cells	1105 image data encompassing cell responses to 372 drugs	Mode of action of the drugs	Chloroquine and Hydroxychloroquine
Martyna et al. (2020) USA	Convolutional Neural Network (CNN)	Molecular similarity in terms of 3D features. Estimated shape representation	6000 small molecules from the ZINC database	Identification of progeny drugs	1634 ZINC drugs, 808 Phase 3 drugs, and 2014 Phase 4 ones
Ton et al. (2020) Canada	Deep Docking (deep learning platform)	Docking score prediction for structure-based virtual screening	1.3 billion compounds from	Active site of 3CLpro	1000 potential ligands identified
Bung et al. (2020) India	Deep-neural network-based generative and predictive models	Smiles representation, generative model using transfer learning, reinforcement learning, virtual screening analysis	1.6 million drug-like small molecules from the ChEMBL database	3CL pro	31 novel drug-like small molecules including 2 structurally similar compound to natural compound 'Aurantiamide'
Zhavoronkov et al. (2020) China	Generative deep learning pipeline	Homology modelling, protease database assembly, co-crystalized fragment	5891, Integrity, ChEMBL, Experimental Pharmacology module and Protegen database	3CL pro	Most recent data package is available at insilico.com/ncov-sprint
Hofmarcher et al. (2020) Austria	ChemAI (deep-neural network)	Prediction of inhibitory effects on viral proteases, Calculation of consensus score for each drug	3.6 million molecules, ZINC and Drugbank	3CLpro, PLpro	A library of top-ranked 30,000 potential CoV-2 inhibitors
Tang et al. (2020) China	Advanced deep Q-learning network with the fragment-based drug design (ADQN-FBDD)	Collection of antiviral agents, split structure, Collection of fragments, ADQN-FBDD, structure-based optimization, molecular docking	284 3CLpro inhibitors from literature review	3CLpro	47 targeted covalent inhibitors
Verma (2020) India	Advanced deep Q-learning network with the fragment-based drug design (ADQN-FBDD)	Variational Autoencoder for molecules generation	Existing FDA approved inhibitors of 3CLpro	3CL pro	10 novel potential inhibitor molecules
Gao et al. (2020) USA	Generative network complex (GNC) with 2D fingerprint based deep-neural network, MathPose, MathDL	Novel molecules generation in terms of SMILES strings, evaluation of druggable properties, 3D structure prediction, estimation of biological properties	ChEMBL, PDBbind	3CL pro	Lopinavir Ritonavir (>15 novel therapeutic candidates identified)
Chenthamarakshan et al. (2020) Singapore	CogMol (deep learning based generative modelling framework)	SMILES, Variational Autoencoder training, Attribute regression modelling attribute-	BindingDB, ZINC	NSP9, Replicase, 3CLpro, RBD	1000 novel drug candidates

(continued)

Table 1. Continued.

Author Country	AI tool	Method/protocol	No. of drugs and database screened	Target(s)	Top-ranked promising candidate drug(s)/molecule(s)
Savioli (2020) United Kingdom	Siamese neural network (SNN)	conditioned molecular generation Virus genome conversion into protein, Splitting of the protein sequence, conversion of filaments peptide to image, Peptide comparisons with SNN	3027 peptides from SATPdb database	HR1 domain on the S protein	PPLases peptide
Gysi et al. (2020) USA	AI-Net (artificial intelligence network)	Network-based <i>in silico</i> drug efficacy screening.	DrugBank (FDA approved drugs)	To perturb the network of the COVID-19 disease module.	Carfilzomi, flutamide, Bortezomib, Mitoxantrone, Ponatinib, list of 81 candidates
Fast et al. (2020) USA	NetMHCpan4 & MARIA (two artificial neural network algorithms)	Antigen presentation prediction, Identification and validation of epitopes	SARS-CoV-2 genome codes for S, M, E, N proteins and least 6 other open reading frames (ORFs)	Identification of potential T-cell and B-cell epitopes	405 potential T-cell epitopes that can be presented by MHC-I and MHC-II, two B-cell epitopes on S protein
Prachar et al. (2020)(60) Denmark	PrdX (feed-forward neural network)	HLA-binding prediction, in vitro peptide MHC stability assay	Assessed 777 peptides	11 HLA allotypes	174 SARS-CoV-2 epitopes
Malone et al. (2020) USA	NEC Immune Profiler suite of tools	Host-infected cell surface antigen presentation and immunogenicity prediction, epitope maps generation	Entire SARS-CoV-2 proteome	Profiling across the most frequent 100 HLA-A, HLA-B and HLA-DR alleles	Identified epitope hotspots for vaccine formulation
Ong et al. (2020) USA	Vaxign-ML machine learning tool	ML model training using bacterial and viral protective antigens, Proteins annotation, antigenicity scoring	Protegen, Uniprot, proteomes	SARS-CoV-2 proteome	S protein, nsp3, 3CL-pro, nsp8, nsp9 and nsp10 predicted to be vaccine candidates
Magar et al. (2020) USA	High throughput deep model (with MD simulation, bioinformatics and structural biology tools)	Potential epitope prediction (netMHC) MHC:Peptide complex stability assay (NeoScreen)	1933 virus-antibody sequences (IEDB)	SARS-Cov-2	Eight stable antibodies

COVID-19 therapeutics. We hereby discuss the application of AI in drug repurposing, novel drug development and vaccine development against SARS-CoV-2.

Role of AI for the repositioning of approved or investigational drugs for COVID-19 therapeutics

A considerable advantage of repositioning (repurposing) FDA approved drugs is that their toxicity profile and pharmacokinetics are well established in human beings besides a relatively smooth regulatory application/approval process. This review has revealed that most of the AI mediated efforts for therapeutics of COVID-19 aim at drug repurposing using a diverse range of strategies, including prediction of interactions between ligands and proteins, enhancing molecular docking simulations, gene expression signatures analysis and others as mentioned below.

AI for prediction of protein–ligand binding affinities

Several studies attempted for AI mediated prediction of the strength of binding interaction between approved drugs and target proteins of SARS-CoV-2. Beck et al. employed a DL-

based drug-target interaction model called Molecule Transfer Drug Target Interaction (MT-DTI) to screen FDA approved antivirals that can effectively target six SARS-CoV-2 related proteins (3CLpro, RdRp, helicase, endoRNAase, 3'-5' exonuclease and 2'-O-ribose-methyltransferase). The MT-DTI model predicted that Atazanavir, an anti-retroviral drug used to treat and prevent HIV, has the highest inhibitory potency against 3CLpro followed by Remdesivir, Efavirenz, ritonavir and Dolutegravir. Additionally, MT-DTI model also predicted that viral proteinases inhibitors Lopinavir, ritonavir and Darunavir have an affinity towards the replication complex components of SARS-CoV-2 with an inhibitory potency. Interestingly, several other drugs, including Tiotropium bromide, a medicine for asthma and chronic obstructive pulmonary disease were also predicted to be a potential anti-COVID-19 candidate by MT-DTI (Beck et al., 2020). Similarly, one more study predicted that drugs for the treatment of respiratory diseases, that is, Almitrine mesylate and Roflumilast have an inhibitory effect on coronavirus (Hu et al., 2020). These findings are significant as respiratory failure is a well-known complication of severe cases of COVID-19. To screen 4895 commercially available drugs against sequence of amino acid of eight SARS-CoV-2 protein targets (Table 1), Hu

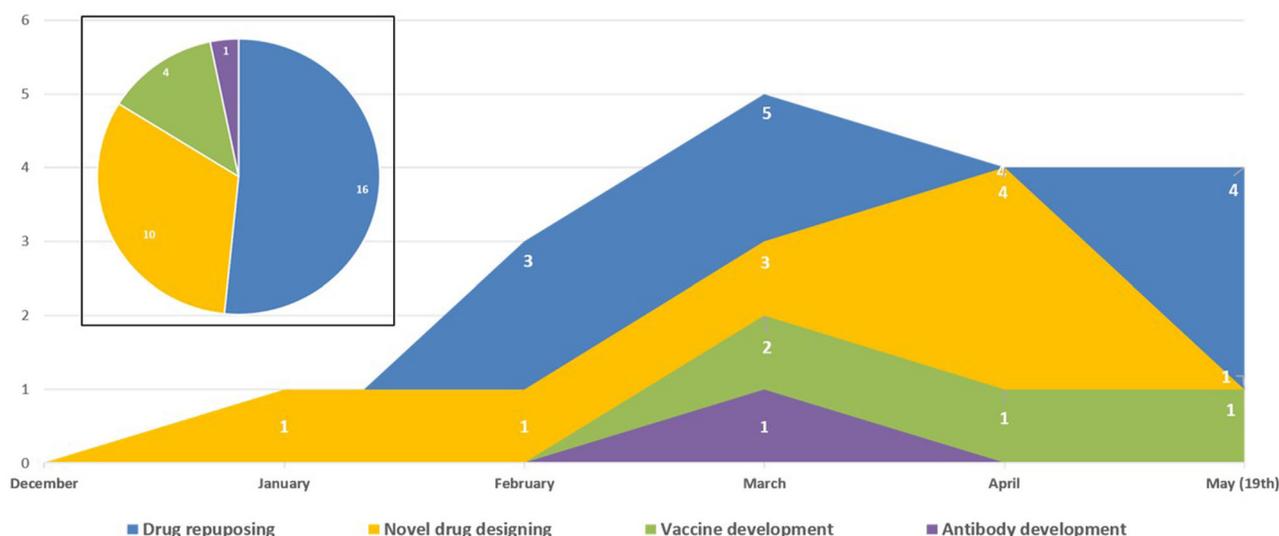


Figure 3. Number of articles using artificial intelligence per therapeutic approach and trend of articles over time. Majority (52%) of the studies applied AI for drug repurposing ($n = 16$) whereas 32% studies utilized AI for novel drug discovery ($n = 10$). Four studies used AI for vaccine development whereas one study generated stable antibodies against SARS-CoV-2 using AI (inset). Figure shows the time trend and number of studies utilizing AI for drug repurposing, novel drug design and vaccine development for COVID-19 therapeutics from 01 December 2019 to 19 May 2020.

Table 2. Target-wise categorization of identified drugs through AI for COVID-19 therapeutics.

Target	Drugs
3CLpro	Atazanavir, Remdesivir, Efavirenz, Abacavir, Darunavir, Almitrine mesylate, Roflumilast, Meglumine, Ganciclovir, Vidarabine Adenosine, Dulcitol, D-Sorbitol, D-Mannitol, Sodium gluconate, Vidarabine, 5'Deoxy-adenosine, IKP-Tri-amino acid peptide, Bedaquiline, Brequinar, Celecoxib, Clofazimine, Conivaptan, Gemcitabine, Tolcapone, Vismodegib, Paritaprevir, Saquinavir, Ritonavir, Amprenavir, Indinavir, Fosamprenavir, Lopinavir, Tipranavi, Paritaprevir, Fosamprenavir
PLpro	Abacavir, Darunavir, Itraconazole, Metoprolol tartrate, Fiboflapon sodium
S protein	Pemirolast, Sulfamethoxazole, Valaciclovir, Sulfanilamide, Tzaobactum, Nitrofurantoin, Protirelin, Benserazide, Sulfaperin
Helicase	Remdesivir, Daclatasvir, Abacavir
RdRp	Grazoprevir, Ganciclovir, Remdesivir, Atazanavir, Abacavir, Darunavir, Almitrine mesylate, Itraconazole, Daclatasvir
3'-5'Exonuclease	Simeprevir, Efavirenz, Remdesivir
EndoRNase	Efavirenz, Atazanavir, Asunaprevir
2'-O-ribose methyltransferase	Remdesivir, Dolutegravir, Atazanavir, Efavirenz, Nilotinib, Telithromycin, Posaconazole, Ergotamine, Lumacaftor, Venetoclax
N-protein	Ergotamine, Venetoclax, Rifapentine, Rifabutin, CVL218 (PARP1 inhibitor)
ACE2	Fosamprenavir, Emricasan, Piperacillin, Glutathione, Glutamine, Brigatinib, Tirofiban Hydrochloride, Aleuritic acid, Glecaprevir, Velpatasvir, Remdesivir, Rifamycin, Oritavancin, Vancomycin, Grazoprevir, Velpatasvir
TMPPSS2	Ombitasvir, Elbasvir, Capecitabine, Cefotiam, Hexetil hydrochloride, Bictegravir

Table 3. Country-wise distribution of studies employing AI in COVID-19 therapeutics.

Country	Publications (n)
USA	11
China	7
India	3
Germany	1
Singapore	2
United Kingdom	2
Taiwan	1
Austria	1
Canada	1
Denmark	1
Republic of Korea	1

et al. fine-tuned a multi-task deep model by using coronavirus-specific datasets and predicted 10 potential inhibitors that can be effective against SARS-CoV-2 infection (Table 1). Abacavir is a known nucleoside analogue and is predicted to possess a high-binding affinity towards RdRp, 3CLpro, PLpro and helicase, whereas Darunavir, a protease inhibitor is

predicted to have an affinity with 3CLpro, RdRp and PLpro of SARS-Cov-2 (Hu et al., 2020).

Zhang et al. employed a DL method, that is, Dense Fully Convolutional Neural Network (DFCNN), for large-scale virtual screening of approx. 1000,000 drug-like compounds from ChemDiv dataset. A list of top 100 predictions that can potentially inhibit 3CLpro of SARS-CoV-2 is rolled out. Likewise, DFCNN was also applied to screen three other Targetmol compound libraries. Table 1 shows top predictions among the approved drugs natural compounds and bio-active compounds that can inhibit 3CLpro of SARS-CoV-2.

Finally, using DFCN, authors performed a virtual screening against a peptide database containing 8000 tri-peptides. They discovered that the tri-peptides formed by isoleucine, lysine and proline amino acids exhibit maximum affinity for 3CLpro binding site (Zhang et al., 2020). Bioactive compounds have been intensively studied in the prevention and treatment of various diseases (Teodoro, 2019). The natural products are relatively safe, whereas small peptides can be easily synthesized, have better stability, negligible

immunogenicity, higher binding affinity and better specificity than smaller compounds (Krujlec & Bratkovič, 2017). These qualities make it worth to check whether any of these molecules can combat SARS-CoV-2 by inhibiting 3CLpro.

In another study, the authors used an AI-based binding affinity prediction platform for screening 657 FDA approved drugs by their potential affinity towards ACE2. They predicted a strong affinity between ACE2 and various drugs, including a beta-lactam antibiotic (Piperacillin), two antiviral agents (Fosamprenavir and Emtricitabine) and glutathione. Although Hydroxychloroquine was predicted to bind to ACE2 but several potential therapeutic agents for COVID-19 viz. Azithromycin and various anti-IL-6 agents showed no affinity (Kim et al., 2020). In a different set of experiments, authors, also screened FDA approved drugs that can down-regulate the gene expression patterns induced by coronaviruses. SARS-CoV infected animal model-based study revealed that glutamine has a very high potential antiviral activity by reversing coronavirus associated changes in gene expression. These results are in line with previous studies demonstrating antiviral activity of both glutathione and glutamine against herpes virus infections (Palamara et al., 1995). Ke et al. used an AI system trained on antiviral drugs and 3CLpro like protease inhibitors and predicted a list of potential compounds active against coronavirus. When analyzed for anti-feline CoV activity *via in vitro* cell-based assay, eight drugs (Bedaquiline, Brequinar, Celecoxib, Clofazimine, Conivaptan, Gemcitabine, Tolcapone and Vismodegib) were found to possess anti-coronavirus activity (Ke et al., 2020).

AI integrated molecular docking simulations for drug repurposing

With the integration of AI, molecular simulations have become more efficient and less expensive. ML-based models, in conjunction with molecular docking simulations, are recently used to recognize molecules that can potentially limit and or distort the host-virus interactions. Karki et al. targeted three different conformations of the ACE2 receptor, that is, open, closed and a closed conformation in complex with the S protein. Authors employed a deep-neural network-based ML approach termed SSnet to identify compounds with high-binding affinities, in combination with a drug docking algorithm Smina to evaluate the potential efficacy of more than billion compounds from large compound libraries (Table 1). A vast list of potential compounds is made available at open-access web interface for further experimentation. Among antiviral, the viral protease inhibitor Grazoprevir, and Glecaprevir, as well as Velpatasvir, which targets non-structural protein (nsp), important for replication and alteration of the host immune response, demonstrated high affinity *via* Smina. These findings suggest that in addition to their primary functions, they may modulate COVID-19 pathology *via* affecting the ACE2 receptor. Remdesivir has a preference for the open conformation of the ACE2 receptor. From antibiotic category, Rifamycin derivatives showed the highest affinities by Smina, and SSnet followed by Oritavancin and Vancomycin. A further novel finding was that hormones estradiol and estradiol bind to ACE2 receptor

adjacent to the Zn²⁺ binding site which primarily controls the open and closed conformations of the receptor (Karki et al., 2020). Batra et al. trained two independent random forest regression models to rapidly determine the Vina scores of a given candidate drug molecule for the targets. These ML models screened FDA approved drugs and approx. One million biomolecules to identify molecules that can strongly bind to either isolated S protein at its host (human) receptor region or to the S protein-ACE2 interface complex. A rank-ordered list of potential FDA approved and novel candidates are provided for further experimental validation (Batra et al., 2020).

AI-based models are also being utilized to narrow down the pool of candidates needed to be docked. For instance, Mahapatra et al. initially trained an ML model with inhibitors of the SARS-CoV 3CLpro and screened more than 2000 FDA approved drugs for SARS-CoV 3CLpro inhibition activity. Out of 471 drugs predicted to have protease inhibitor activity by ML model, top 10 drugs (Table 1) were further assessed by molecular docking. An anti-retroviral drug Atazanavir, a known HIV-protease inhibitor, was found to be the most effective drug. The authors claimed that Atazanavir might be a potential candidate for COVID-19 treatment and warranted a further clinical trial (Mahapatra et al., 2020). In a similar vein, S protein, N protein and 2'-o-ribose methyltransferase protein of SARS-Cov-2 were targeted by a combination of virtual drug screening, molecular docking and supervised ML techniques. Approx. 4000 compounds were screened for binding affinity with 3D homology models of SARS-CoV target proteins. Using clinically established drugs as controls to generate prediction models, Onat et al. utilized supervised ML to study drug-likeness. Further, molecular dynamics study of top-ranked compounds confirmed their ability to bind to the relevant pharmacophore of target proteins. Interestingly, several approved drugs against HCV, that is, Paritaprevir, Simeprevir, Grazoprevir and Velpatasvir in addition to drugs against infectious diseases, against cancer or other diseases were also predicted to be effective against SARS-CoV-2 (Kadioglu Mshjgte, 2020).

AI in the analysis of gene expression signatures for drug repurposing

Another strategy for drug repurposing includes detecting therapies that have identical effects on other well-established treatments. A Singapore based group used Broad Institute's Library of Integrated Network-based Cellular Signatures (LINKS) database that contains gene expression signatures from cells targeted by various molecular and genetic perturbations and utilized a deep-neural network to mine gene expression signatures for experimental and approved drugs with potential activity against coronavirus-borne diseases (Avchaciov et al., 2020). Since COBP2 is required for replication of a genetically similar virus SARS-CoV (Adriaan et al., 2015), which is closely genetically related to SARS-CoV-2 with 79% identity (Lu et al., 2020). Authors assumed that the interactions between the virus and host are same for genetically similar viruses and proceeded with the search for small molecules capable of recreating the effect of the COBP2

genetic knock-out. They rolled out a list of 20 most promising drugs including Niclosamide which is approved for the treatment of tapeworm infections and Nitazoxanide, a commercial antiprotozoal agent with a broad range antiviral activity. Recently, nitazoxanide has been shown to inhibit the SARS-CoV-2, at a low-micromolar concentration (Wang et al., 2020). In another study, a deep-neural network-based model called infinity phenotype has been applied for transcriptional analysis to assess the antiviral efficacy of compounds from natural products or FDA approved drugs. *In vitro* studies using Vero E6 cells observed that Liquiritin, a top scored natural compound with antiviral activity, significantly inhibited replication of SARS-CoV-2 by mimicking type I interferon (Zhu et al., 2020).

AI in biomedical knowledge graph for drug repurposing

'Biomedical knowledge graphs are networks capturing the relationships between different entities such as proteins and drugs to facilitate higher-level exploration of how they connect' (Bullock et al., 2020). Recently, this technique identified Baricitinib as a potential drug for COVID-19 infection. Authors claim that Baricitinib, routinely used for arthritis treatment, can inhibit the AP2-associated protein kinase 1 (AAK1). Since AAK1 enzyme plays a regulatory role in receptor-mediated endocytosis, it may, therefore, interrupt virus entry into the host cells (Richardson et al., 2020). Similarly, Ge et al. employed a data-driven drug repurposing framework that amalgamates ML and statistical analysis methods to screen approx. 6000 approved or experimental drugs. The authors identified PARP1 inhibitor CVL218 exhibiting inhibition of SARS-CoV-2 replication without any cytopathic effect. Besides, wet-lab experiments revealed suppression of CpG-induced production of pro-inflammatory cytokine IL-6 in human PBMCs treated with CVL218. Surprisingly, pharmacokinetic and toxicokinetic studies in rats and monkeys discovered 188-fold higher concentration of CVL218 in lungs as compared to plasma without causing any toxicity. Capability to suppress IL-6 and a tissue-specific enrichment in the lung without any toxicity makes CVL218 alluring candidate for the management of COVID-19 (Ge et al., 2020).

AI in cell image analysis for drug repurposing

AI-aided image segmentation networks including classic U-Net, UNet++, VB-Net is being increasingly employed for medical image analysis. These image processing approaches have allowed early and precise diagnosis of COVID-19 by delineation of the regions of interest (ROIs), for example, lung lobes, bronchopulmonary segments and infected lesions in the chest X-ray or CT scan images (Shi et al., 2020). DL neural networks are also used for drug discovery by image analysis of cytological structures to study the phenotypic profile of human cells under different conditions (Heiser et al., 2019). Perturbed monolayers of HRCE cell lines with active, inactive or mock preparations of SARS-CoV-2 have been used to create a specific phenotypic profile by image analysis of cytological structures. Various candidate compounds were subsequently evaluated for their ability to

suppress the impacts of the SARS-CoV-2 on phenomic profiles of human cells. Interestingly, only Remdesivir but not Chloroquine nor Hydroxychloroquine had shown any beneficial effect in this human cell model. Besides this, weak beneficial class effects of certain beta-blockers, mTOR/PI3K inhibitors and vitamin D analogues were noted. In another study, Han et al. reported a supervised ML method to identify the mechanism of action of drugs based on cell picture data. Based on cell image features of 1024 drugs generated in the LINCS program authors concluded that Chloroquine and Hydroxychloroquine attain antiviral effects by inhibition of T-cell proliferation and reduction in discharge of pro-inflammatory cytokines, thus preventing elevation of pH of endosome with subsequent endocytosis blockage (Han et al., 2020).

AI for identification of progeny drugs for repurposing

Martyna et al. used AI algorithms to identify 'progeny' or second-pass drugs that are analogous to the drugs already being tested (called as parent drug) against COVID-19. These AI algorithms assess similarity based on molecular make-up of the molecules and by the 3D distribution of pharmacophores. The authors identified hundreds of progeny compounds fit for repurposing against the COVID-19 if the currently-tested drugs fail to show the desired effect (Martyna et al., 2020).

Our detailed literature search to check the current status of repurposing drugs identified by AI for therapeutics of COVID-19 (Table 4) has revealed that among the identified drugs, only 20% were examined *in vitro*. Among the drugs, which were assessed *in vitro* ($n=14$), 12 showed *in vitro* efficacy (85%). However, only 4% of ligands were evaluated in animal studies. Around 16% of the identified drugs are in different phases of clinical evaluation, many of which are already part of different treatment guidelines (Figure 4).

AI for novel drug discovery against COVID-19

At this time of global health emergency novel drugs with better optimal features are desperately needed. However, novel drug discovery is a highly costly (2–3 billion USD) time-consuming (>10 years) and daunting task (Harrer et al., 2019). In the past few years, this process has been extensively facilitated by AI. Recently, in a landmark development, the first drug created using AI has moved into its Phase-I trial in record time (Cots et al., 2020). Several research attempts are being made to discover new compounds targeting SARS-CoV-2.

Ton et al. used a novel DL platform deep docking (DD) in combination with Glide (Friesner et al., 2004) and predicted docking scores for 1.3 billion chemical structures from the ZINC library for the active site of 3CLpro. Authors provided a list of 1000 chemically diverse potential ligands of 3CLpro for further characterization by the scientific community. The candidate inhibitors in the provided list are claimed to exhibit superior docking scores in comparison with known protease inhibitors. Authors argue that DD provides a fast prediction of docking scores of various docking tools and enables rapid

Table 4. Current status of repurposing drugs identified by AI for therapeutics of COVID-19.

Drug category	Drug name	<i>In vitro</i>	Preclinical <i>in vivo</i>	Clinical trial	
Antiviral	Atazanavir	Yes, Better than Lopinavir (Fintelman-Rodrigues et al., 2020, Yamamoto et al., 2020)	No data	0 studies	
	Amprenavir	Activity showed (Yamamoto et al., 2020)			
	Abacavir	No data	No data	0 studies	
	Darunavir	No activity <i>in vitro</i> (De Meyer et al., 2020)	No data	0 studies	
	Dolutegravir	Low activity (Touret et al., 2020)	No data	0 studies	
	Efavirenz	No data	No data	0 studies	
	Emricasan	No data	No data	0 studies	
	Fosamprenavir	No data	No data	0 studies	
	Grazoprevir	No data	No data	0 studies	
	Indinavir	Activity showed (Yamamoto et al., 2020)	No data	0 studies	
	Lopinavir	Activity showed (Yamamoto et al., 2020)	No data	59 studies registered	
	Paritaprevir	No data	No data	No data	
	Ritonavir	Activity showed (Yamamoto et al., 2020)	Data is there in ferrets (Park et al., 2020) , no significant diff than PBS	61 studies	
	Remdesivir	Activity showed (Choy et al., 2020)	Showed potent activity (de Wit et al., 2020)	20 studies	
	Saquinavir	Activity showed (Yamamoto et al., 2020)	No data	0 studies	
	Tipranavir	Activity showed (Yamamoto et al., 2020)	No data	0 studies	
	Velpatasvir	No data	No data	0 studies	
	Valaciclovir	No data	No data	0 studies	
	Ganciclovir	No data	No data	0 studies	
	Daclatasvir	No data	No data	0 studies	
	Paritaprevir	No data	No data	0 studies	
	Simeprevir	Activity showed (Lo et al., 2020)	No data	0 studies	
	Grazoprevir	No data	No data	0 studies	
	Velpatasvir	No effect (Liu et al., 2020)	No data	0 studies	
	Glecaprevir	No data	No data	0 studies	
	Grazoprevir	No data	No data	0 studies	
	Non-steroidal anti-androgen	Flutamide	No data	No data	0 studies
		Bortezomib	No data	No data	0 studies
	Proteasome inhibitor	Piperacillin	No data	No data	1 study registered (in combination to Tazobactam)
		Glutathione	No data	No data	Clinically proven efficacy in case series (Horowitz et al., 2020)
PDE-4 inhibitor	Oflumilast	No data	No data	0 studies	
	Liquiritin	No data	No data	0 studies	
Anti-cancer	Carfilzomi	No data	No data	0 studies	
proteasome inhibitor	Almitrine mesylate	No data	No data	0 studies	
	Tolcapone	No data	No data	0 studies	
	Vismodegib	No data	No data	0 studies	
	Pemiroloast	No data	No data	0 studies	
	Sulfamethoxazole	No data	No data	1 study registered	
	Meglumine	No data	No data	0 studies	
	Vidarabine	No data	No data	0 studies	
	Adenosine	No data	No data	0 studies	
	Mannitol	No data	No data	0 studies	
	Dulcitol	No data	No data	0 studies	
	D-sorbitol	No data	No data	0 studies	
	Sodium gluconate	No data	No data	0 studies	
	Tiotropium-bromide	No data	No data	0 studies	
	Sulfanilamide	No data	No data	0 studies	
	Tazobactam,	No data	No data	2 studies registered (in combination to Piperacillin)	
	Nitrofurantoin	No data	No data	0 studies	
	Roflumilast	No data	No data	0 studies	
	Itraconazole	No data	No data	0 studies	
	Metoprolol tartrate	No data	No data	0 studies	
	Fiboflapon sodium	No data	No data	0 studies	

(continued)

Table 4. Continued.

Drug category	Drug name	<i>In vitro</i>	Preclinical <i>in vivo</i>	Clinical trial
	Mitoxantrone	No data	No data	0 studies
	Ponatinib	No data	No data	0 studies
	Baricitinib	No data	No data	13 studies registered
	Niclosamide	No data	Inhibition of inflammation in ferrets	3 studies registered
	Nitazoxanide	No data	No data	12 studies registered
	Emricasan	No data	No data	0 studies
	Glutamine	No data	No data	0 studies
	Rifamycin	No data	No data	0 studies
	Oritavancin	No data	No data	0 studies
	Vancomycin	No data	No data	0 studies
	Bedaquiline	No data	No data	0 study
	Brequinar	No data	No data	1 study registered
	Celecoxib	No data	No data	0 study
	Clofazimine	No data	No data	0 study
	Conivaptan	No data	No data	0 study
	Gemcitabine	Activity Showed (Zhang et al., 2020)	No data	0 study
Lopinavir/Ritonavir (Liu et al., 2020)		Activity Showed (Cao et al., 2020)	No data	0 study

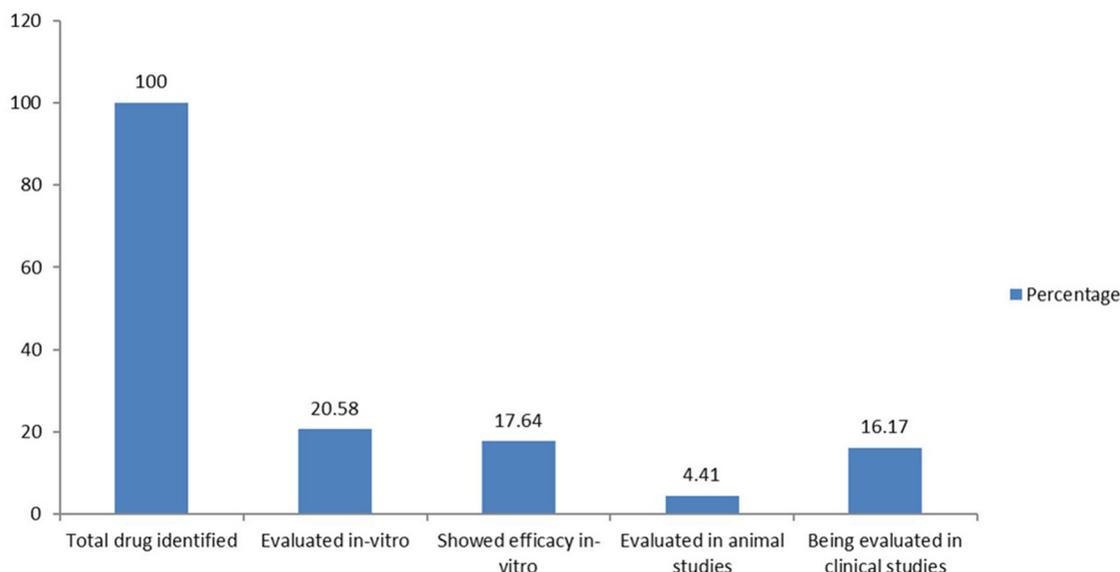


Figure 4. Current status of identified drugs for repurposing for COVID-19. Among the identified drugs, only 20% were evaluated *in vitro*. Among the drugs, which were evaluated *in vitro* ($n = 14$), 12 showed *in vitro* efficacy (85%). However, only 4% ligands were evaluated in animal studies. Around 16% of the identified drugs are in different phases of clinical evaluation.

drug discovery by structure-based virtual screening of billions of molecules in a short time (Ton et al., 2020).

A deep-neural network-based generative model has identified 31 novel molecules capable of inhibiting 3CLpro of the SARS-CoV-2 (Bung et al., 2020). Using special physicochemical property filters in the generative model, the authors ensured that the generated molecules are novel and possess drug-like properties. Virtual screening analysis of the new chemical entities revealed their similarity to HIV-protease inhibitors, however, highly specific for the binding site of 3CLpro. Interestingly, two of these generated small molecules showed high similarity to a natural plant product (Aurantiamide). This is of great importance because compounds similar to natural products are easy to synthesize and will have comparatively fewer side effects. Similarly, using AI-based drug discovery pipeline, Zhavoronkov et al. have also generated novel drug compounds which are published at <https://insilico.com/ncov-sprint> for further

development (Zhavoronkov et al., 2020). Hofmarcher et al. performed a more extensive search for the inhibitors of 3CLpro and PLpro by utilizing a deep-neural network called ChemAI. The authors conducted a large-scale virtual screening of 3.6 million small molecules from ZINC, and Drugbank drug discovery databases. They ranked compounds based on predicted inhibitory effects, toxicity and proximity to known compounds. A library of top-ranked 30,000 potential CoV-2 inhibitors from these studies is provided online for further experimental validation (Hofmarcher et al., 2020).

Tang et al. developed an Advanced Deep Q-learning Network with the Fragment-Based Drug Design (ADQN-FBDD); a unique platform as it does not require any pre-training at all and uses reinforcement learning to generate novel molecules by sequentially adding molecular fragment instead of adding atoms one by one. The authors used 284 SARS-CoV 3CLpro inhibitors as the initial molecule database and created a molecular fragment library by breaking these

molecules into smaller fragments. Joining these fragments, ADQN-FBDD generated 47 potential lead compounds and their derivatives targeting SARS-CoV-2 3CLpro autoencoder (Tang et al., 2020). Similarly, Verma generated novel potential inhibitors molecules against 3CLpro using an advanced DL network with the fragment-based drug design along with Variational autoencoder (Verma, 2020).

Gao et al. employed a machine intelligence-based generative network complex (GNC) (Grow et al., 2019) and predicted over 8000 potentially effective therapeutic candidates. Authors used two 3D DL models trained with different training sets and a list of top 15 novel potential druggable molecules for COVID-19 treatment is provided. Additionally, two existing HIV drugs (Lopinavir and Ritonavir) showed a moderate effect on the treatment of SARS-CoV-2 (Gao et al., 2020). Chenthamarakshan et al. adopt a similar strategy for drug discovery. The author's proprietary framework, that is, Controlled Generation of Molecule (CogMol), designs drugs specific to a given target protein sequence with low off-target activity. A most distinctive feature of this AI-based platform is that once trained, it can handle molecule generation for many target protein sequences, without retraining for every individual target. Using CogMol the authors successfully generated 1000 novel drug candidates that can potentially inhibit NSP9, 3CLpro, replicase and RBD in the S protein of SARS-Cov-2. Validation of these molecules is in progress the researchers proclaim a lower failure in later stages of the drug development pipeline as these molecules were additionally screened by using a multi-task DL classifier to predict *in vitro* and clinical toxicity. A list of top 97 potential candidate molecules designed to inhibit the 3CLpro of SARS-CoV-2 is made available (Chenthamarakshan et al., 2020).

A lesser mutable region, that is, Heptad repeat 1 (HR1) domain on the S protein of SARS-CoV-2 has been targeted for new inhibitors drugs (Savioli, 2020). Utilizing a Siamese Neural Network that is precisely trained to differentiate the whole SARS-CoV-2 protein sequence amongst two different virus families, approx. 3000 peptides from SATPdb database tested towards the specific target revealed a strong affinity (93%) between peptidylprolylcis-trans isomerase (PPlase) peptide and HR1 domain of SARS-CoV-2. Interestingly, several recent studies have already discovered that an immunosuppression drug, cyclosporine (an inhibitor of PPlase) can suppress the reproduction of different coronavirus (Pfefferle et al., 2011; Tanaka et al., 2012).

Gysi et al. used a combination of three network-based drug repurposing approaches, relying on network proximity, diffusion, and AI-based metrics. Multiple ranked lists of promising drugs obtained from different pipelines subjected to a rank aggregation algorithm, generated a list of 81 highly promising repurposing candidates is made available (Gysi et al., 2020).

AI for vaccine and antibody development against COVID-19

The extreme complexity of the human immune system and its variability among different people and groups make

vaccine development a tedious process. AI dependent strategies are being tried to explore various aspects of vaccine development, for example, to know the most appropriate SARS-CoV-2 vaccine targets. Recently, researchers from Stanford University used ML along with other bioinformatics tools from structural biology to identify T-cell and B-cell epitopes of SARS-CoV-2. Two artificial neural network algorithms analyzed the SARS-CoV-2 genome for epitope candidates. They predicted 405 likely T-cell epitopes, with strong MHC-I and MHC-II presentation scores, as well as two potential neutralizing B-Cell epitopes on the S protein. The epitopes predicted in this study can generate more potent vaccines and neutralizing antibodies (Fast et al., 2020). In another attempt, Prachar et al. constructed PrdX; a proof-of-concept prediction model and trained it on historic in-house stability data. Based on high prediction binding scores, this feed-forward neural network identified 174 SARS-CoV-2 epitopes that can bind stably to HLA allotypes. After validating these peptides *in vitro*, their details are made freely available to assist in vaccine design against COVID-19 (Prachar et al., 2020).

To design a universal vaccine, a Japan-based NEC corporation has utilized an AI-based platform to profile the whole SARS-CoV-2 proteome across the most frequent 100 HLA-A, HLA-B and HLA-DR alleles in the entire human population and constructed comprehensive epitope maps. Authors further analyzed these epitope maps and identified 'epitope hotspot' regions in the SARS-CoV-2 that are most likely to be immunogenic across a broad spectrum of HLA types and thus can drive potent T-cell responses in the majority of the global population (Malone et al., 2020).

Ong et al. developed Vaxign-ML, a ML tool to select a potential vaccine candidate that can induce high protective immunity. Authors advocate nsp3 protein as a vaccine candidate over S protein being predicted to have the highest protective antigenicity score amongst the proteins which are not already considered for vaccine development. Apart from the S and nsp3 proteins, four additional vaccine candidates, including 3CLpro, nsp8, nsp9 and nsp10 were purposed based on protective antigenicity score (Ong et al., 2020). ML, molecular docking simulation, bioinformatics and structural biology tools are being used to discover potential neutralizing antibodies for SARS-CoV-2 (Magar et al., 2020). A high throughput deep model screened thousands of synthetic sequences and predicted antibody sequences that can inhibit coronavirus. Molecular dynamics simulations revealed eight stable antibodies that can neutralize COVID-19.

Limitations

We included articles published only in English. Thus any significant research in other languages stand excluded from review.

Conclusion

Overall, this systematic review demonstrates how AI has emerged as a promising solution to tackle the therapeutic aspect of COVID-19 crisis. Majority of the studies have

implicated AI in drug repurposing by screening massive drug databases to find potential candidates against targets proteins of SARS-CoV-2 in a record time. A considerable number of already approved drugs are being investigated for their effectiveness against COVID-19. We have compiled a detailed list of identified drugs that are either approved or are in the late-stage clinical trial and are potentially effective against SARS-CoV2, thereby making the available evidence more accessible to decision-makers. Thousands of potentially effective novel compounds against SARS-CoV-2 have also been identified by screening billions of compounds at an unprecedented speed. However, the clinical efficacy of these molecules for the treatment of COVID-19 is unknown, further studies are warranted to conclude about their effectiveness. Interestingly, some of these compounds are found to be structurally similar to naturally occurring compounds and deserve further *in vitro* and *in vivo* investigation. Finally, the T-cell and B-cell epitopes of SARS-CoV-2 predicted by DL models can be further explored to develop more effective vaccines and neutralizing antibodies.

Authors' contributions

KK conceptualized the study. KK and PS conducted database search, search results screening, detailed review, data extraction, quality assessment and prepared the initial draft. PS and BM did the database search for the status of AI identified drugs. KK and SV made the final draft. MN supervised the project and critically appraised the manuscript. All authors read and approved the final manuscript.

Disclosure statement

No potential conflict of interest was reported by the authors.

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