 doi:10.20944/preprints202207.0004.v1

# A Hybrid AI-driven Algorithm to Uncover Potential Therapeutic Targets for COVID-19 Using Network-based Drug Repurposing

Carlos Eduardo Marchi*[1], David Corrêa Martins Jr.[1]

[1]*Center for Mathematics, Computing and Cognition, Federal University of ABC (UFABC), Santo André 09210-580, SP, Brazil*

* Address correspondence to this author at Center for Mathematics, Computing and Cognition, Federal University of ABC, dos Estados Avenue, 5001, Santo André 09210-580, SP, Brazil; E-mail: carlos.marchi@ufabc.edu.br

**Abstract:** The COVID-19 was described as a respiratory illness, however further studies recognize it as a complex heterogeneous multisystemic disorder. Global efforts have been proposed to combat COVID-19, emerging diverse therapeutic options, in which discovering new drug therapies, development of vaccines and drug repurposing have been considered the most promising approaches to fight the virus. This study aimed to repurpose known drugs for use against the COVID-19, finding better therapeutic options. Seventeen biological databases were used in this study. The genetic algorithm (GA) was performed for a set of drug target classes and COVID-19 proteins as input, whose drug candidates are obtained according to the target similarities found in the target-target similarity predictive network, resulting in a drug-target interaction network. Thus, recommended drugs correspond to the union of the drug subsets found during each GA execution. Twenty-eight drugs were indicated to be the best therapeutic targets for the virus, in special, the Cyclosporine drug was administered as adjuvant to steroid treatment for COVID-19 patients which showed positive outcomes, reducing mortality in moderate and severe cases. The drugs found have used to treat other diseases, evidencing that the COVID-19 is a multisystemic disorder and suggests that the viruses' mechanism of action presents some comorbidity with other human diseases. Evidence shows that the drugs found in this research might act together to fight the virus in a broader fashion, however further studies including *in vitro* and *in vivo* experiments are needed to find the best combination of these drugs.

**Keywords:** SARS-CoV-2; COVID-19; drug repurposing; artificial intelligence; target-target similarity network; drug-target interaction network

## 1. INTRODUCTION

A local outbreak of pneumonia of initially unknown causes was detected in December 2019 in Wuhan city, Hubei Province (China), a city with 11 million inhabitants. The cause behind this pneumonia was further determined as a new coronavirus, called new coronavirus 2019 (2019-nCoV), which in turn causes the severe acute respiratory syndrome coronavirus 2 infection (SARS-CoV-2), also called coronavirus disease (COVID-19) [1–3].

On March 11, 2020, the World Health Organization (WHO) declared COVID-19 to be a global pandemic [4, 5]. This highly contagious disease, transmitted between humans

by both oral and nasal routes via activities such as talking, breathing, coughing, and sneezing [6–8], has spread slightly to more than 185 countries with over 271,963,258 confirmed cases and 5,331,019 confirmed deaths [9]. Symptoms can be life-threatening, with a higher lethality rate in the elderly and people with underlying health conditions [10, 11]. However, the most common clinical manifestations have been fever, dry mouth and cough, fatigue, loss of taste and smell, and shortness of breath [12].

Although early reports described the disease caused by SARS-CoV-2 as a respiratory illness, in some cases leading to viral pneumonia, further studies recognize that COVID-19 is a complex heterogeneous multisystemic disorder, affecting a variety of organs such as lung, heart, kidneys, brain, among others [13, 14], in addition to the fact that patients have different symptoms and complications, such as neuropsychiatric symptoms, endothelial dysfunction, hyper-inflammatory state and thromboembolic disease [14].

Coronaviruses are enveloped RNA viruses belonging to the Coronaviridae family that upon viewing under an electron microscope present crown-like spikes on their surface [15–17]. First identified in 1966 by Tyrrell and Bynoe, coronaviruses affect several animal species including birds, mammals such as bats, cattle, pigs, and humans [15, 16, 18–20]. During pandemic outbreaks, some variants of the virus began infecting humans (HCoVs), including Middle East respiratory syndrome (MERS-CoV, 2014), Alpha (United Kingdom, September-2020), Beta (South Africa, May-2020), Gamma (Brazil, November-2020), Delta (India, October2020), Eta (multiple countries, December-2020), Iota (United States of America, November-2020), Kappa (India, October-2020), Lambda (Peru, December-2020), Mu (Colombia, January-2021) and Omicron (multiple countries, November-2021) [21].

High rates of SARS-CoV-2 transmission, together with their variants have been a global threat, and many countries have adopted non-pharmaceutical health policy strategies, such as social distancing, the use of face masks and contact tracking as the best alternatives to reduce viral spread and demands on healthcare [22, 23]. Furthermore, the viruses have caused interruptions in healthcare systems and in business, in addition to other aspects related to the daily lives of the

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 1 July 2022 doi:10.20944/preprints202207.0004.v1



population such as education, employment and transportation [24].

Global efforts have been proposed to combat COVID-19, the recent results of WHO's Solidarity Clinical Trial have revealed some efficient treatments and recommendations for SARS-CoV-2, however the approved drugs have to be administrated in some conditionals, including systemic corticosteroids and tocilizumab or sarilumab with strong recommendations in patients with severe and critical disease, casirivimab and imdevimab with conditional recommendations in cases of seronegative status (severe and critical COVID-19) or highest risk of severe disease for those with non-severe COVID-19 [25].

Therapeutic options are diverse and is increasing rapidly, where the most significant efforts have been made in discovering new drug therapies, involving virus targets, host cell targets, adjunctive therapy, and developing vaccines [26–30]:

Virus targets – Use of medications to block virus replication, e.g., atazanavir, azvudine, lopinavir, raltegravir, ritonavir and vapreotide (human immunodeficiency virus – HIV); bismuth potassium citrate and oseltamivir (gastrointestinal); boceprevir, daclatasvir, ribavirin and sofosbuvir (hepatitis C); carmofour (antineoplastic), doxycycline (antibacterial) and famotidine (stomach ulcer), favipiravir and triazavirin (influenza); fostamatinib disodium (chronic immune thrombocytopenia), gliclazide (diabetes), memantine (Alzheimer's), penciclovir (herpes), natural product platycodin D (respiratory tract and lung) and remdesivir (Ebola) [27, 29–33].

Host cell targets – Comprises drugs that interfere with infection and viral replication in the host cell, involving its functions, pathways and proteins, such as arbidol (influenza), azithromycin (antibacterial), camostat and nafamostat mesylate (pancreatitis and reflux oesophagitis); captopril and losartan (hypertension and renal/cardiovascular); chloroquine phosphate and hydroxychloroquine (malaria); ivermectin (anthelmintics), nitazoxanide (antiprotozoal), STI-1499 (antibody), teicoplanin (antibacterial), and the natural product withanone [27, 29–33].

Adjunctive therapies – Molecules acting on the host's immune response to reduce inflammation, being baricitinib, sarilumab and tocilizumab (rheumatoid arthritis), bevacizumab (cancer), colchicine (antigout), dexamethasone and methylprednisolone (corticosteroid); and vitamins C and D [27, 29–33].

Vaccines – Considered the most effective method for combating SARS-CoV-2. According to WHO, there are more than 110 vaccines in clinical and more than 184 in pre-clinical development distributed on various platforms, including live attenuated: use of weakened virus (Sinovac), nucleic acid: DNA or messenger RNA (mRNA) genetically modified from the virus used to produce viral proteins in the body (Biotech-Pfizer); subunit: may use one or part of the virus protein, or even another protein similar to the virus structure (Novavax); and viral vectors: another genetically modified virus used to produce viral proteins in the body (Oxford-AstraZeneca) [30, 32, 34, 35].

Although vaccines for COVID-19 were developed in much less time than conventional vaccines and many countries have already adopted mass vaccination campaigns [36], open questions remain regarding antigen optimization and the duration of immunity potential [37]. Another important factor is the high cost involved in the vaccine development process, especially with the licensing time. This can take many years [36], as in the case of the first Ebola vaccine which took 43 years after the virus was discovered to get approved [38–40].

Effectiveness of vaccines for new variants of SARS-CoV-2 is of concern. New studies indicate a significant reduction in protection against the new omicron variant [41, 42]. Despite these studies are small and recent to know the exact level of protection from vaccines or previous infection with SARS-CoV-2, these studies suggest a third dose against omicron [42]. Meanwhile, Pfizer-BioNTech and Moderna, mRNA vaccine manufacturers for COVID-19 have begun the development of an omicron-specific vaccine that could be ready for delivery within 100 days [41, 42]. In light of these facts and the current COVID-19 pandemic situation, drug repurposing is then a powerful, fast and economical alternative solution, which may provide evidence of new or complementary treatments for the virus [43].

Drug repurposing can identify new therapeutic approaches for known drugs [44]. Existing drugs under clinical investigation or approved are safer and their toxicities are known, representing less risk to patients. Time is halved and the financial investment is about ten times less for drug repositioning compared to the implementation of a new drug [45], in addition to the lower risk of failure and use of consolidated and operational pharmaceutical supply chains for the production and distribution of medicines [46]. Another encouraging fact of drug repurposing therapy is related to reducing dosage levels and minimizing adverse reactions. Moreover, this also may increase efficacy through drug activity or synergy [47].

Computational approaches have been increasingly employed in fighting SARS-CoV-2, offering new testable hypotheses for new drug targets or systematic reuse of drug candidates [48–54]. In contrast to *in vitro* and *in vivo* studies, in silico studies are cheaper and faster approaches [48, 55], and can be used to analyze a huge number of compounds, drug combinations and biomedical data available. Therefore, computational methods can be useful for the filtering step, and for thoroughly evaluating medications which warrant a more extensive, experimental, and clinical evaluation [43, 48, 56].

Computational strategies using machine learning has contributed to the prediction of existing drugs with greater potential for effectiveness COVID-19 treatment. Such an approach has been used to predict drug-target interactions (DTI) [43, 53, 57–59], indicating drug binding at the target site, and which binding can cause changes in target behaviors (most drug targets are related to the protein-coupled receptors, enzymes and ion channels). Basically, computational methods are used for DTIs involving ligand, docking and chemogenomic methods [60]:

 doi:10.20944/preprints202207.0004.v1



- Ligand methods: As a rule, similar molecules are associated with similar protein targets [54, 60].
- Docking methods: Identifies drug and protein reactions by analyzing 3D structure [52, 60, 61].
- Chemogenomic methods: Predictions are performed using data from drug and protein omics, encompassing machine learning methods (support vector machine, random forest, k-nearest neighbor, ensemble, artificial neural networks, and deep learning) [53], graphs [54, 62] and networks (protein-protein interactions, gene co-expression, drug-drug interactions, and drug-gene and drug-disease) [51, 53, 54, 60, 63–67].

Although artificial intelligence techniques can contribute to drug repurposing, advances in pharmacogenetics and pharmacogenomics indicate that therapies guided by individual genomic profiles considerably improve the treatment and curing of diseases, something already practiced in other diseases such as in cancer [68]. Thus, host genetic studies playing an important role in COVID-19 can evidence human genetic determinants of the viruses, leading to personalized treatment. This represents a unique opportunity for drug repurposing in precision medicine [59, 69–72]. In this context, the present study is proposed, focusing on discovering new targets for existing drugs to fight COVID-19 with high precision provided by the application of integrative analysis of biological datasets combined with artificial intelligence techniques.

## 2. MATERIALS AND METHODS

### 2.1. Data Sources

Several biological data sources were collected and submitted to data cleaning and wrangling for understanding the relationships between drugs and proteins, as well as for discovering new drug targets (Fig. **1A**). The information available in biological repositories is vast and of great value, requiring data processing for better applicability to this study. This is detailed below:

BindingDB [73] – Got information about protein-ligand binding affinities, including InChI (International Chemical Identifier) and the biological database identifiers: BindingDB, ChEBI (Chemical Entities of Biological Interest) [74], DrugBank [75], PubChem [76] and proteins (UniProt accession numbers).

Brenda [77] – Got information about enzyme classes with UniProt accession numbers.

ChEBI – Got information about ontological chemical entities and biological database identifiers: ChEBI, DrugBank accession number, KEGG (Kyoto Encyclopedia of Genes and Genomes) Compound [78] and KEGG Drug [79].

DrugBank – Got information about the drugs, including DrugBank identifiers (primary and secondary accession numbers), name, name synonyms, status, molecular formula, UNII (Unique Ingredient Identifier), CAS Registry Number, SMILES (canonical simplified molecular), IUPAC name (International Union of Pure and Applied Chemistry), InChI, InChI Key, ATC codes (Anatomical Therapeutic Chemical) and biological repository identifiers: BindingDB, ChEBI, PharmGKB [80], KEGG Compound, KEGG Drug, PubChem Compound, RxNorm [81] and TTD (Therapeutic Target Database) [82].

Ensembl [83] – Got information about genes, such as names, symbols and biological database identifiers: Ensembl and HGNC (Human Gene Nomenclature) [84].

Gene Ontology [85] – Information about gene annotations and mapping between gene ontology terms and proteins (UniProt accession numbers).

HGNC – Got information about genes, such as names, name synonyms, symbols, symbol synonyms, and biological repository identifiers: Ensembl, HGNC e NCBI (National Center for Biotechnology) [86].

HPRD (Human Protein Reference Database) [87] – Information about the proteins and their interactions (UniProt accession number).

KEGG Brite [88] – Got information about target-based classification of drugs (KEGG Drug identifiers).

OFFSIDES [89] – Got information about adverse drug reactions: MedDRA (Medical Dictionary for Regulatory Activities) [90], RxNorm identifiers and frequency.

NCBI – Got information about genes, including names, name synonyms, symbols, symbol synonyms and biological database identifiers: Ensembl and NCBI.

Pfam [91] – Got information about protein domains: Pfam identifiers.

PathBank [92] – Got information about pathways through which drugs act: species (homo sapiens).

Reactome [93] – Got information about pathways through which drugs act: species Reactome [93] – Got information about pathways through which drugs act: species (homo sapiens), ChEBI, DrugBank, PathBank and Reactome identifiers.

Sider [94] – Got information about adverse drug reactions, including mappings and frequencies of side effects. The mapping is between UMLS (Unified Medical Language System) concept [95] and MedDRA identifiers, choosing only mappings with the term PT (preferred term). Additionally, only frequencies of side effects with the term PT containing the following fields: stitch stereo identifier, description of frequency (very frequent, very common, frequent, common, uncommon, infrequent, rare, very rare and postmarketing), lower and upper frequencies, and UMLS concept identifiers and side effect name. UMLs concept identifiers were converted to MedDRA identifiers, and the resulting frequency is according to whether there is a description of frequency, assigning the value 0.9 for very frequent or very common, 0.1 – frequent or common, 0.01 – uncommon or infrequent, 0.001 – rare or postmarketing and 0.0001 – very rare. If there is no description of frequency, then the mean between lower and upper frequencies is obtained.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 1 July 2022 doi:10.20944/preprints202207.0004.v1



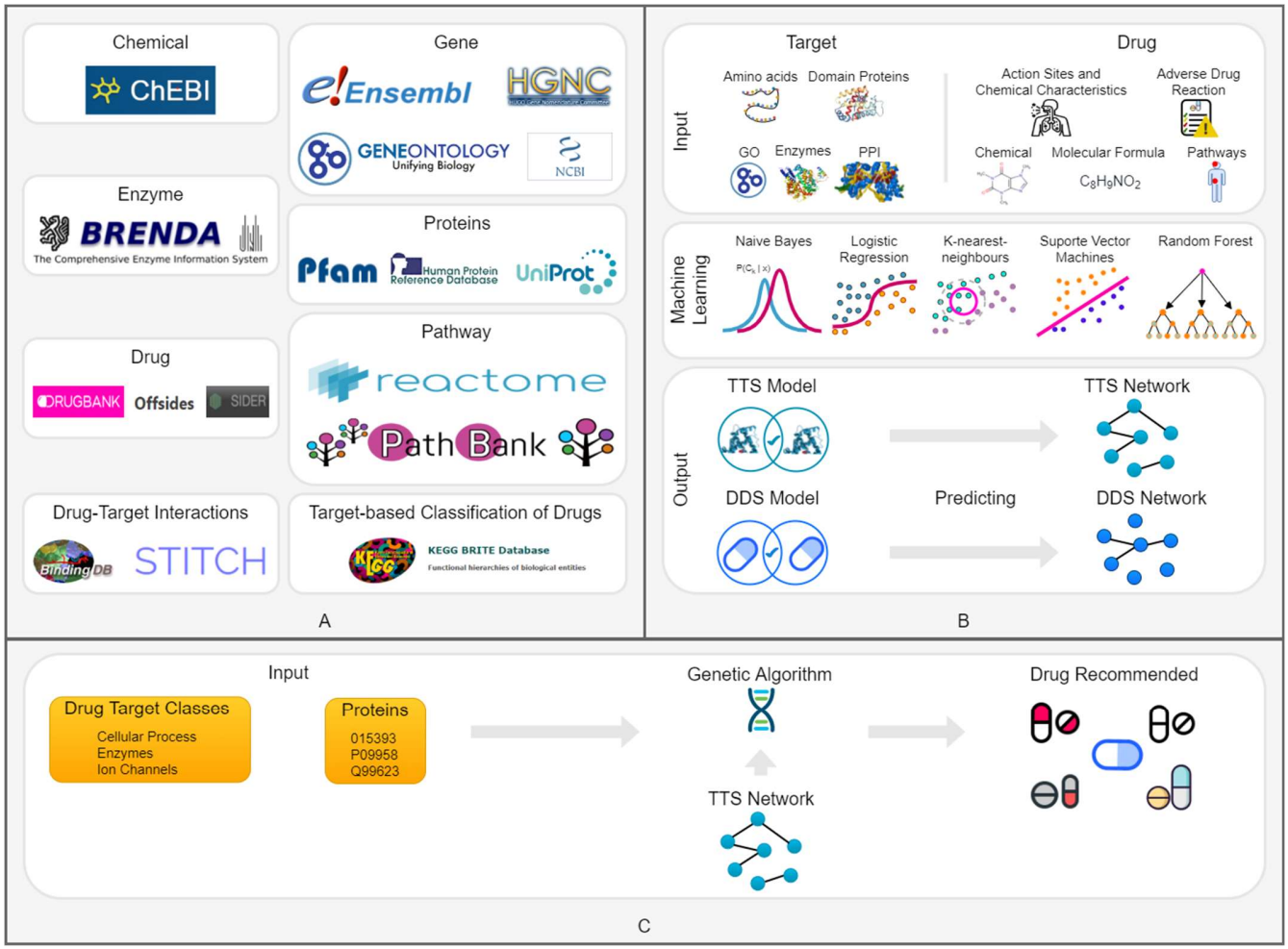


**Fig. (1).** Overview of computational drug repurposing for COVID-19, including biological database sets **(A)**, predicting target-target and drug-drug similarity networks using machine learning techniques **(B)** and recommending potential drugs for SARS-CoV-2 using genetic algorithms to find the best drugs, according to input variables (drug target classes and proteins) and predictive TTS Network **(C)**.

Stitch [96] – Got information between Stitch identifiers and other biological repositories, such as BindingDB, ChEBI, DrugBank and PubChem identifiers (homo sapiens). Additional information includes chemical-chemical connections (homo sapiens) – two chemical identifiers, values of similarity, experimental, database and a combined score. The final score from the connection between the two chemicals is given as a combined score, where values are greater than or equal to 850.

UniProt [97] – Got information about proteins, such as accession numbers, names, recommended names, alternative names, enzyme commission numbers, genes (symbol and Ensembl, HGNC, NCBI identifiers), gene ontology terms (biological process, molecular function and cellular component identifiers), Pfam domains and sequences.

### 2.2. Networks

In this study, target and drug similarity networks were created. As these networks are undirected graphs, they constitute a set of node pairs (edges, links or interactions) that are connected, with all links being bidirectional. Details about the construction of these similarity networks can be seen in Fig. **1B** and as follows

### 2.3. Target-Target Similarity Network (TTS)

TTS are biological networks composed of drug targets at their nodes and their connections occur through similarity between protein sequences, protein domains involved in adverse drug reactions [98], gene ontology annotations, enzyme-catalyzed reactions (enzymes are drug targets for a desirable therapeutic effect, in addition to the fact that they are related to causes of the adverse drug reactions) [98, 99], and direct interaction between two proteins in the protein-protein interaction networks (PPI).

Predictive models for the TTS network result from the application of supervised learning algorithms (binary classifiers) to predict the similarity relationships of drug targets. Among the variety of machine learning algorithms, those widely used by drug repurposing predictions [100–102] are, in special, k-nearest neighbors (KNN), Naive Bayes (NB), logistic regression (LR), random forests (RFs) and support vector machines (SVMs).

 doi:10.20944/preprints202207.0004.v1



With their parameters adjusted by hyperparameter optimization, algorithms were submitted to training, in order to choose a set of ideal hyperparameters for the machine learning algorithm according to the F1-score. Each of these generated hyperparameters models were evaluated by the cross-validation technique, dividing the dataset into ten subsets (10-fold) of the same size, where one subset was used for testing and the rest were used for the parameter estimation.

### 2.4. Drug-Drug Similarity Network (DDS)

DDS are biological networks consisting of drugs in their nodes and their links are through similarity between molecules and chemicals, ATC codes, adverse drug reactions, targets, and pathways of drug actions.

As well as the TTS network, the development of the predictive model for the DDS networks succeeds by applying supervised learning algorithms (binary classifiers) to predict drug similarity relationships: KNN, NB, LR, RFs and SVMs. Furthermore, hyperparameter optimizations and 10-fold cross-validations were applied to each of the algorithms to select the best one based on the final evaluation (F1-score metric).

### 2.5. Drug Recommendation

The drug recommendation process consists of ascertaining the best drugs as potential therapeutic targets for a particular disease, according to the inputs: a set of drug target classes and proteins involved in a given disease (Fig. **1C**).

Drugs are recommended for each drug target class, whose drug candidates (approved status) are obtained according to the target similarities found in the TTS predictive network, resulting in a drug-target interaction network in which the nodes correspond to drugs and proteins, and the links are only predictions between drugs and their targets.

Once defined the drug-target interaction network, the parameters of the genetic algorithms (GA) are adjusted by hyperparameter optimization in order to find the best parameters capable of selecting one or more drug candidates as the best therapeutic target. Thus, the recommended drugs correspond to the union of the drug subsets found during each GA execution for the drug-target class and the set of proteins as input.

## 3. RESULTS

### 3.1. Input Variable Sets

Recommendation of drugs for SARS-CoV-2 was performed with the purpose of discovering potential therapeutic targets capable of blocking virus entry, inhibiting both virus transcription and replication, and reducing inflammation in the bronchi, lungs and pulmonary alveolus. Therefore, 12 target drug classes were chosen, according to some information found in the literature [103–108] relating the virus life cycle in the human body to G protein-coupled receptors, ion channels, nuclear receptors, protein kinases, cytokines and receptors, cell surface molecules and ligands, transporters, enzymes, nucleic acids, signaling molecules, cellular process and organismal systems, for example.

Finally, several studies found proteins associated with COVID-19, which were collected manually via the UniProt website [109]. It is surmised that these proteins can cover the entire SARS-CoV-2 life cycle in the human body. These include O15393, P07711, P09958, P17405, P33076, P51149, P52948, P62937, Q92499, Q96C10, Q9BYF1, Q9BYX4, Q9C000, Q9NRS4, Q9NVJ2, Q9UHD2, Q9Y2I7, O14786, O15455, O43765, O94826, O95721, P01185, P01889, P02649, P04233, P04439, P05109, P05161, P05231, P08887, P09429, P13164, P13747, P17181, P20701, P26715, P30556, P35232, P35613, P40189, P47901, P48551, P49754, P52292, P56962, P68104, P84022, Q01628, Q01629, Q10589, Q13241, Q13568, Q14653, Q16552, Q16553, Q16665, Q4KMQ2, Q5BJD5, Q7Z434, Q8IUC6, Q8N3R9, Q8NAC3, Q8NHX9, Q92985, Q96F46, Q96JC1, Q96PD4, Q99623, Q99836, Q9BV40, Q9NR97, Q9NYK1, and Q9Y6K9.

### 3.2. Repositioned Drugs

Table **1** shows 28 drug candidates recommended by the proposed system as potential therapeutic options for COVID-19 according on the multi-target drug optimal. Such drugs are used for a variety of disorders, including bipolarity, schizophrenia, depression, cancers, hypertension, among others.

### 3.3. Therapeutic Strategies

Studies in the literature using *in silico*, *in vitro*, and *in vivo* experiments and hypotheses, try to explain the use of drugs for COVID-19 therapy. Table **2** briefly shows the details about these studies, whose investigations involve drugs blocking virus entry into the cell, inhibiting virus transcription and replication within the cell, and reducing the inflammation. This leads to the assumption that proteins provided to the system input fully contemplate the viruses' role in humans and that the system is able to prescribe drugs to fight the entire virus life cycle infection.

## 4. DISCUSSION

Although vaccines have been the most promising and efficient therapeutic approaches to combat the COVID-19 pandemic for the present [26–30], the time required to develop a functional vaccine and distribute it to multiple nations is still high [36–40]. As it is a mutant virus [21], current vaccines may not be highly effective against new variants, succeeding new studies and/or requiring multiple doses [41, 42]. Taking these issues into consideration, the drug repurposing already approved for clinical use can be extremely advantageous, and offer more accessible, cost-effective and accurate alternatives [44–46].

The present study was conducted to identify drugs as therapeutic targets for SARS-CoV-2. Analyzing datasets of several types and understanding the relationships between drugs and their targets, it was possible to discover new drug targets and new therapeutic options to fight COVID-19. Twenty-eight drugs related to several diseases, including bipolarity, cancers, depression, heart disease and

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 1 July 2022 doi:10.20944/preprints202207.0004.v1



schizophrenia, were found and indicated to combat the virus (Table 1). This corroborates evidence that the COVID-19 is a multisystemic disorder and suggests that the viruses' mechanism of action presents some comorbidity with other human diseases, showing that diseases can share similar biological processes, functions and pathways.

**Table 1. Collection of existing drugs used for various disorders repurposed for the SARS-CoV-2 treatment.**

| DrugBank ID | Treatment candidates | Indications |
|---|---|---|
| DB00091 | Cyclosporine | Prophylaxis of organ rejection in allogeneic kidney, liver, and heart transplants |
| DB00384 | Triamterene | Edema and hypertension |
| DB00317 | Gefitinib | Non-small cell lung carcinoma |
| DB00328 | Indomethacin | Osteoarthritis, rheumatoid arthritis, gouty arthritis, or ankylosing spondylitis and bursitis or tendinitis |
| DB00619 | Imatinib | Leukemias, bone marrow disorders, tumors of the stomach and digestive system |
| DB00715 | Paroxetine | Depression, major depressive disorder, panic disorder, obsessivecompulsive disorder, anxiety disorders, post-traumatic stress disorder and premenstrual dysphoric disorder |
| DB00927 | Famotidine | Duodenal ulcers, benign gastric ulcers, GERD, and Zollinger-Ellison syndrome |
| DB00458 | Imipramine | Depression and reduced childhood enuresis |
| DB01268 | Sunitinib | Some types of cancer tumors (stomach, intestines, esophagus, pancreas, or kidneys) |
| DB01238 | Aripiprazole | Bipolar disorder, irritability associated with autism spectrum disorder, schizophrenia and Tourette's disorder |
| DB01204 | Mitoxantrone | Prostate cancer, leukemia, progressive or relapsing multiple sclerosis |
| DB00313 | Valproic acid | Seizure disorders, manic episodes related to bipolar and migraine headaches |
| DB00640 | Adenosine | Paroxysmal supraventricular tachycardia |
| DB00620 | Triamcinolone | Allergic disorders, skin conditions, ulcerative colitis, arthritis, lupus, psoriasis, or breathing disorders |
| DB00783 | Estradiol | Menopause symptoms, osteoporosis in menopausal women, low estrogen levels in women with ovarian failure, types of breast cancer and prostate cancer |
| DB00988 | Dopamine | Hemodynamic imbalances, poor perfusion of vital organs, low cardiac output, and hypotension |
| DB01023 | Felodipine | Hypertension |
| DB02546 | Vorinostat | Cutaneous T-cell lymphoma |
| DB00201 | Caffeine | Increase alertness, apnea of prematurity in infants, bronchopulmonary dysplasia caused by premature birth, energy supplements, athletic enhancement products, pain relief products and cosmetic products |
| DB00420 | Promazine | Schizophrenia |
| DB00227 | Lovastatin | Lower LDL cholesterol and reduce the risk of cardiovascular disease |
| DB00563 | Methotrexate | Leukemia, some types of cancer (skin, head and neck, lung, or uterus), psoriasis, rheumatoid arthritis and juvenile rheumatoid arthritis |
| DB00997 | Doxorubicin | Cancer |
| DB00843 | Donepezil | Alzheimer's Disease |
| DB01197 | Captopril | Hypertension, congestive heart failure, kidney problems caused by diabetes and heart attack |
| DB01196 | Estramustine | Metastatic or progressive prostate cancer |
| DB01396 | Digitoxin | Congestive cardiac insufficiency, arrhythmias and heart failure |
| DB01229 | Paclitaxel | Breast cancer, ovarian cancer, lung cancer and AIDS-related Kaposi's sarcoma |

**Table 2. List of drugs identified separated by investigative categories for treating SARS-CoV-2 patients.**

| Treatment candidates | Discovery | Description | References |
|---|---|---|---|
| **Host Cell Targets** | | | |
| Captopril | *In vitro, in vivo* | May inhibit viral entry to the host cell | [109] |
| Doxorubicin | *In silico, in vitro* | Can inhibit viral entry to the host cell | [110, 111] |
| Estradiol | *In vitro* | Can promote cell protection against SARS-CoV-2 | [112] |
| Felodipine | *In vitro* | Can inhibit viral entry to the host cell | [113] |
| Promazine | *In vitro* | May block viral entry to the host cell | [114] |
| Sunitinib | *In silico, in vitro* | May inhibit viral entry to the host cell | [115] |
| **Virus targets** | | | |
| Caffeine | *In silico* | Can control coronavirus replication | [116] |
| Digitoxin | *In vitro* | May inhibit SARS-CoV-2 replication | [117] |
| Estramustine | *In silico* | May inhibit SARS-CoV-2 replication | [118] |
| Famotidine | *In vivo* | May inhibit SARS-CoV-2 replication | [119] |
| Imipramine | *In vitro* | Reduces the viral infection | [120] |
| Mitoxantrone | *In silico* | May inhibit replication | [121] |
| Methotrexate | *In vitro* | Can inhibit viral replication | [122] |
| Paclitaxel | *In silico* | May have potential antiviral properties, however for treating the virus infection nothing is well established | [123] |
| Triamcinolone | *In silico* | May inhibit SARS-CoV-2 replication | [124] |
| Triamterene | *In silico* | May inhibit SARS-CoV-2 replication | [118] |
| **Adjunctive therapy** | | | |
| Adenosine | *In vivo* | Reduces inflammation | [125] |
| Aripiprazole | *In silico, in vivo* | Reduces inflammation | [126, 127] |
| Cyclosporine | *In vivo* | Reduces mortality | [128] |
| Imatinib | *In vivo* | Might reduce mortality | [129] |
| Lovastatin | *In vivo* | May lower risk of mortality | [130] |
| Paroxetine | *In silico* | May reduce mortality and decrease rates of hospitalization | [131] |
| Vorinostat | *In silico* | May reduce inflammation | [132] |
| **Mixed actions** | | | |
| Donepezil | Hypothesis | May block or delay clinical deterioration | [133] |
| Dopamine | Hypothesis | May be involved in entry and propagation of viruses | [134] |
| Indomethacin | *In vivo* | Can inhibit replication, having both anti-inflammatory and antiviral activity | [135] |
| Gefitinib | Hypothesis | May inhibit viral entry, metabolism or reproduction | [136] |
| Valproic acid | Hypothesis | May inhibit viral entry to the host cell and may reduce inflammation | [137] |

In fact, the World Health Organization found there are no therapeutic agents capable of fully combating COVID-19, while some drugs have been recommended for patients with specific conditions [25]. None of the twenty-eight drugs indicated for COVID-19 was able to fight the virus completely, but only partially, in which most studies have been conducted *in vitro* and *in vivo* (Table **2**). Similar to cocktails for cancer and HIV [68], perhaps more comprehensive drug investigation can aid in combating COVID-19 as well. Studies have suggested that more drug

 doi:10.20944/preprints202207.0004.v1



combinations might be better to minimizing adverse reactions, increase synergy and efficacy [138–140]. Besides, the use of drug in combination might fully cover the role of human coronavirus, such as blocking the virus entry into the cell, inhibiting virus transcription and replication within the cell, and reducing inflammation which makes it difficult for lungs to absorb and transport oxygen to the rest of the body.

Some efforts have been directed towards the discovery synergistic drug combinations [139–141]. Similarly, the drugs hypothesized to fight COVID-19 (Table **2**) might be better used as a cocktail to fight the virus, including six drugs which block COVID-19 infection, ten which inhibit virus replication, seven which reduce inflammation and five therapeutic agents with multiple mechanisms of action. Combining one or more drugs from those categories might result in better therapeutic approaches for patients, however it is necessary clinical studies to validate this hypothesis.

Despite the fact that the results indicate drug relationships for COVID-19, the best combination or synergy of these drugs is still unknown. In this sense, further studies with *in vitro* and *in vivo* experiments are essential to validate effective drug combinations. Additionally, there may be several potential drug combinations to treat different cases in COVID-19 patients, which require precise and synergistic drug approaches for therapies guided by individual genomic profiles.

This computational framework was able to discover new drug targets through TTS prediction, however using DDS prediction in conjunction with TTS might result in better drug recommendations for the disease. Drug synergy studies are also important and can be included in the drug recommendation step, possibly becoming the system more effective for drug repurposing.

## CONCLUSION

The COVID-19 pandemic has brought several challenges, especially within both the healthcare system and economic sectors [24]. Due to this emergency, repurposing existing drugs has been an important therapeutic approach to fight the coronavirus. Computational methods are a great opportunity for preliminary filtering of drug candidates, while also saving time, effort and financial resources [48, 56]. This research has aimed at developing a computational system which recommends existing drugs as potential therapeutic targets for SARS-CoV-2 making use of integrative analysis of biological data sets and artificial intelligence techniques.

Results have indicated 28 drugs which could be effective for COVID-19. However, in order to discover their best combination and synergy, further *in vitro* and *in vivo* studies are still necessary. Even though there are some limitations, this computational framework may provide a great option for repurposing drugs for COVID-19, offering new perspectives for precision drug and medicine.

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

## HUMAN AND ANIMAL RIGHTS

No animals/humans were used for studies that are basis of this research.

## CONSENT FOR PUBLICATION

Not applicable.

## AVAILABILITY OF DATAS AND MATERIALS

All data supporting the findings of this this study are included in this published article.

## FUNDING

None.

## CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

## ACKNOWLEDGEMENTS

The authors would like to thank Dr. Fabio Albuquerque Marchi for comments and assistance with language and writing that greatly improved the manuscript.

## LIST OF ABBREVIATIONSS

| | | |
|---|---|---|
| 2019-nCoV | = | New Coronavirus 2019 |
| AIDS | = | Acquired Immunodeficiency Syndrome |
| ATC | = | Anatomical Therapeutic Chemical |
| ChEBI | = | Chemical Entities of Biological Interest |
| COVID-19 | = | Coronavirus Disease 2019 |
| DDS | = | Drug-Drug Similarity |
| DNA | = | Deoxyribonucleic Acid |
| DTI | = | Drug-Target Interactions |
| GA | = | Genetic Algorithms |
| GERD | = | Gastroesophageal Reflux disease |
| HCoVs | = | Human Coronaviruses |
| HGNC | = | Human Gene Nomenclature |
| HIV | = | Human Immunodeficiency Virus |
| HPRD | = | Human Protein Reference Database |
| IUPAC | = | International Union of Pure and Applied Chemistry |
| KEGG | = | Kyoto Encyclopedia of Genes and Genomes |
| KNN | = | K-Nearest Neighbors |
| LDL | = | Low-Density Lipoproteins |
| LR | = | Logistic Regression |
| MedDRA | = | Medical Dictionary for Regulatory Activities |
| MERS-CoV | = | Middle East respiratory Syndrome Coronavirus |
| mRNA | = | Messenger RNA |
| NB | = | Naive Bayes |
| NCBI | = | National Center for Biotechnology |
| PPI | = | Protein-Protein Interaction |
| PT | = | Preferred Term |
| RFs | = | Random Forests |
| RNA | = | Ribonucleic Acid |

| | | |
|---|---|---|
| SARS-CoV-2 | = | Severe Acute Respiratory Syndrome Coronavirus 2 |
| SMILES | = | Simplified Molecular Input Line Entry System |
| SVMs | = | Support Vector Machines |
| TTD | = | Therapeutic Target Database |
| TTS | = | Target-Target Similarity Network |
| UMLS | = | Unified Medical Language System |
| UNII | = | Unique Ingredient Identifier |
| WHO | = | World Health Organization |

## REFERENCES


[1] World Health Organization (WHO). Novel Coronavirus (2019-nCoV) Situation Report – 52. Data as reported by 12 March 2020. Available from https://www.who.int/docs/default-source/coronaviruse/20200312-sitrep-52-covid-19.pdf?sfvrsn=e2bfc9c0_2.

[2] Perrella A, Carannante N, Berretta M, Rinaldi M, Maturo N, Rinaldi L. Novel Coronavirus 2019 (Sars-CoV2): a global emergency that needs new approaches? Eur Rev Med Pharmacol Sci. 2020 Feb;24(4):2162–4.

[3] Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19): A Review. JAMA. 2020 Aug 25;324(8):782–93.

[4] McKee DL, Sternberg A, Stange U, Laufer S, Naujokat C. Candidate drugs against SARS-CoV-2 and COVID-19. Pharmacol Res. 2020 Jul;157:104859.

[5] Chen Y, Li L. SARS-CoV-2: virus dynamics and host response. Lancet Infect Dis. 2020 May;20(5):515–6.

[6] Ghinai I, McPherson TD, Hunter JC, Kirking HL, Christiansen D, Joshi K, et al. First known person-to-person transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in the USA. The Lancet. 2020 Apr 4;395(10230):1137–44.

[7] Pung R, Chiew CJ, Young BE, Chin S, Chen MI-C, Clapham HE, et al. Investigation of three clusters of COVID-19 in Singapore: implications for surveillance and response measures. Lancet. 2020 Mar 28;395(10229):1039–46.

[8] Hamner L, Dubbel P, Capron I, Ross A, Jordan A, Lee J, et al. High SARS-CoV-2 Attack Rate Following Exposure at a Choir Practice - Skagit County, Washington, March 2020. MMWR Morb Mortal Wkly Rep. 2020 May 15;69(19):606–10.

[9] WHO Coronavirus (COVID-19) Dashboard [Internet]. [cited 2021 Dez 20]. Available from: https://covid19.who.int.

[10] Verity R, Okell LC, Dorigatti I, Winskill P, Whittaker C, Imai N, et al. Estimates of the severity of coronavirus disease 2019: a model-based analysis. Lancet Infect Dis. 2020 Jun;20(6):669–77.

[11] Eastin C, Eastin T. Clinical Characteristics of Coronavirus Disease 2019 in China. J Emerg Med. 2020 Apr;58(4):711–2.

[12] Menni C, Valdes AM, Freidin MB, Sudre CH, Nguyen LH, Drew DA, et al. Real-time tracking of self-reported symptoms to predict potential COVID-19. Nat Med. 2020 Jul;26(7):1037–40.

[13] Roberts CM, Levi M, McKee M, Schilling R, Lim WS, Grocott MPW. COVID-19: a complex multisystem disorder. Br J Anaesth. 2020/06/20 ed. 2020 Sep;125(3):238–42.

[14] Cordon-Cardo C, Pujadas E, Wajnberg A, Sebra R, Patel G, Firpo-Betancourt A, et al. COVID-19: Staging of a New Disease. Cancer Cell. 2020 Nov 9;38(5):594–7.

[15] Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. The Lancet. 2020 Feb 22;395(10224):565–74.

[16] Almazán F, Sola I, Zuñiga S, Marquez-Jurado S, Morales L, Becares M, et al. Coronavirus reverse genetic systems: infectious clones and replicons. Virus Res. 2014 Aug 30;189:262–70.

[17] Payne S. Family Coronaviridae. Viruses. 2017;149–58.

[18] Woo PCY, Lau SKP, Lam CSF, Lau CCY, Tsang AKL, Lau JHN, et al. Discovery of seven novel Mammalian and avian coronaviruses in the genus deltacoronavirus supports bat coronaviruses as the gene source of alphacoronavirus and betacoronavirus and avian coronaviruses as the gene source of gammacoronavirus and deltacoronavirus. J Virol. 2012 Apr;86(7):3995–4008.

[19] Kandeil A, Gomaa M, Shehata M, El-Taweel A, Kayed AE, Abiadh A, et al. Middle East respiratory syndrome coronavirus infection in non-camelid domestic mammals. Emerg Microbes Infect. 2019;8(1):103–8.

[20] Tyrrell DA, Bynoe ML. Cultivation of viruses from a high proportion of patients with colds. Lancet. 1966 Jan 8;1(7428):76–7.

[21] Tracking SARS-CoV-2 variants [Internet]. [cited 2021 Dez 20]. Available from: https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/.

[22] Li Y, Campbell H, Kulkarni D, Harpur A, Nundy M, Wang X, et al. The temporal association of introducing and lifting non-pharmaceutical interventions with the time-varying reproduction number (R) of SARS-CoV-2: a modelling study across 131 countries. The Lancet Infectious Diseases. 2021 Feb 1;21(2):193–202.

[23] Walker PGT, Whittaker C, Watson OJ, Baguelin M, Winskill P, Hamlet A, et al. The impact of COVID-19 and strategies for mitigation and suppression in low- and middle-income countries. Science. 2020 Jul 24;369(6502):413–22.

[24] Fontanarosa PB, Bauchner H. COVID-19-Looking Beyond Tomorrow for Health Care and Society. JAMA. 2020 May 19;323(19):1907–8.

[25] World Health Organization. Therapeutics and COVID-19: living guideline, 7 December 2021. World Health Organization; 2021.

[26] Petherick A. Developing antibody tests for SARS-CoV-2. Lancet. 2020 Apr 4;395(10230):1101–2.

[27] Kaddoura M, AlIbrahim M, Hijazi G, Soudani N, Audi A, Alkalamouni H, et al. COVID-19 Therapeutic Options Under Investigation. Front Pharmacol. 2020 Aug 6;11:1196.

[28] Siddique R, Bai Q, Shereen MA, Nabi G, Han G, Rashid F, et al. Evidence and speculations: vaccines and therapeutic options for COVID-19 pandemic. Hum Vaccin Immunother. 2021 Apr 3;17(4):1113–21.

[29] Senger MR, Evangelista TCS, Dantas RF, Santana MV da S, Gonçalves LCS, de Souza Neto LR, et al. COVID-19: molecular targets, drug

repurposing and new avenues for drug discovery. Mem Inst Oswaldo Cruz. 2020;115:e200254.

[30] Umakanthan S, Chattu VK, Ranade AV, Das D, Basavarajegowda A, Bukelo M. A rapid review of recent advances in diagnosis, treatment and vaccination for COVID-19. AIMS Public Health. 2021 Feb 1;8(1):137–53.

[31] Pujari R, Thommana MV, Ruiz Mercedes B, Serwat A. Therapeutic Options for COVID-19: A Review. Cureus. 12(9):e10480.

[32] Zhu Y, Li J, Pang Z. Recent insights for the emerging COVID-19: Drug discovery, therapeutic options and vaccine development. Asian J Pharm Sci. 2021 Jan;16(1):4–23.

[33] Sarkar C, Mondal M, Torequl Islam M, Martorell M, Docea AO, Maroyi A, et al. Potential Therapeutic Options for COVID-19: Current Status, Challenges, and Future Perspectives. Front Pharmacol. 2020 Sep 15;11:572870.

[34] COVID-19 vaccine tracker and landscape [Internet]. [cited 2021 Aug 5]. Available from: https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines.

[35] Policy (OIDP) O of ID and H. Vaccine Types [Internet]. HHS.gov. 2021 [cited 2021 Aug 5]. Available from: https://www.hhs.gov/immunization/basics/types/index.html.

[36] Ritchie H, Ortiz-Ospina E, Beltekian D, Mathieu E, Hasell J, Macdonald B, et al. Coronavirus Pandemic (COVID-19). Our World in Data [Internet]. 2020 Mar 5 [cited 2021 Aug 6]; Available from: https://ourworldindata.org/covid-vaccinations.

[37] Lurie N, Saville M, Hatchett R, Halton J. Developing Covid-19 Vaccines at Pandemic Speed. N Engl J Med. 2020 May 21;382(21):1969–73.

[38] Gouglas D, Le TT, Henderson K, Kaloudis A, Danielsen T, Hammersland NC, et al. Estimating the cost of vaccine development against epidemic infectious diseases: a cost minimisation study. The Lancet Global Health. 2018 Dec 1;6(12):e1386–96.

[39] Lupton HaroldW, Lambert RhondaD, Bumgardner DonaldL, Moe JamesB, Eddy GeraldA. Inactivated vaccine for Ebola virus efficacious in guineapig model. Inactivated vaccine for Ebola virus efficacious in guineapig model. The Lancet. 1980 Dec 13;316(8207):1294–5.

[40] First Ebola vaccine approved. Nature Biotechnology. 2020 Jan 1;38(1):6–6.

[41] Mahase E. Covid-19: Do vaccines work against omicron—and other questions answered. BMJ. 2021 Dec 10;375:n3062.

[42] Burki TK. Omicron variant and booster COVID-19 vaccines. The Lancet Respiratory Medicine. 2021 Dec 17.

[43] Galindez G, Matschinske J, Rose TD, Sadegh S, Salgado-Albarrán M, Späth J, et al. Lessons from the COVID-19 pandemic for advancing computational drug repurposing strategies. Nat Comput Sci. 2021 Jan;1(1):33–41.

[44] Ashburn TT, Thor KB. Drug repositioning: identifying and developing new uses for existing drugs. Nat Rev Drug Discov. 2004 Aug;3(8):673–83.

[45] Cha Y, Erez T, Reynolds IJ, Kumar D, Ross J, Koytiger G, et al. Drug repurposing from the perspective of pharmaceutical companies. Br J Pharmacol. 2018 Jan;175(2):168–80.

[46] Pushpakom S, Iorio F, Eyers PA, Escott KJ, Hopper S, Wells A, et al. Drug repurposing: progress, challenges and recommendations. Nat Rev Drug Discov. 2019 Jan;18(1):41–58.

[47] Fitzgerald JB, Schoeberl B, Nielsen UB, Sorger PK. Systems biology and combination therapy in the quest for clinical efficacy. Nat Chem Biol. 2006 Sep;2(9):458–66.

[48] Ciliberto G, Cardone L. Boosting the arsenal against COVID-19 through computational drug repurposing. Drug Discov Today. 2020 Jun;25(6):946–8.

[49] Ekins S, Mottin M, Ramos PRPS, Sousa BKP, Neves BJ, Foil DH, et al. Déjà vu: Stimulating open drug discovery for SARS-CoV-2. Drug Discov Today. 2020 May;25(5):928–41.

[50] Dyall J, Coleman CM, Hart BJ, Venkataraman T, Holbrook MR, Kindrachuk J, et al. Repurposing of clinically developed drugs for treatment of Middle East respiratory syndrome coronavirus infection. Antimicrob Agents Chemother. 2014 Aug;58(8):4885–93.

[51] Zhou Y, Hou Y, Shen J, Huang Y, Martin W, Cheng F. Network-based drug repurposing for novel coronavirus 2019- nCoV/SARS-CoV-2. Cell Discov. 2020 Mar 16;6(1):1–18.

[52] Ton A-T, Gentile F, Hsing M, Ban F, Cherkasov A. Rapid Identification of Potential Inhibitors of SARS-CoV-2 Main Protease by Deep Docking of 1.3 Billion Compounds. Mol Inform. 2020 Aug;39(8):e2000028.

[53] Beck BR, Shin B, Choi Y, Park S, Kang K. Predicting commercially available antiviral drugs that may act on the novel coronavirus (SARS-CoV-2) through a drug-target interaction deep learning model. Comput Struct Biotechnol J. 2020;18:784–90.

[54] Ge Y, Tian T, Huang S, Wan F, Li J, Li S, et al. A data-driven drug repositioning framework discovered a potential therapeutic agent targeting COVID-19. bioRxiv. 2020 Mar 12;2020.03.11.986836.

[55] Santos R, Ursu O, Gaulton A, Bento AP, Donadi RS, Bologa CG, et al. A comprehensive map of molecular drug targets. Nat Rev Drug Discov. 2017 Jan;16(1):19–34.

[56] Sharma PP, Bansal M, Sethi A, Pena L, Goel VK, Grishina M, Chaturvedi S, Kumar D, Rathi B. Computational methods directed towards drug repurposing for COVID-19: advantages and limitations. RSC Advances. 2021;11(57):36181-98.

[57] Mottaqi MS, Mohammadipanah F, Sajedi H. Contribution of machine learning approaches in response to SARS-CoV-2 infection. Inform Med Unlocked. 2021;23:100526.

[58] Keshavarzi Arshadi A, Webb J, Salem M, Cruz E, Calad-Thomson S, Ghadirian N, et al. Artificial Intelligence for COVID-19 Drug Discovery and Vaccine Development. Front Artif Intell. 2020;3:65.

[59] Zhou Y, Wang F, Tang J, Nussinov R, Cheng F. Artificial intelligence in COVID-19 drug repurposing. Lancet Digit Health. 2020 Dec;2(12):e667–76.

[60] El-Behery H, Attia A-F, El-Feshawy N, Torkey H. Efficient machine learning model for predicting drug-target interactions with case study for Covid-19. Comput Biol Chem. 2021 Aug;93:107536.

[61] Acharya A, Agarwal R, Baker MB, Baudry J, Bhowmik D, Boehm S, et al. Supercomputer-Based Ensemble Docking Drug Discovery Pipeline with Application to Covid-19. J Chem Inf Model. 2020 Dec 1;60(12):5832–52.

[62] Sadegh S, Matschinske J, Blumenthal DB, Galindez G, Kacprowski T, List M, et al. Exploring the SARS-CoV-2 virus-host-drug interactome for drug repurposing. Nat Commun. 2020 Jul 14;11(1):3518.

[63] Gordon DE, Jang GM, Bouhaddou M, Xu J, Obernier K, White KM, et al. A SARS-CoV-2 protein interaction map reveals targets for drug repurposing. Nature. 2020 Jul;583(7816):459–68.

[64] Auwul MR, Rahman MR, Gov E, Shahjaman M, Moni MA. Bioinformatics and machine learning approach identifies potential drug targets and pathways in COVID-19. Brief Bioinform. 2021 Apr 12;bbab120.

[65] Cantürk S, Singh A, St-Amant P, Behrmann J. Machine-Learning Driven Drug Repurposing for COVID-19. arXiv:200614707. 2020 Jun 25.

[66] Rajput A, Thakur A, Mukhopadhyay A, Kamboj S, Rastogi A, Gautam S, et al. Prediction of repurposed drugs for Coronaviruses using artificial intelligence and machine learning. Computational and Structural Biotechnology Journal. 2021 Jan 1;19:3133–48.

[67] Nussinov R, Jang H, Tsai C-J, Cheng F. Review: Precision medicine and driver mutations: Computational methods, functional assays and conformational principles for interpreting cancer drivers. PLOS Computational Biology. 2019 Mar 28;15(3):e1006658.

[68] König IR, Fuchs O, Hansen G, von Mutius E, Kopp MV. What is precision medicine? Eur Respir J. 2017 Oct 1;50(4):1700391.

[69] Mirnezami R, Nicholson J, Darzi A. Preparing for precision medicine. N Engl J Med. 2012 Feb 9;366(6):489–91.

[70] Ashley EA. Towards precision medicine. Nat Rev Genet. 2016 Sep;17(9):507–22.

[71] Collins FS, Varmus H. A New Initiative on Precision Medicine. New England Journal of Medicine. 2015 Feb 26;372(9):793–5.

[72] Liu T, Lin Y, Wen X, Jorissen RN, Gilson MK. BindingDB: a web-accessible database of experimentally determined protein-ligand binding affinities. Nucleic Acids Res. 2007 Jan;35(Database issue):D198-201.

[73] Hastings J, de Matos P, Dekker A, Ennis M, Harsha B, Kale N, et al. The ChEBI reference database and ontology for biologically relevant chemistry: enhancements for 2013. Nucleic Acids Research. 2013 Jan 1;41(D1):D456– 63.

[74] Wishart DS, Knox C, Guo AC, Shrivastava S, Hassanali M, Stothard P, et al. DrugBank: a comprehensive resource for in silico drug discovery and exploration. Nucleic Acids Res. 2006 Jan 1;34(Database issue):D668–72.

[75] Kim S, Chen J, Cheng T, Gindulyte A, He J, He S, et al. PubChem in 2021: new data content and improved web interfaces. Nucleic Acids Research. 2021 Jan 8;49(D1):D1388–95.

[76] Jeske L, Placzek S, Schomburg I, Chang A, Schomburg D. BRENDA in 2019: a European ELIXIR core data resource. Nucleic Acids Research. 2019 Jan 8;47(D1):D542–9.

[77] Hashimoto K, Tokimatsu T, Kawano S, Yoshizawa AC, Okuda S, Goto S, et al. Comprehensive analysis of glycosyltransferases in eukaryotic genomes for structural and functional characterization of glycans. Carbohydr Res. 2009 May 12;344(7):881–7.

[78] Kanehisa M, Araki M, Goto S, Hattori M, Hirakawa M, Itoh M, et al. KEGG for linking genomes to life and the environment. Nucleic Acids Res. 2008 Jan;36(Database issue):D480-484.

[79] Whirl-Carrillo M, Huddart R, Gong L, Sangkuhl K, Thorn CF, Whaley R, et al. An Evidence-Based Framework for Evaluating Pharmacogenomics Knowledge for Personalized Medicine. Clin Pharmacol Ther. 2021 Jul 3.

[80] Nelson SJ, Zeng K, Kilbourne J, Powell T, Moore R. Normalized names for clinical drugs: RxNorm at 6 years. J Am Med Inform Assoc. 2011;18(4):441–8.

[81] Wang Y, Zhang S, Li F, Zhou Y, Zhang Y, Wang Z, et al. Therapeutic target database 2020: enriched resource for facilitating research and early development of targeted therapeutics. Nucleic Acids Res. 2020 Jan 8;48(D1):D1031–41.

[82] Yates AD, Achuthan P, Akanni W, Allen J, Allen J, Alvarez-Jarreta J, et al. Ensembl 2020. Nucleic Acids Research. 2020 Jan 8;48(D1):D682–8.

[83] Braschi B, Denny P, Gray K, Jones T, Seal R, Tweedie S, et al. Genenames.org: the HGNC and VGNC resources in 2019. Nucleic Acids Research. 2019 Jan 8;47(D1):D786–92.

[84] The Gene Ontology Consortium. The Gene Ontology Resource: 20 years and still GOing strong. Nucleic Acids Research. 2019 Jan 8;47(D1):D330–8.

[85] Sayers EW, Beck J, Brister JR, Bolton EE, Canese K, Comeau DC, et al. Database resources of the National Center for Biotechnology Information. Nucleic Acids Res. 2020 Jan 8;48(D1):D9–16.

[86] Keshava Prasad TS, Goel R, Kandasamy K, Keerthikumar S, Kumar S, Mathivanan S, et al. Human Protein Reference Database--2009 update. Nucleic Acids Res. 2009 Jan;37(Database issue):D767-772.

[87] Kanehisa M, Goto S, Hattori M, Aoki-Kinoshita KF, Itoh M, Kawashima S, et al. From genomics to chemical genomics: new developments in KEGG. Nucleic Acids Res. 2006 Jan 1;34(Database issue):D354–7.

[88] Tatonetti NP, Ye PP, Daneshjou R, Altman RB. Data-Driven Prediction of Drug Effects and Interactions. Science Translational Medicine. 2012 Mar 14;4(125):125ra31.

[89] Brown EG, Wood L, Wood S. The medical dictionary for regulatory activities (MedDRA). Drug Saf. 1999 Feb;20(2):109–17.

[90] El-Gebali S, Mistry J, Bateman A, Eddy SR, Luciani A, Potter SC, et al. The Pfam protein families database in 2019. Nucleic Acids Research. 2019 Jan 8;47(D1):D427–32.

[91] Wishart DS, Li C, Marcu A, Badran H, Pon A, Budinski Z, et al. PathBank: a comprehensive pathway database for model organisms. Nucleic Acids Research. 2020 Jan 8;48(D1):D470–8.

[92] Fabregat A, Jupe S, Matthews L, Sidiropoulos K, Gillespie M, Garapati P, et al. The Reactome Pathway Knowledgebase. Nucleic Acids Research. 2018 Jan 4;46(D1):D649–55.

[93] Kuhn M, Letunic I, Jensen LJ, Bork P. The SIDER database of drugs and side effects. Nucleic Acids Research. 2016 Jan 4;44(D1):D1075–9.

[94] Bodenreider O. The Unified Medical Language System (UMLS): integrating biomedical terminology. Nucleic Acids Res. 2004 Jan 1;32(Database issue):D267–70.

[95] Szklarczyk D, Santos A, von Mering C, Jensen LJ, Bork P, Kuhn M. STITCH 5: augmenting protein–chemical interaction networks with tissue and affinity data. Nucleic Acids Research. 2016 Jan 4;44(D1):D380–4.

[96] The UniProt Consortium. UniProt: a worldwide hub of protein knowledge. Nucleic Acids Research. 2019 Jan 8;47(D1):D506–15.

[97] Takarabe M, Shigemizu D, Kotera M, Goto S, Kanehisa M. Network-based analysis and characterization of adverse drug-drug interactions. J Chem Inf Model. 2011 Nov 28;51(11):2977–85.

[98] Meek TD. Enzymes as Drug Targets. Burger's Medicinal Chemistry and Drug Discovery. 2003 Jan 15:1-51.

[99] Mayr A, Klambauer G, Unterthiner T, Steijaert M, K. Wegner J, Ceulemans H, et al. Large-scale comparison of machine learning methods for drug target prediction on ChEMBL. Chemical Science. 2018;9(24):5441–51.

[100] Iwata H, Mizutani S, Tabei Y, Kotera M, Goto S, Yamanishi Y. Inferring protein domains associated with drug side effects based on drug-target interaction network. BMC Syst Biol. 2013 Dec 13;7(Suppl 6):S18.

[101] 102. Chen X, Yan CC, Zhang X, Zhang X, Dai F, Yin J, et al. Drug–target interaction prediction: databases, web servers and computational models. Briefings in Bioinformatics. 2016 Jul 1;17(4):696–712.

[102] Abdel Hameid R, Cormet-Boyaka E, Kuebler WM, Uddin M, Berdiev BK. SARS-CoV-2 may hijack GPCR signaling pathways to dysregulate lung ion and fluid transport. American Journal of Physiology-Lung Cellular and Molecular Physiology. 2021 Mar 1;320(3):L430–5.

[103] McClenaghan C, Hanson A, Lee S-J, Nichols CG. Coronavirus Proteins as Ion Channels: Current and Potential Research. Frontiers in Immunology. 2020;11:2651.

[104] Croce L, Gangemi D, Ancona G, Liboà F, Bendotti G, Minelli L, et al. The cytokine storm and thyroid hormone changes in COVID-19. J Endocrinol Invest. 2021;44(5):891–904.

[105] Heaton BE, Trimarco JD, Hamele CE, Harding AT, Tata A, Zhu X, et al. SRSF protein kinases 1 and 2 are essential host factors for human coronaviruses including SARS-CoV-2. bioRxiv. 2020 Jan 1;2020.08.14.251207.

[106] Chen L, Marishta A, Ellison CE, Verzi MP. Identification of Transcription Factors Regulating SARS-CoV-2 Entry Genes in the Intestine. Cell Mol Gastroenterol Hepatol. 2020 Aug 15;11(1):181–4.

[107] Rex DAB, Dagamajalu S, Kandasamy RK, Raju R, Prasad TSK. SARS-CoV-2 signaling pathway map: A functional landscape of molecular mechanisms in COVID-19. J Cell Commun Signal. 2021 Jun 28;1–8.

[108] UniProt [Internet]. [cited 2021 Jun 29]. Available from: https://covid-19.uniprot.org/uniprotkb?query=*&facets=model_organism:Human.

[109] Pedrosa MA, Valenzuela R, Garrido-Gil P, Labandeira CM, Navarro G, Franco R, et al. Experimental data using candesartan and captopril indicate no double-edged sword effect in COVID-19. Clinical Science. 2021 Feb 1;135(3):465–81.

[110] Al-Motawa MS, Abbas H, Wijten P, de la Fuente A, Xue M, Rabbani N, et al. Vulnerabilities of the SARS-CoV-2 Virus to Proteotoxicity—Opportunity for Repurposed Chemotherapy of COVID-19 Infection. Frontiers in Pharmacology. 2020;11:1579.

[111] Sajid Jamal QM, Alharbi AH, Ahmad V. Identification of doxorubicin as a potential therapeutic against SARS-CoV-2 (COVID-19) protease: a molecular docking and dynamics simulation studies. null. 2021 Apr 7;1–15.

[112] Lemes RMR, Costa AJ, Bartolomeo CS, Bassani TB, Nishino MS, Pereira GJ da S, et al. 17β-estradiol reduces SARS-CoV-2 infection in vitro. Physiological Reports. 2021;9(2):e14707.

[113] Straus MR, Bidon M, Tang T, Whittaker GR, Daniel S. FDA approved calcium channel blockers inhibit SARS CoV 2 infectivity in epithelial lung cells. bioRxiv. 2020 Jan 1;2020.07.21.214577.

[114] Glebov OO. Understanding SARS-CoV-2 endocytosis for COVID-19 drug repurposing. FEBS J. 2020 Jun 2;10.1111/febs.15369.

[115] Wang P-G, Tang D-J, Hua Z, Wang Z, An J. Sunitinib reduces the infection of SARS-CoV, MERS-CoV and SARS-CoV-2 partially by inhibiting AP2M1 phosphorylation. Cell Discov. 2020 Oct 13;6(1):1–5.

[116] Elzupir AO. Caffeine and caffeine-containing pharmaceuticals as promising inhibitors for 3-chymotrypsin-like protease of SARS-CoV-2. J Biomol Struct Dyn. :1–8.

[117] Cho J, Lee YJ, Kim JH, Kim S il, Kim SS, Choi B-S, et al. Antiviral activity of digoxin and ouabain against SARS-CoV-2 infection and its implication for COVID-19. Sci Rep. 2020 Oct 1;10(1):16200.

[118] Haneczok J, Delijewski M. Machine learning enabled identification of potential SARS-CoV-2 3CLpro inhibitors based on fixed molecular fingerprints and Graph-CNN neural representations. J Biomed Inform. 2021 Jul 1;119:103821.

[119] Malone RW, Tisdall P, Fremont-Smith P, Liu Y, Huang X-P, White KM, et al. COVID-19: Famotidine, Histamine, Mast Cells, and Mechanisms. Front Pharmacol. 2021 Mar 23;12:633680.

[120] Fred SM, Kuivanen S, Ugurlu H, Casarotto PC, Levanov L, Saksela K, et al. Antidepressant and antipsychotic drugs reduce viral infection by SARS-CoV-2 and fluoxetine show antiviral activity against the novel variants in vitro. bioRxiv. 2021 Jan 1;2021.03.22.436379.

[121] Lokhande KB, Doiphode S, Vyas R, Swamy KV. Molecular docking and simulation studies on SARS-CoV-2 Mpro reveals Mitoxantrone, Leucovorin, Birinapant, and Dynasore as potent drugs against COVID-19. J Biomol Struct Dyn. :1–12.

[122] Caruso A, Caccuri F, Bugatti A, Zani A, Vanoni M, Bonfanti P, et al. Methotrexate inhibits SARS-CoV-2 virus replication "in vitro." Journal of Medical Virology. 2021;93(3):1780–5.

[123] Das S, Camphausen K, Shankavaram U. In silico Drug Repurposing to combat COVID-19 based on Pharmacogenomics of Patient Transcriptomic Data. Res Sq. 2020 Jun 30;rs.3.rs-39128.

[124] Abo Elmaaty A, Alnajjar R, A. Hamed MI, Khattab M, M. Khalifa M, A. Al-Karmalawy A. Revisiting activity of some glucocorticoids as a potential inhibitor of SARS-CoV-2 main protease: theoretical study. RSC Advances. 2021;11(17):10027–42.

[125] Caracciolo M, Correale P, Mangano C, Foti G, Falcone C, Macheda S, et al. Efficacy and Effect of Inhaled Adenosine Treatment in Hospitalized COVID-19 Patients. Front Immunol. 2021 Mar 18;12:613070.

[126] Crespo-Facorro B, Ruiz-Veguilla M, Vázquez-Bourgon J, Sánchez-Hidalgo AC, Garrido-Torres N, Cisneros JM, et al. Aripiprazole as a

Candidate Treatment of COVID-19 Identified Through Genomic Analysis. Front Pharmacol. 2021 Mar 2;12:646701.

[127] Kawana S, Nishiyama S. Pustular psoriasis and aseptic purulent arthritis: possible role of leukotrienes B4 and C4 in a flare of synovitis. Dermatology. 1995 Jan 1;190(1):35–8.

[128] Galvez-Romero JL, Palmeros-Rojas O, Real-Ramírez FA, Sánchez-Romero S, Tome-Maxil R, Ramírez-Sandoval MP, et al. Cyclosporine A plus low-dose steroid treatment in COVID-19 improves clinical outcomes in patients with moderate to severe disease. A pilot study. J Intern Med. 2020 Dec 3;10.1111/joim.13223.

[129] Aman J, Duijvelaar E, Botros L, Kianzad A, Schippers JR, Smeele PJ, et al. Imatinib in patients with severe COVID-19: a randomised, double-blind, placebo-controlled, clinical trial. Lancet Respir Med. 2021 Jun 17;S2213- 2600(21)00237-X.

[130] Zhang X-J, Qin J-J, Cheng X, Shen L, Zhao Y-C, Yuan Y, et al. In-Hospital Use of Statins Is Associated with a Reduced Risk of Mortality among Individuals with COVID-19. Cell Metabolism. 2020 Aug 4;32(2):176-187.e4.

[131] Creeden JF, Imami AS, Eby HM, Gillman C, Becker KN, Reigle J, et al. Fluoxetine as an anti-inflammatory therapy in SARS-CoV-2 infection. Biomedicine & Pharmacotherapy. 2021 Jun 1;138:111437.

[132] Barh D, Tiwari S, Weener ME, Azevedo V, Góes-Neto A, Gromiha MM, et al. Multi-omics-based identification of SARS-CoV-2 infection biology and candidate drugs against COVID-19. Computers in Biology and Medicine. 2020 Nov 1;126:104051.

[133] Hashimoto K. Repurposing of CNS drugs to treat COVID-19 infection: targeting the sigma-1 receptor. Eur Arch Psychiatry Clin Neurosci. 2021 Mar 1;271(2):249–58.

[134] Khalefah MM, Khalifah AM. Determining the relationship between SARS-CoV-2 infection, dopamine, and COVID-19 complications. Journal of Taibah University Medical Sciences. 2020 Dec 1;15(6):550–3.

[135] Amici C, Di Caro A, Ciucci A, Chiappa L, Castilletti C, Martella V, et al. Indomethacin has a potent antiviral activity against SARS coronavirus. Antivir Ther. 2006;11(8):1021–30.

[136] Weisberg E, Parent A, Yang PL, Sattler M, Liu Q, Liu Q, et al. Repurposing of Kinase Inhibitors for Treatment of COVID-19. Pharm Res. 2020;37(9):167.

[137] Pitt B, Sutton NR, Wang Z, Goonewardena SN, Holinstat M. Potential repurposing of the HDAC inhibitor valproic acid for patients with COVID-19. European Journal of Pharmacology. 2021 May 5;898:173988.

[138] Sun W, Sanderson PE, Zheng W. Drug combination therapy increases successful drug repositioning. Drug Discovery Today. 2016 Jul 1;21(7):1189–95.

[139] Jin W, Barzilay R, Jaakkola T. Discovering Synergistic Drug Combinations for COVID with Biological Bottleneck Models. arXiv preprint arXiv:201104651. 2020.

[140] Schloer S, Brunotte L, Mecate-Zambrano A, Zheng S, Tang J, Ludwig S, et al. Drug synergy of combinatory treatment with remdesivir and the repurposed drugs fluoxetine and itraconazole effectively impairs SARS-CoV-2 infection in vitro. British Journal of Pharmacology. 2021 Jun 1;178(11):2339–50.

[141] Shyr ZA, Cheng Y-S, Lo DC, Zheng W. Drug combination therapy for emerging viral diseases. Drug Discovery Today. 2021 Oct 1;26(10):2367–76.