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

CHAPTER

14

Databases, DrugBank, and virtual screening platforms for therapeutic development

Sushil Kumar Middha[1], *Anjlina David*[2], *Shoumi Haldar*[2], *Hankhray Boro*[3], *Prachurjya Panda*[4], *Nikitha Bajare*[5], *Ligi Milesh*[6], *V.R. Devaraj*[7] *and Talambedu Usha*[5]

[1]Department of Biotechnology, Maharani Lakshmi Ammanni College for Women, Bangalore, Karnataka, India [2]School of Applied Sciences, REVA University, Rukmini Knowledge Park, Bangalore, Karnataka, India [3]Department of Biotechnology, Bodoland University, Kokrajhar, Assam, India [4]The Shraga Segal Department of Microbiology, Immunology, and Genetics, Faculty of Health Science, Ben-Gurion University of the Negev, Be'er Sheva, Israel [5]Department of Biochemistry, Maharani Lakshmi Ammanni College for Women, Bangalore, Karnataka, India [6]Department of Surgery, Wisconsin Institute of Medical Research, University of Wisconsin-Madison, Madison, WI, United States [7]Department of Biochemistry, Bengaluru City University, Bengaluru, Karnataka, India

14.1 Introduction

The outbreak of the severe acute respiratory syndrome-Coronavirus-2 (SARS-CoV-2) was first detected in Wuhan, China in late December 2019; which is now a global pandemic (Wuhan Municipal health). SARS-CoV-2 is an enveloped, nonsegmented, single-stranded-positive-sense RNA with at least 12 open reading frames (ORFs), coding for 16 nonstructural proteins and four structural proteins (Chen et al., 2020; Lai et al., 2020) SARS-CoV-2 continues to infect millions of people, and has caused thousands of deaths in its first wave, worldwide (Goyal et al., 2021). SARS-CoV-2 has infected millions of people and caused thousands of deaths in its first wave, worldwide (Dong E, 2020). As a result, there is a huge amount of research on the discovery of potential therapeutics

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against SARS-CoV-2. The common symptoms are pneumonia-like including fever, dry cough, shortness of breath, dyspnea, and body pain which sometimes may lead to severe acute respiratory syndromes (Huang et al., 2020; Usha et al., 2017).

Both viral and human proteins are potential drug targets. The most important viral target molecules scrutinized for the repurposing of drugs are "SARS-CoV-2 Spike protein (S Protein), main protease (3CLpro, Mpro), papain-like proteinase (PLpro), and RNA-dependent RNA polymerase (RdRp)" (Ou et al., 2020; Zhang et al., 2020), and "the main targets on the human cell membrane are angiotensin-converting enzyme 2 (ACE2) and transmembrane protease serine 2 (TMPRSS2)" (Aronson & Ferner, 2020). Excluding these, several other targets have been scrutinized on both viral and human sides, for example, the methyltransferase and furin, respectively (Bestle et al., 2020). Moreover, at the initial phase of the pandemic, several drugs which were previously tested on "animal models" and undergone "clinical trial" were announced with assured medical safety (Usha et al., 2017) but were found to be ineffective or paradoxically toxic "to patients, such as hydroxychloroquine or chloroquine phosphate." Similarly, "Kaletra," a combination of lopinavir with ritonavir was also considered to be a promising candidate (Jeon et al., 2020) but later found to be insufficiently effective "for SARS-CoV-2" (Cao et al., 2020). Some of these drugs have also shown severe side effects including arterial diseases and increased mortality rate. However, numerous new potential drug candidates have been suggested by using different data-processing methods, which address different viral and human targets (Hufsky et al., 2021; Sadegh et al., 2020; Usha et al., 2020) (Fig. 14.1).

The replication mechanism of "SARS-CoV-2" has been studied extensively. This virus utilizes the "human receptor ACE2" to invade the cell same as SARS (Gralinski & Menachery, 2020; Wan et al., 2020; Xu et al., 2020; Zhou, Dai, et al., 2020; Zhou, Yang, et al., 2020). "It is expressed as a membrane-bound protein" in various organs including "lungs, heart, kidneys, stomach, spleen, intestines, bone marrow, kidney, liver, brain, testis, and placenta" (Donoghue et al., 2000; Shenoy et al., 2011; Soler et al., 2008). Besides, it has been shown that "SARS-CoV-2" is dependent on TMPRSS2, which can be a potential target in therapy. TMPRSS2 prepares the S-protein of SARS-Cov-2 so that the virus can enter ACE2 which also suggests that the binding of ACE2 to the S-protein may have a higher affinity when compared to SARS. This could delineate the infection caused by "SARS-CoV-2," which was not observed in SARS, as less ACE2 was expressed in the upper respiratory system (Hoffmann et al., 2020). Numerous datasets have tried to integrate the plethora of ongoing knowledge, concentrated data from published research articles, review papers, and preprints about the potential drug, targets, replication, screening, and other therapeutic interventions. Nations worldwide now are publishing official COVID-19 statistics, however, the understandings offered by these numbers remain unfamiliar both for public and clinical research. This may be because of limited access to data: the statistics are dispersed across many internet sites and policy papers, in an array of various formats (Dong et al., 2020). The resulting database is (i) upto date constantly through a grouping of computerized scraping and handbook and authentication, and (ii) utterly replicable, with the provided sources for every observation. In addition, the database incorporates a wide range of metadata offering comprehensive descriptions of the collected statistics for each country (Hasell et al., 2020). To know the potential of the drug discovered and its target sites, virtual screening (VS) is required. Presently, VS is regularly

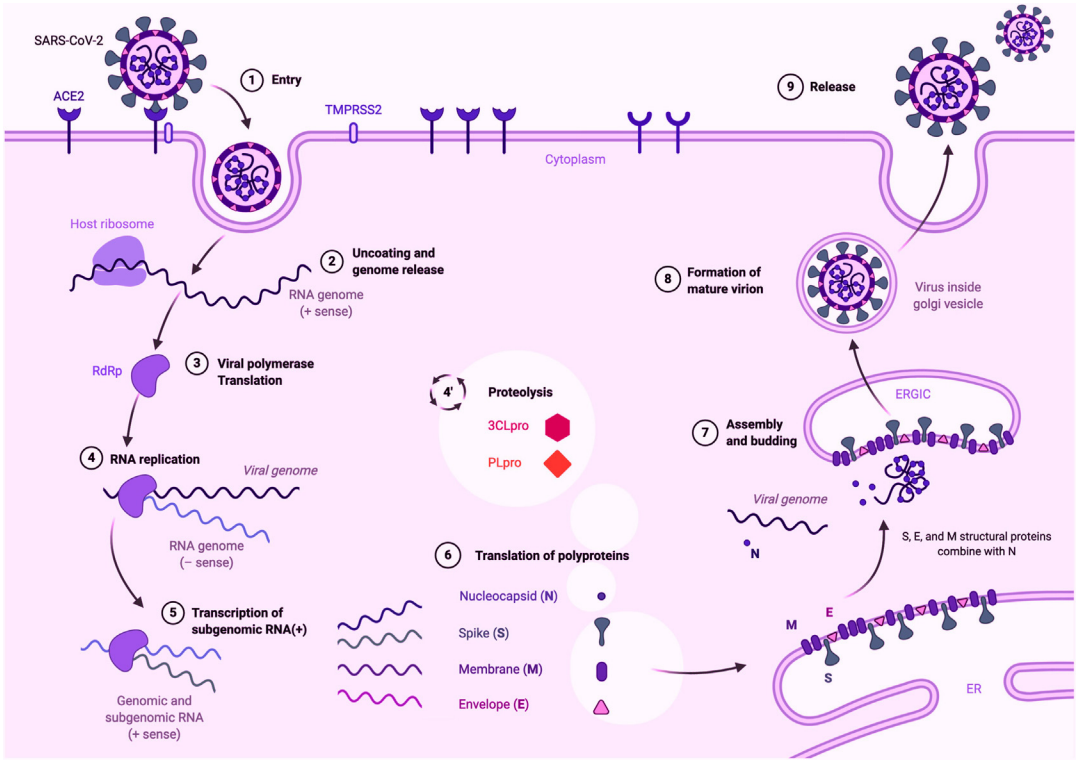

FIGURE 14.1 Replication cycle severe acute respiratory syndrome-Coronavirus-2 inside a Human Host. Source: *From Martin, R., Löchel, H.F., Welzel, M., Hattab, G., Hauschild, A.-C., & Heider, D. (2020). CORDITE: The curated CORona Drug InTERactions database for SARS-CoV-2.* IScience, 23(7), *101297. https://doi.org/10.1016/j.isci.2020.101297*.

used in academics and industry as a predictive method in discerning protein−ligand interactions (Verma et al., 2021). Structure-based drug design by VS and docking studies using the High-throughput screening (HTS) method has become an important step in the identification of the chief molecule for the diagnosis of the disease. It is proven to be an effective tool for antiviral drug discovery (Lin et al., 2020). However, the generated statistics from the calculations and trials are standardized in these databases for comprehensive reference. Hence, in this review, we summarize the potential drug targets involved in the process of viral transmission, mutagenesis, site of replication, VS, molecular docking, in the form of datasets to reach out for information to the public and the researchers. We hope this review will provide collective information about the identification of potential targets, clues, and clinical applications to fight SARS-CoV-2.

14.1.1 Databases for severe acute respiratory syndrome

Table 14.1 summarizes the currently available databases for SARS.

TABLE 14.1 Different databases for virology studies.

S. no.	Databases	URL	Reference
1	LitCovid	https://www.ncbi.nlm.nih.gov/research/coronavirus/	Arab-Zozani (2020)
2	GESS	https://wan-bioinfo.shinyapps.io/GESS/	Fang et al. (2021)
3	CORDITE	https://cordite.mathematik.uni-marburg.de/	Martin et al. (2020)
4	SARSCOVIDB	https://sarscovidb.org/	
5	DockCoV2	https://covirus.cc/drugs/	Wang Q et al. (2020)
6	H2V	http://www.zhounan.org/h2v/	Zhou et al. (2021)
7	SARS-CoV-2 3D	https://sars3d.com/	Alsulami. et al. (2021)
8	COVID-19 CG	covidcg.org	Chen et al. (2020).
9	CoV-AbDab	http://opig.stats.ox.ac.uk/webapps/coronavirus	Singer et al., (2020)
10	CoV-GLUE	http://cov-glue.cvr.gla.ac.uk/	Singer et al. (2020)
11	CoV-2ID	http://covid.portugene.com/	Carneiro et al. (2020)
12	**ZINCPharmer**	http://zincpharmer.csb.pitt.edu/	Koes & Camacho (2012)
13	VIStEDD	https://scicrunch.org/resolver/RRID:SCR_018793	Gupta et al. (2020)
14	SMART	https://smart.embl.de	Letunic (2018)
15	IEDB	https://www.iedb.org/	Vita et al. (2019)
16	SWISS-MODEL	https://swissmodel.expasy.org/	Waterhouse et al. (2018)
17	I-TASSER	https://zhanggroup.org/I-TASSER/	Yang & Zhang (2015)
18	DrugBank	https://go.drugbank.com/	Wishart et al. (2018)

14.2 LitCovid

The database is frequently updated with newly published articles and comprises the most inclusive collection of global research papers so far on the new coronavirus, COVID-19 disease. This site has a more advanced search engine than other accessible resources and classifies about 35% more related articles compared to formal keyword-based searches for entries such as COVID-19, nCOV, 2019-nCoV, and other relevant terms. Also, the articles available on this site are characterized by various topics and subtopics, including general information and news, signs and symptoms, clinical characteristics, and conclusions from assessments and trials analysis, transmission modes of COVID-19, such as human-to-human, diagnosis, therapeutic procedures, and vaccine development, case reports and demonstration and estimation of the drift of SARS-CoV-2 spread (Chen et al., 2020).

14.2.1 Limitations

This site is based on the PubMed database, and articles in different journals that are not listed on this database might not be accessible. Another drawback is the lack of a keen searching characteristic for the content of this site (Arab-Zozani & Hassanipour, 2020).

14.3 Gess

This hub enables the user to forage and "download single nucleotide variants" (SNVs) at any single or multiple "SARS-CoV-2" genomic locations, or in a selected genomic site or protein, or country of interest. GESS shows geographical distributions of SNVs around the world and in all US states and shows time-dependent blue-prints for SNV occurrences that reflect the evolution of "SARS-CoV-2 genomes" (Mavian et al., 2020). The GESS database is designed using the R language. The complete genome sequences of SARS-CoV-2 were recorded from the GISAID database and processed as a document (Ugurel et al., 2020).

14.4 CORDITE

CORDITE is presently the most systemized drug interactions database for SARS-CoV-2, and consequently, it provides the possibility to boost up research in the realms of virology and drug design. In addition, original studies also give an option for reviews and comments in the database. The usage of moderators aids the manual systemization of details from the articles and preprints could be obtained through the web interface or the open API. Users can immediately get access through the journals, interactions, therapeutics, targets, *meta*analysis, and clinical trials. This access may offer easier integration for a future perspective that may need systematic data (Martin et al., 2020).

14.4.1 Limitations

CORDITE integrates available studies on therapeutics for COVID-19; however, the preprints have not been peer-reviewed. Thus, CORDITE cannot ensure guarantee the dependability of the research and its results, in particular, the efficiency of the drugs (Martin et al., 2020).

14.5 SARSCOVIDB

The database was firstly designed by searching the exact terms "COVID" and "SARS-CoV-2," with a manual doublecheck for "differential expression of genes or proteins after SARS-CoV-2 infection," regardless of the host. The SARSCOVIDB contains differential gene expression measurements, at mRNA and protein levels (da Rosa et al., 2021).

General Information Stored in the SARSCOVIDB, includes:

- SARSCOVIDB ID reference: documentation of the entry in the SARSCOVIDB.
- Gene name: official gene name for each stored entry.
- Protein name: official protein name for each stored entry.
- Host/sample: host model used to generate SARS-COV-2 infection data.
- Sample: description of the sample, such as if it is a human biological sample (blood, urine, serum, etc.) or experimental sample (cell line or animal tissue thjnnbd0faZISOhg3256FG, h6ested in vitro).
- Virus reference: SARS-CoV-2 strain reference or geographic origin of the SARS-CoV + 2 viral isolate or clinical sample.
- Methods: methods used to measure gene expression at the level of RNA and/or protein after SARS-CoV-2 infection.
- Expression: indicates the identified gene expression status (up and/or downregulated) in response to SARS-CoV-2 infection.
- Article: article title used as a data source.
- DOI: direct link to the original reference where the data came from.
- The type of sample indicates if the data were generated using clinical or experimental samples (da Rosa et al., 2021).

14.5.1 DockCoV2

This database employs the most commonly used drug databases to provide a computational representation of molecular docking in order to speed up the process of searching specific drugs (Kim et al., 2019). Through this database, users can obtain potential drug candidates against SARS-CoV-2 through the docking scores of candidate drugs with important drug-relevant data DockCoV2 focuses on predicting 2285 Food and Drug Administration (FDA)-approved and 1478 Taiwan NHI-approved drugs targeting seven proteins relating to the mechanism of entry of virus and its replication (Wang et al., 2020).

14.5.2 H2V

H2V is the first-ever database of "human proteins and genes" that answer to SARS-CoV-2, SARS-CoV, and Middle East respiratory syndrome-Coronavirus (MERS-CoV) infection. The database enables us to study how the human body responds to viral infections. To facilitate speedy drug search, H2V provides a search engine to find drugs against the given protein based on the UniProt accession number. Based on the search, potential drugs and their DrugBank identifiers will then be displayed on the lower part of the same page. To help users visualize the dynamic changes occurring in all genes/proteins over time post-infection, H2V provides a utility called "Data animation" (Wan et al., 2020; Xu et al., 2020; Zhou, Yang, et al., 2020).

14.6 Severe acute respiratory syndrome-Coronavirus-2 three-dimensional

- SARS-CoV-2 three-dimensional is a complete database providing important data for drugs against COVID-19.
- It offers collective computational and experimental three-dimensional conformations data on a single platform.
- "The database comprises of protomers, homo-oligomers, hetero-oligomers, and transmem-brane modeled proteins, which also includes ligands and cofactors. It provides the prediction of allosteric and small ligand-binding sites prediction. SARS-CoV-2 three-dimensional provides protein−protein interactions between SARS-CoV-2 and human proteins. • It also includes protein−ligand docking and saturation mutagenesis."
- The database is frequently updated with new mutational findings and a series of genomic sequence and structure-based approaches are exploited to analyze the influences of mutations (Alsulami et al., 2021).

14.7 Coronavirus disease-2019 CG

COVID-19 CG is an efficient, cooperating, powerful, and fully scalable online application that tracks SARS-CoV-2 single-nucleotide variants (SNVs), lineages, and clades without subsampling. COVID-19 CG is free, open access that allows users to analyze according to their date and site of interest. Users can also select and compare trends in SARS-CoV-2 lineage, clade, or SNV frequency across multiple locations as it will start using case studies. COVID-19 CG provides features that are complement other current public browsers and were intended to allow these specific user groups: Vaccine and drug developers can inform the design and trials for their vaccine, antibody, or small molecule by using COVID-19 CG to rapidly classify all the variants in their SARS-CoV-2 target protein or antigen, together with the rate of each variant in their geographical site of interest. Researchers can use COVID-19 CG to create theories and determine whether the variations present in the location of therapeutic application may influence their specific antigen (Chen et al., 2020).

14.8 Coronavirus-AbDab

CoV-AbDab is a determination to file all coronavirus binding/counteracting antibodies and nanobodies stated in hypothetical journals and commercial copyrights. The following information is documented for each entry:

1. The published name of the antibody/nanobody.
2. Antigens that the antibody/nanobody has been confirmed to bind and/or counteract.
3. The protein domain is targeted by the antibody/nanobody.
4. The developing origin of the antibody/nanobody.

5. Sequence data incorporates: (a) the entire variable domain sequence for the antibody/nanobody, importance to the CDR3 regions, and (b) V and J gene germline projects.
6. Links to any accessible data involving the antibody/nanobody.
7. A homologous model of the antibody/nanobody.
8. References to the prime literature on the antibody/nanobody.
9. Timestamps to show when the antibody/nanobody was added or updated lately.
10. Steps were taken to follow up on access (Raybould et al., 2021).

14.9 Coronavirus-GLUE

CoV-GLUE (http://cov-glue.cvr.gla.ac.uk/) is an online application free for the public for tracking and studying variation within SARS-CoV-2 gene sequences, allowing to fetch data from EpiCoV (Shu & McCauley, 2017). Its first objective is to track the chief elements of variation as they occur in outbreaks, associated with sampling data. Second, enables users to propose their own consensus data for assessment and obtain an interactive report describing genomic variability. CoV-GLUE upholds a searchable database of amino-acid classification variations within all 26 of the viral proteins, as proposed on NCBI RefSeq NC_045512. CoV-GLUE presently shows 8778 amino acid substitutes detected in outbreak sequences from EpiCoV. Besides this, CoV-GLUE also provides an online site for each variation, with a table of sequences displaying them, which may be filtered by categories containing international region, country, date and time of collection, and phylogenetic ancestry (Singer et al., 2020).

14.10 CoV2ID

The database gives a detailed web page for individual oligonucleotides and a search engine to access tables with numeric data and several sequence arrangements. The "CoV2ID database presently contains 145 oligonucleotides from 21 protocols: 64 PCR primers, 57 LAMP primers, 20 probes, and four target generation oligonucleotides. The oligonucleotides are in the ORF1ab, S, ORF3a, E, M, and N genes." The database gives access for searching, filtering, and downloading data from the different oligonucleotides allotted according to the SARS-CoV-2 reference gene sequences. For individual oligonucleotide, it finds information of the sequence, type of method used first, site in the reference genome, etc. The database shows which oligonucleotide binds to which region of the SARS-CoV-2 using different procedures (Ciobotaru et al., 1979).

14.11 ZINC

An online tool from the ZINC database, called "ZINC-Pharmer" is used for pharmacophore-based screening of drugs. The 3D-conformation of the Mpro of COVID-19 and "SDF" extension file of inhibitor N3 are uploaded into the ZINC-Pharmer to generate pharmacophore structures of the ligand within the range of receptors. This type of screening

is significant for the documentation of appropriate inhibitors against the target, the novel drug-like compounds are predicted and facilitated further (Koes & Camacho, 2012).

14.12 VIStEDD

The change and development for each protein were combined into VIStEDD. It has been designed for viruses that may come up in the future. Within the SARS-CoV-2 page, a list of each of the 24 proteins, where each protein can be clicked to fetch information. Each protein has an individual link, a rotational video of protein, characteristic of each protein, a tool to buy a three-dimensional print of the protein, the amino acid program from molecular dynamics simulations (MDS), and the table of data for each amino acid in protein (Gupta et al., 2020).

14.13 SMART

"SMART can be used in two different modes: normal or genomic. The main difference is in the underlying protein database used. In Normal SMART, Swiss-Prot, SP-TrEMBL and stable Ensembl proteomes are used. In Genomic SMART, only the proteomes of completely sequenced genomes are used; Ensembl for metazoans and Swiss-Prot for the rest." The complete list of genomes in Genomic SMART is available at http://smart.embl-heidelberg.de/. The protein database in Normal SMART has significant redundancy, even though identical proteins are removed. If you use SMART to explore domain architectures or want to find exact domain counts in various genomes, consider switching to Genomic mode. The numbers in the domain annotation pages will be more accurate, and there will not be many protein fragments corresponding to the same gene in the architecture query results (Letunic & Bork, 2018).

14.14 Immune epitope database

The Immune Epitope Database (IEDB) is a freely available resource funded by NIAID. It catalogs experimental data on antibody and T cell epitopes studied in humans, non-human primates, and other animal species in the context of infectious disease, allergy, autoimmunity, and transplantation. The IEDB also hosts tools to assist in the prediction and analysis of epitopes (Vita et al., 2019).

14.15 SWISS-MODEL

The main objective of the SWISS-MODEL database is to give access to an updated set of interpreted three-dimensional protein models generated by automatic homologous modeling for relative model organisms and new structural information for all genomic sequences in UniProtKB. Daily updates confirm that reporting the targets are complete,

that models are designed using sequence and template structure databases. Enables users to assess the superiority of the models using the modern QMEAN results. If a sequence has not been modeled, allows users to design models interactively through the SWISS-MODEL database (Waterhouse et al., 2018).

14.16 Iterative threading assembly refinement

Iterative Threading ASSEmbly Refinement (I-TASSER) is a stratified approach for predicting protein structures and for structure-based function annotation. Firstly, the structural templates from the PDB are identified using LOMETS multiple threading approach, with full-length atomic models being designed from iterative template-based fragment assembly simulations. Functional views of the target are then gained using re-threading the three-dimensional models through BioLiP, a protein function database. Currently, the server is actively developed to give the exact protein structure and predictions using state-of-the-art systems (Yang & Zhang, 2015).

14.16.1 DrugBank

DrugBank is an online site that offers free-to-access for the public, containing information on potential drugs and their targets. As both a bioinformatics and a cheminformatics resource, combine detailed information of drug is needed with complete and specific drug targets. DrugBank hub is widely used by the drug industry, pharmacists, chemists, physicians, students, researchers, and the public. Because of its wide scope, complete referencing, and detailed descriptions of data, DrugBank is allowing chief progressions across the medicine industry (Wishart et al., 2018).

14.17 Drugs against severe acute respiratory syndrome-Coronavirus-2

14.17.1 DrugBank

The drug-repurposing (techniques) has been used to treat a variety of infectious diseases, including the COVID-19 pandemic (Goyal et al., 2021). The workflow for drug repurposing differs from that of conventional drug production. There are fewer steps and various parameters to follow in drug repurposing: compound detection, acquisition, production, and postmarket safety monitoring by the FDA (Dotolo et al., 2021). Computational drug repositioning methods used on COVID-19 are divided into three categories: (i) network-based models, (ii) structure-based approaches, and (iii) machine/deep learning methods (Usha et al., 2022).

14.17.2 Drug repurposing for Coronavirus disease-2019 available in DrugBank

The tried and tested drug discovery outlook entails many years of careful research and development on deadline for a large investment that cannot be validated for the current

universal infection. To some extent, the world calls for a quick and profitable approach to suppressing and controlling viral infection (Usha et al., 2020). It is possible to identify lead drug-like compounds for COVID-19 using computational screening approaches and by selecting appropriate chemical space. Many factors influence the severity of a viral infection, including intrinsic pathogenicity, mortality rate, and basic reproduction number (Jin et al., 2020). The authors have tabulated the drugs repurposed for COVID-19 available in the DrugBank (Murugan et al., 2020) (Table 14.2).

14.18 Advantages and disadvantages

14.18.1 Ritonavir/lopinavir

It is a nucleoside analog and protease inhibitor combination used to treat human immunodeficiency virus (HIV) type 1 (Osborne et al., 2020). As a result, "multiple trials in COVID-19 are currently underway to determine whether LPVr is an effective treatment, including the worldwide RECOVERY trial and the World Health Organization's (WHO) SOLIDARITY trial" (https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments). Importantly, "LPVr is a cytochrome P450 3A4 inhibitor, it cannot be used with other medicines that are cytochrome P450 3A4 substrates, such as chloroquine, which can cause QT prolongation" (Naksuk et al., 2020). Statistics were generated for a variety of endpoints, including the risk of death, the "risk and duration of invasive mechanical ventilation, the risk of non-invasive ventilation, and the requirement for oxygen" (Cao et al., 2020). One of the most critical risks is QT interval prolongation, which increases the risk of unexpected cardiac death (Giudicessi et al., 2020). "Patients infected with COVID-19 are already susceptible to developing cardiac arrhythmias due to the virus's effects on metabolic dysfunction, myocardial inflammation, and the sympathetic nervous system" (Guzik et al., 2020).

14.18.2 Chloroquine

The use of antimalarial drugs like chloroquine (CQ) and hydroxychloroquine (HCQ) for the treatment of SARS-CoV-2 has created a lot of flutters (Gao et al., 2020). In February 2020, an editorial published by a French group, CQ and HCQ were proposed for use against SARS-CoV-2 (Colson et al., 2020). On March 20, 2020, Chinese researchers published a concise report emphasizing the superiority of HCQ over CQ as a prophylactic drug (Zhou, Dai, et al., 2020). The advantage of HCQ over CQ is its safety during pregnancy (Shah et al., 2020). As a result, if proven to be beneficial, HCQ could be used as a COVID-19 prophylactic drug. Usage of CQ has been associated with a variety of issues, such as the occurrence of long-term musculoskeletal symptoms in patients treated with CQ compared to placebo in a clinical trial, a variety of cardiovascular side effects including QT prolongation, and other unknown adverse reactions due to narrow safety margin (Martin et al., 2020). Another major issue is the toxicity of these drugs (Roques et al., 2018). If a drug is used without concrete scientific evidence, it causes mass hysteria and

TABLE 14.2 Drugs used for severe acute respiratory syndrome-Coronavirus-2 (go.drugbank.com). Repurposed Drugs for SARS-CoV-2.

S. no.	Drugs	Description	Target	Type
1	Ritonavir [Stower, H]	In the treatment of HIV infection, an HIV protease inhibitor is used in conjunction with other antivirals	Human immunodeficiency virus type 1 protease	Target
			Cytochrome P450 2D6	Enzyme
			Cytochrome P450 2C9	Enzyme
			Cytochrome P450 2C19	Enzyme
			Cytochrome P450 2B6	Enzyme
			Cytochrome P450 2C8	Enzyme
			P-glycoprotein 1	transporter
			Multidrug resistance-associated protein 1	transporter
			Canalicular multispecific organic anion transporter 1	transporter
			Solute carrier organic anion transporter family member 1A2	transporter
			ATP-binding cassette subfamily G member 2	Transporter
			Solute carrier organic anion transporter family member 1B1	Transporter
			Cytochrome P450 1A2	Enzyme
			Nuclear receptor subfamily 1 group I member 2	Target
			Serum albumin	Carrier
			Cytochrome P450 3 A4	Enzyme
			Cytochrome P450 3 A5	Enzyme
			Cytochrome P450 3A7	Enzyme
			UDP-glucuronosyltransferases (UGTs)	Enzyme
			Solute carrier organic anion transporter family member 2B1	Transporter
			Bile salt export pump	Transporter
			Alpha-1-acid glycoprotein 1	Carrier
			Solute carrier organic anion transporter family member 1B3	Transporter

2	Chloroquine [Moore, N]	Antimalarial medication is used to treat infections caused by Plasmodium vivax, Plasmodium malariae, Plasmodium ovale, and Plasmodium falciparum. It's also used as second-line therapy for rheumatoid arthritis	Tumor necrosis factor	Target
			Toll-like receptor 9	Target
			GlutathioneS-transferase A2	Target
			Cytochrome P450 2D6	Enzyme
			Cytochrome P450 3A4	Enzyme
			Cytochrome P450 1A1	Enzyme
			Cytochrome P450 2CB	Enzyme
			Cytochrome P450 3A5	Enzyme
			GlutathioneS-transferase	Target
			P-glycoprotein 1	Transporter
			Serum albumin	Carrier
			Alpha-1-acid glycoprotein	Carrier
			High mobility group protein B1	Target
			GlutathioneS-transferase Mu 1	Target
			Angiotensin-converting enzyme 2	Target
3	Darunavir [Riva, A.]	An HIV protease inhibitor is used to treat (HIV) human immuno- deficiency virus infection in patients who have previously received antiretroviral therapy	Human immunodeficiency virus type 1 protease	Target

(*Continued*)

TABLE 14.2 (Continued)

S. no.	Drugs	Description	Target	Type
			Cytochrome P450 3A4	Enzyme
			Solute carrier organic anion transporter family member 1B1	Transporter
			P-glycoprotein 1	Transporter
			Serum albumin	Carrier
			alpha-1-acid glycoprotein 1	Carrier
			Cytochrome P450 2D6	Enzyme
4	Lopinavir [Gregoire, M]	An HIV-1 protease inhibitor is used in the treatment of (HIV) human immunodeficiency virus infection in combination with ritonavir	Human immunodeficiency virus type 1 protease	Target
			Cytochrome P450 3A4	Enzyme
			Cytochrome P450 2D6	Enzyme
			Cytochrome P450 2C19	Enzyme
			P-glycoprotein 1	Transporter
			Cytochrome P450 2B6	Enzyme
			Cytochrome P450 2C9	Enzyme
			Cytochrome P450 3A Subfamily	Enzyme
			Solute carrier organic anion transporter family member 1B1	Transporter
			Solute carrier organic anion transporter family member 1B3	Transporter
			Bile salt export pump	Transporter
			Cytochrome P450 1A2	Enzyme
			alpha-1-acid glycoprotein 1	Carrier
			Serum albumin	Carrier
5	Galidesivir [Abdo A]	Galidesivir is an adenosine analog being studied for use against the Zaire Ebolavirus.	RNA-directed RNA polymerase L	Target

		It was found to be effective in increasing survival rates from infection caused by a variety of pathogens in animal studies		
6	Favipiravir [Qingxian Cai]	An antiviral that is used to treat influenza and has the potential to treat other viral infections	RNA-directed RNA polymerase catalytic subunit	Target
			Aldehyde oxidase	Enzyme
			Xanthine dehydrogenase/oxidase	Enzyme
			Cytochrome P450 2C8	Enzyme
			Serum albumin	Carrier
			alpha-1-acid glycoprotein	Carrier
			P-glycoprotein 1	Transporter
			Solute carrier family 22-member 6	Transporter
			Solute carrier family 22-member 8	Transporter
			Solute carrier family 22-member 12	Transporter
			Cytochrome P450 2E1	Enzyme
7	Umifenovir [Dong Huang]	A dual direct-acting antiviral/host-targeting agent is used to treat and prevent influenza and other respiratory viruses	UDP- glucuronosyltransferase 1−9	Enzyme
			UDP- glucuronosyltransferase 2B7	Enzyme
			Cytochrome P450 3A4	Enzyme
			Cytochrome P450 2E1	Enzyme
			Cytochrome P450 1A2	Enzyme
			Cytochrome P450 2D6	Enzyme
			Cytochrome P450 2C9	Enzyme

(*Continued*)

TABLE 14.2 (Continued)

S. no.	Drugs	Description	Target	Type
			Cytochrome P450 3A5	Enzyme
			Dimethylaniline monooxygenase [N-oxide-forming] 3	Enzyme
			Dimethylaniline monooxygenase [N-oxide-forming] 1	Enzyme
8	Human interferon Beta [Jalkanen, J]	A polypeptide medication used to treat relapsing forms of Multiple Sclerosis (Ms)	Cytochrome P450 1A2	Enzyme
			Interferon alpha/ beta receptor 1	Target
			Serum albumin	Carrier
9	TMC-310911 [Ibrahim, M.A.A]	It is a novel investigational protease inhibitor (PI) with structural similarity to the currently available Darunavir. It is being studied for its potential use in HIV-1 infection	HIV-1 protease	Target
10	Fingolimod [Christian Foerch]	A sphingosine 1-phosphate receptor modulator is used to treat patients with relapsing-remitting multiple sclerosis (Ms) and is being studied to manage COVID-19 lung complications	Sphingosine-1 phosphate receptor 5	Target
			Sphingosine kinase 1	Enzyme
			Cytochrome P450 2E1	Enzyme
			Leukotriene-B(4) omega-hydroxylase 1	Enzyme
			Histone deacetylase 1	Target
			Excitatory amino acid transporter 2	Transporter
			Excitatory amino acid transporter 1	Transporter
			P-glycoprotein 1	Transporter
			Multidrug resistance-associated protein 1	Transporter
			Sphingosine-1 phosphate receptor 1	Target

			Sphingosine-1 phosphate receptor 4	Target
			Sphingosine-1 phosphate receptor 3	Target
11	Methylprednisolone [Wang, Y]	A corticosteroid that is used to treat inflammation or immune reaction in various organ systems, endocrine conditions, and neoplastic disease	Glucocorticoid receptor	Target
			Cytochrome P450 3A4	Enzyme
			P-glycoprotein 1	Transporter
			Cytochrome P450 3A subfamily	Enzyme
			Cytochrome P450 2A6	Enzyme
			Cytochrome P450 1B1	Enzyme
			Cytochrome P450 2B6	Enzyme
			Cytochrome P450 2CB	Enzyme
			Cytochrome P450 2C9	Enzyme
			Cytochrome P450 2C19	Enzyme
			Annexin A1	Target
			20-Ketosteroid reductase (20-hydroxysteroid dehydrogenase)	Enzyme
			11 beta-hydroxysteroid dehydrogenases	Enzyme
			Serum albumin	Carrier
12	Bevacizumab [Pang, J.,]	A monoclonal antivascular endothelial growth factor antibody that is used in conjunction with antineoplastic agents to a variety of cancer	vascular endothelial growth factor A	Target
			Complement C1q subcomponent subunit A	Target
			Complement C1q subcomponent subunit B	Target

(*Continued*)

TABLE 14.2 (Continued)

S. no.	Drugs	Description	Target	Type
			Complement C1q subcomponent subunit C	Target
			Low-affinity immunoglobulin gamma Fc region receptor III-A	Target
			Low-affinity immunoglobulin gamma Fc region receptor II-a	Target
			Low-affinity immunoglobulin gamma Fc region receptor II-b	Target
			Low-affinity immunoglobulin gamma Fc region receptor II-c	Target
			High-affinity immunoglobulin gamma Fc receptor I	Target
13	Leronlimab [Yang, B.,]	A humanized monoclonal antibody is being studied	C-C chemokine receptor type 5	Target
14	Azithromycin [Bleyzac, N]	A macrolide antibiotic that is used to treat a wide range of bacterial infections	23S ribosomal RNA	Target
			P-glycoprotein 1	Transporter
			Cytochrome P450 3A4	Enzyme
			Protein-arginine deiminase type 4	Target
			Canalicular multi-specific organic anion transporter 1	Transporter
15	Elbasvir [Mario Milani]	A NS5A inhibitor and antiviral are used to treat hepatitis C infections	Non-structural protein 5A	Target
			P-glycoprotein 1	Transporter
			Cytochrome P450 3A4	Enzyme
			Cytochrome P450 3A5	Enzyme
			Cytochrome P450 3A7	Enzyme
			Cytochrome P450 3A43	Enzyme

16	Tocilizumab [Alzghari, S. K.]	An interleukin-6 (IL-6) receptor antagonist is used to treat Cytokine bacterial infections. Giant Cell Arteritis (GCA), and Rheumatoid Arthritis (RA)	Interleukin-6 receptor subunit alpha	Target
			Cytochrome P450 3A4	Enzyme
17	GS-441524 [E. Susan Amirian,]	A nucleoside analog antiviral that is being studied for use in the treatment of Ebola and SARS-CoV-2 infections	Replicase polyprotein 1 ab	Target
			RNA-directed RNA polymerase L	Target
18	Metenkefalin [Peng, Y.]	An investigational endogenous opioid is being studied for the treatment of COVID-19	Carboxypeptidase A6	Enzyme
			Delta-type opioid receptor	Target
			Mu-type opioid receptor	Target
19	Vazegepant [Sarah M.]	It is a calcitonin gene-related peptide (CGRP) receptor antagonist that is currently in phase 3 trials in an intranasal formulation for the treatment of Migraine	calcitonin gene-related peptide type 1 receptor	Target
20	Ibuprofen [Abu Esba]	An NSAID and nonselective COX inhibitor that is used to treat mild to moderate pain, fever, and inflammation	Prostaglandin G/H synthase 1	Target
			Prostaglandin G/H synthase 2	Target
			Cytochrome P450 2C9	Enzyme
			Serum albumin	Carrier
			Multidrug resistance-associated protein 4	Transporter
			Multidrug resistance-associated protein 1	Transporter

(*Continued*)

TABLE 14.2 (Continued)

S. no.	Drugs	Description	Target	Type
			Solute carrier organic anion transporter family member 1A2	Transporter
			Solute carrier family 22 members 6	Transporter
			Solute carrier family 22 members 8	Transporter
			Solute carrier family 22 members 11	Transporter
			Solute carrier organic anion transporter family member 2B1	Transporter
			P-glycoprotein 1	Transporter
			UDP- glucuronosyltransferase 1−3	Enzyme
			UDP- glucuronosyltransferase 1−9	Enzyme
			UDP- glucuronosyltransferase 2B4	Enzyme
			UDP- glucuronosyltransferase 2B7	Enzyme
			Cytochrome P450 2C8	Enzyme
			Cytochrome P450 2C19	Enzyme
			Apoptosis regulator Bcl-2	Target
			Thrombomodulin	Target
			Fatty acid-binding protein, intestinal	Target
			Peroxisome proliferator-activated receptor gamma	Target
			Cystic fibrosis transmembrane conductance regulator	Target
			Peroxisome proliferator-activated receptor alpha	Target
			Platelet glycoprotein lb alpha chain	Target
			Protein S100-A7	Target
			Alpha-methyl acyl-CoA racemase	Enzyme
			Cytochrome P450 3A4	Enzyme

21	Anti-SARS-CoV-2 REGN -COV2 [Ning, L.]	Is a new antibody mixture developed by Regeneron for the prevention and treatment of SARS-COV-2, the virus that causes COVID-19	Spike glycoprotein	Target
22	Dexamethasone [Kelleni, M.T.]	A glucocorticoid comes in a variety of forms and is used to treat a variety of inflammatory conditions, including bronchial asthma, as well as endocrine and rheumatic disorders	Glucocorticoid receptor	Target
			Annexin A1	Target
			Nitric oxide synthase, inducible	Target
			Nuclear receptor subfamily 0 group B member 1	Target
			Cytochrome P450 3A4	Enzyme
			Cytochrome P450 3A5	Enzyme
			Cytochrome P450 3A7	Enzyme
			Bile salt export pump	Transporter
			P-glycoprotein 1	Transporter
			Canalicular multispecific organic anion transporter 1	Transporter
			Solute carrier organic anion transporter family member 1A2	Transporter
			ATP-binding cassette sub-family G member 2	Transporter
			Steroid 17-alpha hydroxylase/17,20 lyase	Enzyme
			Cytochrome P450 1A1	Enzyme
			Cytochrome P450 2A6	Enzyme
			Cytochrome P450 2B6	Enzyme
			Cytochrome P450 2C19	Enzyme
			Cytochrome P450 2CB	Enzyme

(*Continued*)

TABLE 14.2 (Continued)

S. no.	Drugs	Description	Target	Type
			Cytochrome P450 2E1	Enzyme
			Cytochrome P450 3A43	Enzyme
			Cytochrome P450 4A11	Enzyme
			Nuclear receptor subfamily 1 group I member 2	Target
			Cytochrome P450 11B1, mitochondrial	Enzyme
			Serum albumin	Carrier
			Corticosteroid 11-beta-dehydrogenase isozyme 2	Enzyme
			Corticosteroid 11-beta-dehydrogenase isozyme 1	Enzyme
			Solute carrier family twenty-two member 8	Transporter
23	Colchicine [Parra-Medina]	An alkaloid is used to treat the inflammatory symptoms of Familial Mediterranean Fever as well as the symptomatic relief of pain in gout attacks (FMF)	Tubulin beta chain	Target
			Cytochrome P450 3A4	Enzyme
			P-glycoprotein 1	Transporter
			Cytochrome P450 2B6	Enzyme
			Cytochrome P450 2C8	Enzyme
			Cytochrome P450 2E1	Enzyme
			Serum albumin	Carrier
24	Bamlanivimb [Gottlieb RL]	A human IgG1 monoclonal antibody that neutralizes the SARS-CoV-2 Spike (S) protein for use in patients aged twelve and up who are at high risk of developing severe COVID-19	spike glycoprotein	Target

25	GC-376 free acid [Hu, Y.]	It is a 3C-like protease (3CLpro or Mpro) inhibitor that prevents the cleavage and activation of functional viral proteins required for host cell replication and transcription	Replicase polyprotein 1ab	Target
			Replicase polyprotein 1a	Target
26	GC-373 [Cáceres, C. J.]	It is a peptide aldehyde that is metabolized from the bisulfite adduct, GC-376 free acid [A219031, A219036]. It is an inhibitor of Mpro(otherwise known as 3CLpro)	Replicase polyprotein 1ab	Target
			Replicase polyprotein 1a	Target
27	Ifenprodil [Hashimoto]	N-methyl-D-aspartate (NMDA) receptors (NMDARs) are members of the ionotropic glutamate receptor family, with key roles in brain development and neurological function. [A220118, A220128] NMDARS are heterotetramers that typically involve a dimer	Glutamate receptor ionotropic, NMDA 1	Target
			Glutamate receptor ionotropic, NMDA 2B	Target
			G protein-activated inward rectifier potassium channel 1	Target
			G protein-activated inward rectifier potassium channel 2	Target
			G protein-activated inward rectifier potassium channel 4	Target
28	Abivertinib [Alizadehmohajer, N.]	It is a tyrosine kinase inhibitor that targets mutant forms of both the human epidermal growth factor receptor (EGFR) and Bruton's tyrosine kinase (BTK)	Epidermal growth factor receptor	Target

(*Continued*)

TABLE 14.2 (Continued)

S. no.	Drugs	Description	Target	Type
			Tyrosine-protein kinase BTK	Target
29	Etesevimab [Frishman, Wiliam]	It (LY-CoV016, also known as JS016) is a fully human and recombinant monoclonal antibody that targets the SARS-CoV-2 surface Spike protein receptor-binding domain. [L16651, L16661]	Spike glycoprotein	Target
30	Baricitinib [Linda Petrone]	A Janus kinase inhibitor is used to treat moderate to severe rheumatoid arthritis that has responded poorly to at least one TNF antagonist	Solute carrier family twenty-two member 8	Transporter
			ATP-binding cassette sub-family G member 2	Transporter
			Multidrug and toxin extrusion protein 2	Transporter
			Cytochrome P450 3A4	Enzyme
			Tyrosine-protein kinase JAK1	Target
			Tyrosine-protein kinase JAK2	Target
			Solute carrier family twenty-two member 6	Transporter
			Solute carrier family twenty-two member 2	Transporter
			Solute carrier organic anion transporter family member 1B3	Transporter
			Protein-tyrosine kinase 2-beta	Target
			Tyrosine-protein kinase JAK3	Target
			P-glycoprotein 1	Transporter
31	ATYR1923 [Ahamad, S.]	It is a fusion protein comprised of the immuno-modulatory domain of arthritis that has responded poorly to at least one TNF antagonist. It is a selective modulator of neuropilin-2	Neuropilin-2	Target

32	PF-07304814 [Vandyck, K.]	It is a small molecule prodrug that targets the 3Clpro protease (Mpro), which viruses such as SARS-CoV-2 use to assemble and multiply. Once upon a time, it was administered via intravenous infusion	Replicase polyprotein 1ab	Target
33	PF-07321332 [Paules and Fauci]	An oral protease inhibitor in clinical trials for the treatment of SARS-CoV-2 infections	Replicase polyprotein 1ab	Target

From Wishart, D. S., Feunang, Y. D., Guo, A. C., Lo, E. J., Marcu, A., Grant, J. R., Sajed, T., Johnson, D., Li, C., Sayeeda, Z., Assempour, N., Iynkkaran, I., Liu, Y., Maciejewski, A., Gale, N., Wilson, A., Chin, L., Cummings, R., Le, D., … Wilson, M. (2018). DrugBank 5.0: a major update to the DrugBank database for 2018. Nucleic Acids Research, *D1074–D1082*. https://doi.org/10.1093/nar/gkx1037.

deprives the legitimate population, such as patients with lupus and rheumatoid arthritis, off the use of these drugs (American College of Rheumatology et al., 2020). In the future, if ongoing clinical trials successfully exhibit prophylactic efficacy in CQ and HCQ targeted prophylaxis may be preferred over mass prophylaxis (Martin & Vinetz, 2018).

14.18.3 Darunavir

In COVID-19 patients, some retrospective studies suggested a potentially beneficial effect of HIV protease inhibitors such as Darunavir in combination with Lopinavir. "Although HCQ, azithromycin, and ritonavir/darunavir (RD) generally well undergo, all three are correlated with a high risk of QTc prolongation and cardiac arrhythmias (Moschini et al., 2021). After several trials, the QTc interval gradually increased from 438 Ms (421−454) on day 0 to 448 Ms (429−483) on day 3 and 452 Ms (430−490) on day 7 (baseline vs day 3, $p = 0.001$; baseline vs day 7, $p = 0.001$; day 3 vs day 7, $p = 0.001$)." There are several limitations. For starters, the sample size was small. Second, the study population was made up of two consecutive series of patients with different characteristics, making comparisons between groups impossible. Furthermore, the study lacked a control group of patients who received only HCQ. Finally, higher risk subjects may have been underrepresented in the sample because individuals with prolonged QTc intervals at baseline were excluded, as recommended by international guidelines (Moschini et al., 2021).

14.18.4 Galidesivir

Galidesivir is an adenosine analog being studied for use against the Zaire Ebolavirus (Tchesnokov et al., 2019). Galidesivir was effective in increasing survival rates from infections caused by various pathogens, including Ebola, Marburg, Yellow Fever, and Zika viruses, in animal studies. It demonstrated broad-spectrum antiviral activity in vitro against a variety of negative and positive-sense RNA viruses (Westover et al., 2018), Adding Galidesivir to the SARS-CoV-2 cell culture may inhibit its growth. Furthermore, clinical trials have shown that this drug is safe and well-tolerated in both the intramuscular (IM) or intravenous (IV) injection and oral routes (Julander et al., 2021).

14.18.5 Favipiravir

Favipiravir, a purine analog, and potent RdRp inhibitor approved for influenza treatment are also being considered for COVID-19 treatment (Arab-Zozani et al., 2020). It has been used to treat life-threatening infections such as Ebola, Lassa fever, and rabies, and its therapeutic usefulness in these diseases has been established (Mohamed AA et al., 2020). Favipiravir is a promising COVID-19 treatment that may reduce hospitalization and the need for mechanical ventilation (Hassanipur et al., 2021).

14.18.6 Umifenovir

Earlier clinical and basic research found that Umifenovir could reduce SARS virus replication in vitro (Lu et al., 2020). The use of Umifenovir for COVID-19 is still unknown (Deng et al., 2020). Reportedly, there is no antiviral treatment for this novel disease, it is critical to assess the efficacy and safety of Umifenovir in COVID-19 (Lian et al., 2020). It has a broad-spectrum antiviral agent, has been proposed as a potential COVID-19 treatment (Huang et al., 2020). Umifenovir was not found to shorten the duration of SARS-CoV-2 negativity or improve prognosis in non-ICU patients after three different studies (Huang et al., 2021).

14.18.7 Human interferon beta

Type 1 interferons, particularly IFN-beta, have been identified as potential leading therapeutics for severe COVID-19 and are currently being evaluated in the REMAP-CAP and the WHO's Solidarity Trial (Jalkanen et al., 2020). In phase II clinical trial, combination treatments with IFN-beta, lopinavir-ritonavir, and ribavirin demonstrated that the arm containing IFN-beta was superior in eliminating the virus from nasopharyngeal swabs (Cheung et al., 2020). Critically ill COVID-19 patients with elevated levels of plasma cytokines (particularly IL-6) exhibit immune exhaustion and poor IFN responses (Blanco-Melo et al., 2020). Even in such cases, IFN-beta would most likely benefit these patients because it is the most potent antiviral and antiinflammatory agent of all interferons. It can induce the desired immune boost while also downregulating IL-6 and IL-8 (Laver et al., 2008) and inhibit neutrophil extravasation into the lungs (Kiss et al., 2007).

14.18.8 TMC-310911

It is a protease inhibitor that is still being studied in clinical experiments to cure HIV infection. It has exhibited in vitro activity against HIV strains that have developed resistance to other protease inhibitors. SARS-CoV main protease (SARS) is being targeted by researchers to investigate their possible mode of inhibition (Soremekun et al., 2021).

14.18.9 Fingolimod

Fingolimod, a sphingosine 1 phosphate (S1P) analog, is used to treat multiple sclerosis patients' immune systems. Fingolimod binds to S1P receptors on lymphocytes, causing receptor internalization and lymphocyte retention in lymphoid organs (Foerch et al., 2020). As a result, lymphopenia is observed in the peripheral blood T-cell compartment. A clinical trial (NCT04280588) was conducted to determine the potential of fingolimod for a novel coronavirus disease (COVID-19) (https://clinicaltrials.gov/ct2/show/NCT04280588) (Guan et al., 2020).

14.18.10 Methylprednisolone

Corticosteroid therapy is not recommended for routine usage in cases of viral pneumonia due to its potential damage effects on the lungs (Russell et al., 2020). GLUCOCOVID is a randomized, open-label, controlled, two-arm, parallel-group trial being conducted in five Spanish hospitals (Hospital Universitario Mar-qués de Valdecilla, Hospital Universitario Río Hortega, Hospital El Bierzo, Hospital Laredo, and Hospital Sierrallana). The study's goal was to determine the efficacy of combining MP with standard therapy in patients with moderate to severe cancer. It is an abbreviation for COVID-19 (Corral-Gudino et al., 2021).

14.18.11 Bevacizumab

It is a humanized anti-VEGF monoclonal antibody used in treating patients suffering from severe COVID-19. The visible effect of bevacizumab on oxygenation was clearly improved after a 24-hour of treatment. This suggests that the clinical benefits of bevacizumab treatment occur at an early stage. In comparison to the control group, a significantly greater number of patients improved their 28-day oxygen-support status (control, 62% vs bevacizumab, 92%) as well as the discharge rate (control, 46% vs bevacizumab, 65%). In addition, bevacizumab-treated patients had less deterioration in oxygen-support status when compared to the control group (control, 19% vs bevacizumab, 0%) (Pang et al., 2021).

14.18.12 Leronlimab

It (PRO 140) is a humanized IgG4, C−C chemokine receptor type 5 (CCR5), monoclonal antibody receptor antagonist that was initially studied for the treatment of HIV, where it was shown to be effective and well-tolerated, and is now being studied for the treatment of COVID-19 (Dhody et al., 2018). COVID-19 patients are given 700 mg of Leronlimab subcutaneously once a week for 2 weeks. Macrophages, T regulatory cells, and dendritic cells all have CCR5 receptors. The binding of Leronlimab to the CCR5 receptor inhibits CCL5 competitively (Jiao et al., 2021). Because of its good safety profile in HIV patients, mechanism of action, and basic science physiology, Leronlimab was also considered as a potential treatment option for COVID-19 (Agresti et al., 2021).

14.18.13 Azithromycin

In a randomized study of infants, it was shown to be effective against the respiratory syncytial virus (Beigelman et al., 2015). In vitro and in a clinical setting, azithromycin had a synergistic antiviral effect against SARS-CoV-2 when combined with HCQ. The mechanisms of AZM's antiviral effect support a broad spectrum of antiviral activity. Azithromycin appears to inhibit virus entry into cells (Tran et al., 2019). Furthermore, it can boost the immune response to viruses through a variety of mechanisms. Azithromycin stimulates the production of type 1 and 3 interferons as well as virus-recognition genes

such as MDA5 and RIG-I (Zeng et al., 2019). These mechanisms are universally involved in the innate response to infectious agents, including SARS-CoV-2 (Gyselinck et al., 2021).

14.18.14 Elbasvir

Elbasvir reacts with RdRP, proteinase, and helicase of SARS-CoV-2. Although reusing an approved drug is by far the most excellent approach to instantly develop innovative therapeutics against this novel pathogen, researchers surveyed FDA-approved antiviral medications for docking prospects with SARS-CoV-2 proteins (Balasubramaniam & Reis, 2020).

14.18.15 Tocilizumab

It (TCZ) is a synthetic monoclonal antibody that serves as an IL-6 receptor antagonist. It is currently used to treat rheumatoid arthritis, but this could potentially be useful in treating COVID-19 patients who really are unwell, Though the usefulness of tocilizumab in noncritically sick patients with SARS-CoV-2 is yet unclear (Gupta et al., 2020).

14.18.16 GS-441524

It is converted into pharmacologically active triphosphate type (GS-443902) in cells and tissues, which inhibits viral RNA polymerases without any effect on host RNA or DNA polymerases (Siegel et al., 2017). When compared in humans, Remdesivir demonstrated high protein binding (80%−90%), and GS-441524 revealed extremely low protein interaction in plasma (<20%) (Tempestilli et al., 2020).

14.18.17 Ibuprofen

It is a nonsteroidal antiinflammatory medicine (NSAID) typically used as an antipyretic and analgesic. The most prescribed antipyretics are acetaminophen and ibuprofen (Bushra & Aslam, 2010). The coronavirus (COVID-19) pandemic, resulted in widespread ibuprofen supply disruptions (Abu Esba et al., 2021). However, later throughout the news, it was reported that ibuprofen must be sidestepped because it could exacerbate COVID-19 effects (Moore et al., 2020).

14.18.18 Anti-severe acute respiratory syndrome-Coronavirus-2 REGN-Coronavirus-2

It is a combination of two highly effective neutralizing antibodies (REGN10933/Casirivimab and REGN10987/Imdevimab), targeting two separate, nonoverlapping epitopes on the Spike protein of SARS-CoV-2. This can greatly decrease virus load, loss of weight, and pneumonia side effects, which provide conclusive proof for a clinical study (Baum, Fulton, et al., 2020). People with a strong viral load at the start of the infection or

who still haven't established an immune response have a stronger benefit (Weinreich et al., 2021).

14.18.19 Dexamethasone

It is a recombinant corticosteroid that suppresses the immune system across a broad range, has greater efficacy than cortisone (Theoharides & Conti, 2020). For their ability to reduce the transcription of genes of several pro-inflammatory cytokines, chemokines, and adhesion molecules, they have antiinflammatory capabilities (Sharun et al., 2020) and may be effective in combating the COVID-19-related cytokine storm (Lim & Pranata, 2020).

14.18.20 Bamlanivimab/Etesevimab

It is a set of anti-Spike neutralizing monoclonal antibodies produced from two distinct COVID-19 patients in North America and China, separately (Jones et al., 2020). In clinical trials, they may improve viral load reduction and reduce treatment-emergent resistance variants (Baum, Ajithdoss, et al., 2020).

14.18.21 Ifenprodil

In a small handful of nations, including Japan and France, it has been utilized as a cerebral vasodilator. Ifenprodil is a prototypical antagonist of the N-methyl-D-aspartate receptor (NMDAR) of the GluN2B subunit. Ifenprodil has a strong affinity for the sigma-1 and sigma-2 receptors and repurposes them for COVID-19 (Hashimoto, 2021).

14.19 Virtual screening platforms

14.19.1 Introduction of virtual screening platforms

VS is a computerized process for the identification of amalgam that binds to a specific target, typically an enzyme or receptor, from a large compound library (Gimeno et al., 2019). It is typically approached hierarchically in the form of a work plan, consecutively assimilating numerous procedures that act as filters to get rid of undesirable compounds (Cruz-Monteagudo et al., 2017). VS methods can be classified into two major groups: (a) ligand-based methods and (b) receptor-based methods (Table 14.3).

The availability of high-resolution structures of many SARS-CoV-2 proteins (Table 14.4) enabled the identification of lead drug candidates for SARS-CoV-2 in a timely manner using in silico screening methods. Previous studies have shown that the number of compounds screened in a structure-based in silico screen affects the quality of the resulting hits and that the potency of the hits derived increases as the number of compounds screened increases (Lyu et al., 2019).

TABLE 14.3 Popular software used in virtual screening.

S. No.	Software	URL	References
1	AutoDock VINA	https://vina.scripps.edu/	Trott and Olson (2010)
2	AIDrugApp	https://sars-covid-app.herokuapp.com	Karade and Karade (2020)
3	VSDK	http://www.pharm.kobegakuin.ac.jp/~akaho/english_top.html	N/A
4	DockoMatic	dockmatic2.1_src.tar.gz	Bullock et al. (2013)
5	PyRx	https://pyrx.sourceforge.io/	Mahdian (2022)
6	VirtualFlow	https://virtual-flow.org/	Gorgulla et al. (2020)

Modified from Usha, T., Dhivya, S., Goyal, A., Kumar, C., & Middha, S. (2017). Recent Updates on Computer-aided Drug Discovery: Time for a Paradigm Shift. Current Topics in Medicinal Chemistry, 17*(30), 3296–3307. https://doi.org/10.2174/1568026618666180101163651.*

14.19.2 High-throughput screening

Designing widely diversified biological libraries and analyzing them via HTS is a much more realistic way to progress a strain improvement program as well as to manufacturing size. Jin et al. (2020) reported that cinanserin, a well-characterized serotonin antagonist, has a cation−π interactions with H41 and E166 of Mpro and the potential to become an antiviral drug lead (Jin et al., 2020). The same study also indicated (a) Ebselen, (b) Disulfiram, (c) Tideglusib, (d) Carmofur, (e) Shikonin, (f) PX-12 as a potent viral target for M^{pro} (Fig. 14.2).

14.20 Webservers

There are few webservers that were developed by researchers and freely accessible to understand or predict targets or binding sites. For example, "D3Targets-2019-nCoV" (https://www.d3pharma.com/D3Targets-2019-nCoV/index.php) (Shi et al., 2020). This server has "20 viral proteins and 22 human proteins recorded in virus infection, replication and release, with 69 different conformations and 557 potential ligand-binding pockets (Yang & Zhang, 2015)." The authors have not included nonpeer-reviewed publications webservers or yet published servers in this chapter.

14.21 Conclusion

In this paper, we gave an overview of the characteristic features, symptoms, replication cycle of SARS-CoV-2. This novel virus spread majorly through respiratory droplets and close contact. It is a human-borne disease and is spread from human to human. The main objective is to discuss the different types of drugs approved to use against SARS-CoV-2 viral diseases, selected from the DrugBank database. While peer-studied journals, assessments, s and trials, online tools are fastening up the sharing of COVID-19 information, allowing quick and free access for both public and researchers. Different databases are

TABLE 14.4 Target proteins of Coronavirus disease-2019 available in protein data bank (PDB).

S. no.	Protein name	Alternative name	Target site	Structure in PDB	Reference from PDB
1	ACE2	Angiotensin-converting enzyme 2	Spike RDB binding region – site 1	6m17	Yan et al. (2020)
			Spike RDB binding region – site 1	6m18	Yan et al. (2020)
			Spike RDB binding region – site 2	6m17	Yan et al. (2020)
			Dynamic pocket 1besides spike RDB binding region	NA	
			Dynamic pocket 2 besides spike RDB binding region	NA	
2	TMPRSS2	Transmembrane protease serine 2	Active site	NA	
3	Spike	S-protein, S	Spike RDB – ACE2 interface	6w41	Yuan (2020)
4	ORF7a	Protein 7a	Blind docking	6w37	Nelson (n.d.)
5	nsp3-macrodomain	phosphatase, (macro) X domain	Active site	6w6y chain A(closed active site)	Michalska et al. (2020)
			Active site	6w6y chain B (opened active site)	Michalska, et al. (2020)
6	nsp3-Plpro	PLpro, PLP, papain-like protease	Active site	6w9c	Osiluk (2020)
			Accessory pocket	6w9c	Osiluk (2020)
			DUB binding site	6w9c	Osiluk (2020)
			Active site and accessory pocket	6wx4*	Rut et al. (2020)
7	nsp5	Mpro, main protease	Active site	6lu7	Jin et al. (2020)
			Active site	6m0k*	Dai et al. (2020)
			Dimerization site	6wqf	Kneller et al. (2020)
			a-helix 5 attachment site	NA	

8	nsp7	Replicase polyprotein 1ab	Blind docking (nsp8 PPI, nsp12 PPI)	6wiq	Wilamowski et al. (2021)
9		Primase complex	nsp7 PPI	6wiq	Wilamowski et al. (2021)
			nsp12 PPI	7bv1	Yin et al. (2020)
10	nsp10	Replicase	Dimerization interface – site 1	6w4b	Billesbølle et al. (2020)
			Dimerization interface – site 2	6w4b	Dai et al. (2020); Tan et al., https://www.rcsb.org/structure/6w4b (yet to be published).
11			nsp16 PPI	6w4h	Rosas-Lemus et al. (2020)
			nsp16 PPI	NA	
			nsp14 PPI	NA	
12	nsp12	RNA-dependent RNA polymerase (RdRP)	RNA binding interface – site 1	7bv1	Yin et al. (2020)
			RNA binding interface – site 2	7bv1	Yin et al. (2020)
			Nucleotide-binding site	7bv1	Yin et al. (2020)
			nsp8 PPI	6m71	Gao et al. (2020)
			nsp7/8 PPI	7bv1	Yin et al. (2020)
13	nsp13	Helicase	Active site	NA	
			RNA binding interface – site 1	NA	
			RNA binding interface – site 2	NA	
14	nsp14	Exoribonuclease, N7 methyltransferase, N7-Mtase	nsp10 PPI	NA	
			Active site (ExoN)	NA	
			Active site (N7-MT)	NA	
15	nsp15	Endoribonuclease, XendoU	Active site	6w01	Kim et al. (2020)
16	nsp16	20-O-MTase,2′-O methyltransferase	nsp10 PPI	6w4b	Billesbølle et al. (2020)
			Active site(2′-O MT)	6w4b	Billesbølle et al. (2020)

(*Continued*)

TABLE 14.4 (Continued)

S. no.	Protein name	Alternative name	Target site	Structure in PDB	Reference from PDB
17	Nucleoprtein	N, NC, NP, RNP, ribonucleocapsid protein	NTD- RNA binding site	6yi3	Dinesh et al. (2020)
			NTD-oligomerization site	6yi3	Dinesh et al. (2020)
			CTD- dimerization interface	6wji	Minasov, 2020. https://www.rcsb.org/structure/6wji (yet to be published).
			CTD- oligomerization site	6wji	Minasov, 2020. https://www.rcsb.org/structure/6wji (yet to be published).

Data from Gorgulla, C., Boeszoermenyi, A., Wang, Z. F., Fischer, P. D., Coote, P. W., Padmanabha Das, K. M., Malets, Y. S., Radchenko, D. S., Moroz, Y. S., Scott, D. A., Fackeldey, K., Hoffmann, M., Iavniuk, I., Wagner, G., & Arthanari, H. (2020). An open-source drug discovery platform enables ultra-large virtual screens. Nature, 580*(7805), 663–668. https://doi.org/10.1038/s41586-020-2117-z.*

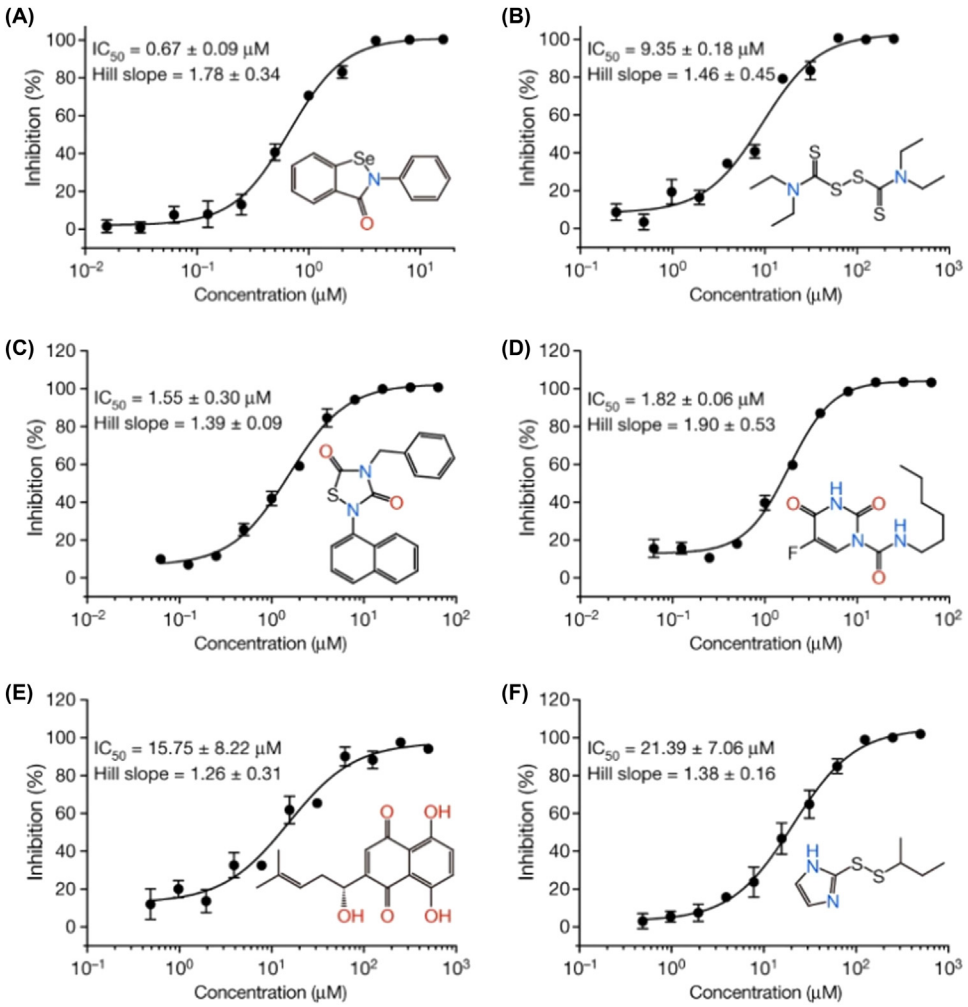

FIGURE 14.2 Drug leads inhibit the activity of severe acute respiratory syndrome Mpro. Source*: Data from Jin, Z., Du, X., Xu, Y., Deng, Y., Liu, M., Zhao, Y., Zhang, B., Li, X., Zhang, L., Peng, C., Duan, Y., Yu, J., Wang, L., Yang, K., Liu, F., Jiang, R., Yang, X., You, T., Liu, X., … Yang, H. (2020). Structure of Mpro from SARS-CoV-2 and discovery of its inhibitors. Nature, 582(7811), 289–293. https://doi.org/10.1038/s41586-020-2223-y.*

incorporated in this paper with their individual links to easily fetch detailed information and statistical data of SARS-CoV-2, COVID-19 disease. This paper also provides popular software used for the VS of potential drugs and their specific targets. HTS plays an important role in the discovery of antiviral drugs from high-content compound libraries. These databases maintain some of the applications to record the SARS-CoV-2 approach, site, gene, and mutagenesis of this novel virus are really advantageous. By understanding the complexity and mechanism of all viral proteins, virtual trials, molecular docking, therapeutic intervention, and developing vaccination may provide a lead for COVID-19

treatment to curtail the death rate. VS and molecular docking are effective ways of discovering a potential drug that inhibits the protein responsible for the pathogenesis of the viral particle. Therefore, this chapter provides a piece of complete information about the SARS-CoV-2 virus, potential drugs, and VS methods. And also provides a different database to reach out for information related to the COVID-19 pandemic and its future.

14.22 Future prospective

The scenario of the outbreak is taking on entirely different characteristics. We will know whether the vaccines are efficiently working to control SARS-CoV-2 spread which remains a far goal to accomplish or is already there. The unprecedented mass and simultaneous vaccination of the population will undoubtedly reveal heterogeneity in vaccination responses and some individuals may not produce robust antibody responses or be protected. And in the future, the hottest issue will be vaccines availability and its unbiased distribution in and around the world. Thus, the vaccine may become a fortunate measure of power. And in the long run, maybe more than one vaccine will be needed to ensure reasonable universal access, shield, and immunity against viral alternates. Hence, vaccination is the only important approach to end this outbreak which provides an effective measure of hope in the future.

Countries should work in isolation from each other to prolong the pandemic. Unless the countries work together to gage up prevention efforts, the risk of rising in the cases including other disasters will remain a constant threat.

References

(N.d.). Retrieved June 7, 2021, from https://www.drugbank.com/?_ga = 2.150391219.480430687.1623046628-554615112.1623046628.

Abu Esba, L. C., Alqahtani, R. A., Thomas, A., Shamas, N., Alswaidan, L., & Mardawi, G. (2021). Ibuprofen and NSAID use in COVID-19 infected patients is not associated with worse outcomes: A prospective cohort study. *Infectious Diseases and Therapy*, *10*(1), 253–268. Available from https://doi.org/10.1007/s40121-020-00363-w.

Agresti, N., Lalezari, J. P., Amodeo, P. P., Mody, K., Mosher, S. F., Seethamraju, H., Kelly, S. A., Pourhassan, N. Z., Sudduth, C. D., Bovinet, C., ElSharkawi, A. E., Patterson, B. K., Stephen, R., Sacha, J. B., Wu, H. L., Gross, S. A., & Dhody, K. (2021). Disruption of CCR5 signaling to treat COVID-19-associated cytokine storm: Case series of four critically ill patients treated with leronlimab. *Journal of Translational Autoimmunity*, *4*, 100083. Available from https://doi.org/10.1016/j.jtauto.2021.100083.

Alsulami, A. F., Thomas, S. E., Jamasb, A. R., Beaudoin, C. A., Moghul, I., Bannerman, B., Copoiu, L., Vedithi, S. C., Torres, P., & Blundell, T. L. (2021). SARS-CoV-2 3D database: understanding the Coronavirus proteome and evaluating possible drug targets. *Briefings in Bioinformatics*, *22*(2), 769–780. Available from https://doi.org/10.1093/bib/bbaa404.

Arab-Zozani, M., & Hassanipour, S. (2020). Features and limitations of LitCovid hub for quick access to literature about Covid-19. *Balkan Medical Journal*, *37*(4), 231–232. Available from https://doi.org/10.4274/balkanmedj.galenos.2020.2020.4.100.

Arab-Zozani, M., Hassanipour, S., & Ghoddoosi-Nejad, D. (2020). Favi-piravir for treating patients with novel Coronavirus (COVID-19): Protocol for a systematic review and *meta*-analysis of randomised clinical trials. *BMJ Open*, *10*(7).

Aronson, J. K., & Ferner, R. E. (2020). Drugs and the renin-angiotensin system in Covid-19. *The BMJ*, 369. Available from https://doi.org/10.1136/bmj.m1313.

Balasubramaniam, M., & Reis, R. J. S. (2020). Computational target-based drug repurposing of elbasvir, an antiviral drug predicted to bind multiple SARS-CoV-2 proteins. *ChemRxiv : The Preprint Server for Chemistry*. Available from https://doi.org/10.26434/chemrxiv.12084822.v2.

Baum, A., Ajithdoss, D., Copin, R., Zhou, A., Lanza, K., Negron, N., Ni, M., Wei, Y., Mohammadi, K., Musser, B., Atwal, G. S., Oyejide, A., Goez-Gazi, Y., Dutton, J., Clemmons, E., Staples, H. M., Bartley, C., Klaffke, B., Alfson, K., & Kyratsous, C. A. (2020). REGN-COV2 antibodies prevent and treat SARS-CoV-2 infection in rhesus macaques and hamsters. *Science (New York, N.Y.)*, *370*(6520), 1110–1115. Available from https://doi.org/10.1126/science.abe2402.

Baum, A., Fulton, B. O., Wloga, E., Copin, R., Pascal, K. E., Russo, V., Giordano, S., Lanza, K., Negron, N., Ni, M., Wei, Y., Atwal, G. S., Murphy, A. J., Stahl, N., Yancopoulos, G. D., & Kyratsous, C. A. (2020). Antibody cocktail to SARS-CoV-2 spike protein prevents rapid mutational escape seen with individual antibodies. *Science (New York, N.Y.)*, *369*(6506), 1014–1018. Available from https://doi.org/10.1126/science.abd0831.

Beigelman, A., Isaacson-Schmid, M., Sajol, G., Baty, J., Rodriguez, O. M., Leege, E., Lyons, K., Schweiger, T. L., Zheng, J., Schechtman, K. B., Castro, M., & Bacharier, L. B. (2015). Randomized trial to evaluate azithromycin's effects on serum and upper airway IL-8 levels and recurrent wheezing in infants with respiratory syncytial virus bronchiolitis. *The Journal of Allergy and Clinical Immunology*, *135*(5), 1171–1178. Available from https://doi.org/10.1016/j.jaci.2014.10.001, e1.

Bestle, D., Heindl, M. R., Limburg, H., Van, T. V. L., Pilgram, O., Moulton, H., Stein, D. A., Hardes, K., Eickmann, M., Dolnik, O., Rohde, C., Becker, S., Klenk, H. D., Garten, W., Steinmetzer, T., & Böttcher-Friebertshäuser, E. (2020). TMPRSS2 and furin are both essential for proteolytic activation and spread of SARS-CoV-2 in human airway epithelial cells and provide promising drug targets. *BioRxiv*. Available from https://doi.org/10.1101/2020.04.15.042085.

Billesbølle, C. B., Azumaya, C. M., Kretsch, R. C., Powers, A. S., Gonen, S., Schneider, S., Arvedson, T., Dror, R. O., Cheng, Y., & Manglik, A. (2020). Structure of hepcidin-bound ferroportin reveals iron homeostatic mechanisms. *Nature*, *586*(7831), 807–811. Available from https://doi.org/10.1038/s41586-020-2668-z.

Blanco-Melo, D., Nilsson-Payant, B. E., Liu, W.-C., Uhl, S., Hoagland, D., Møller, R., Jordan, T. X., Oishi, K., Panis, M., Sachs, D., Wang, T. T., Schwartz, R. E., Lim, J. K., Albrecht, R. A., & tenOever, B. R. (2020). Imbalanced host response to SARS-CoV-2 drives development of COVID-19. *Cell*, *181*(5), 1036–1045. Available from https://doi.org/10.1016/j.cell.2020.04.026, e9.

Bullock, C., Cornia, N., Jacob, R., et al. (2013). DockoMatic 2.0: high throughput inverse virtual screening and homology modeling. *J Chem Inf Model*, *53*(8), 2161–2170. Available from https://doi.org/10.1021/ci400047w.

Bushra, R., & Aslam, N. (2010). An overview of clinical pharmacology of Ibuprofen. *Oman Medical Journal*, *25*(3), 155–1661. Available from https://doi.org/10.5001/omj.2010.49.

Cao, B., Wang, Y., Wen, D., Liu, W., Wang, J., Fan, G., Ruan, L., Song, B., Cai, Y., Wei, M., Li, X., Xia, J., Chen, N., Xiang, J., Yu, T., Bai, T., Xie, X., Zhang, L., Li, C., & Wang, C. (2020). A trial of lopinavir-ritonavir in adults hospitalized with severe Covid-19. *New England Journal of Medicine*, *382*(19), 1787–1799. Available from https://doi.org/10.1056/NEJMoa2001282.

Carneiro, J., et al. (2020). *CoV2ID: Detection and Therapeutics Oligo Database for SARS-CoV-2*. Available from https://doi.org/10.1101/2020.04.19.048991.

Chen, Q., Allot, A., & Lu, Z. (2020). Keep up with the latest coronavirus research. *Nature*, *579*(7798), 193. Available from https://doi.org/10.1038/d41586-020-00694-1.

Cheung, K. S., Hung, I. F. N., Chan, P. P. Y., Lung, K. C., Tso, E., Liu, R., Ng, Y. Y., Chu, M. Y., Chung, T. W. H., Tam, A. R., Yip, C. C. Y., Leung, K.-H., Fung, A. Y.-F., Zhang, R. R., Lin, Y., Cheng, H. M., Zhang, A. J. X., To, K. K. W., Chan, K.-H., & Leung, W. K. (2020). Gastrointestinal manifestations of SARS-CoV-2 infection and virus load in fecal samples from a Hong Kong cohort: Systematic review and *meta*-analysis. *Gastroenterology*, *159*(1), 81–95. Available from https://doi.org/10.1053/j.gastro.2020.03.065.

Ciobotaru, G., Bogdan, C., & Berbescu, C. (1979). Hyperfunctional dysphonias in children. *Revista de Chirurgie, Oncologie, Radiologie, o.r.l., Oftalmologie, Stomatologie. Oto-Rino-Laringologia*, *24*(1), 23–28.

Colson, P., Rolain, J.-M., & Raoult, D. (2020). Chloroquine for the 2019 novel coronavirus SARS-CoV-2. *International Journal of Antimicrobial Agents*, *55*(3), 105923. Available from https://doi.org/10.1016/j.ijantimicag.2020.105923.

Corral-Gudino, L., Bahamonde, A., Arnaiz-Revillas, F., Gómez-Barquero, J., Abadía-Otero, J., García-Ibarbia, C., Mora, V., Cerezo-Hernández, A., Hernández, J. L., López-Muñíz, G., Hernández-Blanco, F., Cifrián, J. M., Olmos, J. M., Carrascosa, M., Nieto, L., Fariñas, M. C., & Riancho, J. A. (2021). Methylprednisolone in adults

hospitalized with COVID-19 pneumonia. *Wiener Klinische Wochenschrift*, *133*(7–8), 303–311. Available from https://doi.org/10.1007/s00508-020-01805-8.

Cruz-Monteagudo, M., Schürer, S., Tejera, E., Pérez-Castillo, Y., Medina-Franco, J. L., Sánchez-Rodríguez, A., & Borges, F. (2017). Systemic QSAR and phenotypic virtual screening: Chasing butterflies in drug discovery. *Drug Discovery Today*, *22*(7), 994–1007. Available from https://doi.org/10.1016/j.drudis.2017.02.004.

da Rosa, R. L., Yang, T. S., Tureta, E. F., de Oliveira, L. R. S., Moraes, A. N. S., Tatara, J. M., Costa, R. P., Borges, J. S., Alves, C. I., Berger, M., Guimarães, J. A., Santi, L., & Beys-da-Silva, W. O. (2021). SARSCOVIDB-A new platform for the analysis of the molecular impact of SARS-CoV-2 viral infection. *ACS Omega*, *6*(4), 3238–3243. Available from https://doi.org/10.1021/acsomega.0c05701.

Dai, W., Zhang, B., Jiang, X. M., Su, H., Li, J., Zhao, Y., Xie, X., Jin, Z., Peng, J., Liu, F., Li, C., Li, Y., Bai, F., Wang, H., Cheng, X., Cen, X., Hu, S., Yang, X., Wang, J., Liu, X., Xiao, G., Jiang, H., Rao, Z., Zhang, L. K., Xu, Y., Yang, H., & Liu, H. (2020). Structure-based design of antiviral drug candidates targeting the SARSCoV-2 main protease. *Science*, *368*(6497), 1331–1335. Available from https://doi.org/10.1126/science.abb4489.

Deng, L., Li, C., Zeng, Q., Liu, X., Li, X., Zhang, H., Hong, Z., & Xia, J. (2020). Arbidol combined with LPV/r vs LPV/r alone against Coronavirus disease 2019: A retrospective cohort study. *Journal of Infection*, *81*(1), e1–e5. Available from https://doi.org/10.1016/j.jinf.2020.03.002.

Dhody, K., Pourhassan, N., Kazempour, K., Green, D., Badri, S., Mekonnen, H., Burger, D., & Maddon, P. J. (2018). PRO 140, a monoclonal antibody targeting CCR5, as a long-acting, single-agent maintenance therapy for HIV-1 infection. *HIV Clinical Trials*, *19*(3), 85–93. Available from https://doi.org/10.1080/15284336.2018.1452842.

Dinesh, D. C., Chalupska, D., Silhan, J., Koutna, E., Nencka, R., Veverka, V., & Boura, E. (2020). Structural basis of RNA recognition by the SARS-CoV-2 nucleocapsid phosphoprotein. *PLoS Pathog*, *16*(12), e1009100. Available from https://doi.org/10.1371/journal.ppat.1009100.

Dong, E., Du, H., & Gardner, L. (2020). An interactive web-based dashboard to track COVID-19 in real time. *The Lancet Infectious Diseases*, *20*(5), 533–534. Available from https://doi.org/10.1016/S1473-3099(20)30120-1.

Donoghue, M., Hsieh, F., Baronas, E., Godbout, K., Gosselin, M., Stagliano, N., Donovan, M., Woolf, B., Robison, K., Jeyaseelan, R., Breitbart, R. E., & Acton, S. (2000). A novel angiotensin-converting enzyme-related carboxypeptidase (ACE2) converts angiotensin I to angiotensin 1-9. *Circulation Research*, *87*(5), E1–E9. Available from https://doi.org/10.1161/01.res.87.5.e1.

Dotolo, S., Marabotti, A., Facchiano, A., & Tagliaferri, R. (2021). A review on drug repurposing applicable to COVID-19. *Briefings in bioinformatics*, *22*(2), 726–741. Available from https://doi.org/10.1093/bib/bbaa288.

Fang, S., Li, K., Shen, J., Liu, S., Liu, J., Yang, L., Hu, C. D., & Wan, J. (2021). GESS: a database of global evaluation of SARS-CoV-2/hCoV-19 sequences. *Nucleic Acids Res.*, *49*(D1), D706–D714. Available from https://doi.org/10.1093/nar/gkaa808, PMID: 33045727; PMCID: PMC7778918.

Foerch, C., Friedauer, L., Bauer, B., Wolf, T., & Adam, E. H. (2020). Severe COVID-19 infection in a patient with multiple sclerosis treated with fingolimod. *Mult Scler Relat Disord.*, *42*, 102180. Available from https://doi.org/10.1016/j.msard.2020.102180.

Gao, J., Tian, Z., & Yang, X. (2020). Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. *BioScience Trends*, *14*(1), 72–73. Available from https://doi.org/10.5582/bst.2020.01047.

Gao, Y., Yan, L., Huang, Y., Liu, F., Zhao, Y., Cao, L., Wang, T., Sun, Q., Ming, Z., Zhang, L., Ge, J., Zheng, L., Zhang, Y., Wang, H., Zhu, Y., Zhu, C., Hu, T., Hua, T., Zhang, B., Yang, X., Li, J., Yang, H., Liu, Z., Xu, W., Guddat, L. W., Wang, Q., Lou, Z., & Rao, Z. (2020). Structure of the RNA-dependent RNA polymerase from COVID-19 virus. *Science*, *368*(6492), 779–782. Available from https://doi.org/10.1126/science.abb7498.

Gimeno, A., Ojeda-Montes, M. J., Tomás-Hernández, S., Cereto-Massagué, A., Beltrán-Debón, R., Mulero, M., Pujadas, G., & Garcia-Vallvé, S. (2019). The light and dark sides of virtual screening: What is there to know? *International Journal of Molecular Sciences*, *20*(6). Available from https://doi.org/10.3390/ijms20061375.

Giudicessi, J. R., Noseworthy, P. A., Friedman, P. A., & Ackerman, M. J. (2020). Urgent guidance for navigating and circumventing the QTc-prolonging and torsadogenic potential of possible pharmacotherapies for Coronavirus disease 19 (COVID-19). *Mayo Clinic Proceedings*, *95*(6), 1213–1221. Available from https://doi.org/10.1016/j.mayocp.2020.03.024.

Gorgulla, C., Boeszoermenyi, A., Wang, Z. F., et al. (2020). An open-source drug discovery platform enables ultra-large virtual screens. *Nature*, *580*, 663–668. Available from https://doi.org/10.1038/s41586-020-2117-z.

Goyal, A. K., Middha, S. K., & Usha, T. (2021). Could nature be the solution-A review on selected folklore medicinal plants with antiviral activities repurposed for COVID-19 treatment. *Indian J of traditional Knowledge*, *20*(4), 891–901.

Gralinski, L. E., & Menachery, V. D. (2020). Return of the Coronavirus: 2019-nCoV. *Viruses*, *12*(2). Available from https://doi.org/10.3390/v12020135.

Guan, W., Ni, Z., Hu, Y., Liang, W., Ou, C., He, J., Liu, L., Shan, H., Lei, C., Hui, D. S. C., Du, B., Li, L., Zeng, G., Yuen, K. Y., Chen, R., Tang, C., Wang, T., Chen, P., Xiang, J., & Zhong, N. (2020). Clinical characteristics of coronavirus disease 2019 in China. *New England Journal of Medicine*, *382*(18), 1708–1720. Available from https://doi.org/10.1056/NEJMoa2002032.

Gupta, R., Charron, J., Stenger, C. L., Painter, J., Steward, H., Cook, T. W., Faber, W., Frisch, A., Lind, E., Bauss, J., Li, X., Sirpilla, O., Soehnlen, X., Underwood, A., Hinds, D., Morris, M., Lamb, N., Carcillo, J. A., Bupp, C., & Prokop, J. W. (2020). SARS-CoV-2 (COVID-19) structural and evolutionary dynamicome: Insights into functional evolution and human genomics. *Journal of Biological Chemistry*, *295*(33), 11742–11753. Available from https://doi.org/10.1074/jbc.ra120.014873.

Guzik, T. J., Mohiddin, S. A., Dimarco, A., Patel, V., Savvatis, K., Marelli-Berg, F. M., Madhur, M. S., Tomaszewski, M., Maffia, P., D'Acquisto, F., Nicklin, S. A., Marian, A. J., Nosalski, R., Murray, E. C., Guzik, B., Berry, C., Touyz, R. M., Kreutz, R., Dao, W. W., & McInnes, I. B. (2020). COVID-19 and the cardiovascular system: Implications for risk assessment, diagnosis, and treatment options. *Cardiovascular Research*, *116*(10), 1666–1687. Available from https://doi.org/10.1093/cvr/cvaa106.

Gyselinck, I., Liesenborghs, L., Landeloos, E., Belmans, A., Verbeke, G., Verhamme, P., Vos, R., & Janssens, W. (2021). Direct antivirals working against the novel coronavirus: azithromycin (DAWn-AZITHRO), a randomized, multicenter, open-label, adaptive, proof-of-concept clinical trial of new antivirals working against SARS-CoV-2-azithromycin trial. *Trials*, *22*(1), 126. Available from https://doi.org/10.1186/s13063-021-05033-x.

Hasell, J., Mathieu, E., Beltekian, D., Macdonald, B., Giattino, C., Ortiz-Ospina, E., Roser, M., & Ritchie, H. (2020). A cross-country database of COVID-19 testing. *Scientific Data*, *7*(1). Available from https://doi.org/10.1038/s41597-020-00688-8.

Hashimoto, K. (2021). Repurposing of CNS drugs to treat COVID-19 infection: targeting the sigma-1 receptor. *European Archives of Psychiatry and Clinical Neuroscience*, *271*(2), 249–258. Available from https://doi.org/10.1007/s00406-020-01231-x.

Hassanipour S., Arab-Zozani M., Amani B., Heidarzad F., Fathalipour M., Martinez-de-Hoyo R. The efficacy and safety of Favipiravir in treatment of COVID-19: a systematic review and meta-analysis of clinical trials [published correction appears in *Sci Rep*. 2022 Feb 1;12(1):1996]. Sci Rep. 2021;11(1):11022. Published 2021 May 26. Available from https://doi.org/10.1038/s41598-021-90551-6

Hoffmann, M., Kleine-Weber, H., Schroeder, S., Krüger, N., Herrler, T., Erichsen, S., Schiergens, T. S., Herrler, G., Wu, N. H., Nitsche, A., Müller, M. A., Drosten, C., & Pöhlmann, S. (2020). SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell*, *181*(2), 271–280. Available from https://doi.org/10.1016/j.cell.2020.02.052, e8.

Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., Zhang, L., Fan, G., Xu, J., Gu, X., Cheng, Z., Yu, T., Xia, J., Wei, Y., Wu, W., Xie, X., Yin, W., Li, H., Liu, M., & Cao, B. (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet (London, England)*, *395*(10223), 497–506. Available from https://doi.org/10.1016/S0140-6736(20)30183-5.

Huang, D., Yu, H., Wang, T., Yang, H., Yao, R., & Liang, Z. (2021). Efficacy and safety of umifenovir for Coronavirus disease 2019 (COVID-19): A systematic review and *meta*-analysis. *Journal of Medical Virology*, *93*(1), 481–490. Available from https://doi.org/10.1002/jmv.26256.

Hufsky, F., Lamkiewicz, K., Almeida, A., Aouacheria, A., Arighi, C., Bateman, A., Baumbach, J., Beerenwinkel, N., Brandt, C., Cacciabue, M., Chuguransky, S., Drechsel, O., Finn, R. D., Fritz, A., Fuchs, S., Hattab, G., Hauschild, A.-C., Heider, D., Hoffmann, M., & Marz, M. (2021). Computational strategies to combat COVID-19: Useful tools to accelerate SARS-CoV-2 and Coronavirus research. *Briefings in Bioinformatics*, *22*(2), 642–663. Available from https://doi.org/10.1093/bib/bbaa232.

Jalkanen, J., Hollmén, M., & Jalkanen, S. (2020). Interferon beta-1a for COVID-19: Critical importance of the administration route. *Critical Care*, *24*(1). Available from https://doi.org/10.1186/s13054-020-03048-5.

Jeon, S., Ko, M., Lee, J., Choi, I., Byun, S. Y., Park, S., Shum, D., & Kim, S. (2020). Identification of antiviral drug candidates against SARS-CoV-2 from FDA-approved drugs. *Antimicrobial Agents and Chemotherapy*. Available from https://doi.org/10.1128/aac.00819-20.

Jiao, X., Wang, M., Zhang, Z., Li, Z., Ni, D., Ashton, A. W., Tang, H.-Y., Speicher, D. W., & Pestell, R. G. (2021). Leronlimab, a humanized monoclonal antibody to CCR5, blocks breast cancer cellular metastasis and enhances cell death induced by DNA damaging chemotherapy. *Breast Cancer Research: BCR*, *23*(1), 11. Available from https://doi.org/10.1186/s13058-021-01391-1.

Jin, Z., Du, X., Xu, Y., Deng, Y., Liu, M., Zhao, Y., Zhang, B., Li, X., Zhang, L., Peng, C., Duan, Y., Yu, J., Wang, L., Yang, K., Liu, F., Jiang, R., Yang, X., You, T., Liu, X., & Yang, H. (2020). Structure of Mpro from SARS-CoV-2 and discovery of its inhibitors. *Nature*, *582*(7811), 289–293. Available from https://doi.org/10.1038/s41586-020-2223-y.

Jin, Z., Du, X., Xu, Y., Deng, Y., Liu, M., Zhao, Y., Zhang, B., Li, X., Zhang, L., Peng, C., Duan, Y., Yu, J., Wang, L., Yang, K., Liu, F., Jiang, R., Yang, X., You, T., Liu, X., Yang, X., Bai, F., Liu, H., Liu, X., Guddat, L. W., Xu, W., Xiao, G., Qin, C., Shi, Z., Jiang, H., Rao, Z., & Yang, H. (2020). Structure of Mpro from SARS-CoV-2 and discovery of its inhibitors. *Nature*, *582*(7811), 289–293. Available from https://doi.org/10.1038/s41586-020-2223-y, Epub 2020 Apr 9.

Jones, B. E., Brown-Augsburger, P. L., Corbett, K. S., Westendorf, K., Davies, J., Cujec, T. P., Wiethoff, C. M., Blackbourne, J. L., Heinz, B. A., Foster, D., Higgs, R. E., Balasubramaniam, D., Wang, L., Bidshahri, R., Kraft, L., Hwang, Y., Žentelis, S., Jepson, K. R., Goya, R., & Falconer, E. (2020). LY-CoV555, a rapidly isolated potent neutralizing antibody, provides protection in a non-human primate model of SARS-CoV-2 infection. *BioRxiv*. Available from https://doi.org/10.1101/2020.09.30.318972.

Julander, J. G., Demarest, J. F., Taylor, R., Gowen, B. B., Walling, D. M., Mathis, A., & Babu, Y. S. (2021). An update on the progress of galidesivir (BCX4430), a broad-spectrum antiviral. *Antiviral research*, *195*, 105180. Available from https://doi.org/10.1016/j.antiviral.2021.105180.

Karade, D., & Karade, V. (2020). *AIDrugApp: Artificial Intelligence-based Web-App for Virtual Screening of Inhibitors against SARS-COV-2*. *ChemRxiv*. Cambridge: Cambridge Open Engage. Available from https://doi.org/10.26434/chemrxiv.13312661.v1.

Kim, S., Chen, J., Cheng, T., Gindulyte, A., He, J., He, S., Li, Q., Shoemaker, B. A., Thiessen, P. A., Yu, B., Zaslavsky, L., Zhang, J., & Bolton, E. E. (2019). PubChem 2019 update: Improved access to chemical data. *Nucleic Acids Research*, *47*(1), D1102–D1109. Available from https://doi.org/10.1093/nar/gky1033.

Kim, Y., Jedrzejczak, R., Maltseva, N. I., Wilamowski, M., Endres, M., Godzik, A., Michalska, K., & Joachimiak, A. (2020). Crystal structure of Nsp15 endoribonuclease NendoU from SARS-CoV-2. *Protein Sci*, *29*(7), 1596–1605. Available from https://doi.org/10.1002/pro.3873.

Kiss, J., Yegutkin, G. G., Koskinen, K., Savunen, T., Jalkanen, S., & Salmi, M. (2007). IFN-β protects from vascular leakage via up-regulation of CD73. *European Journal of Immunology*, *37*(12), 3334–3338. Available from https://doi.org/10.1002/eji.200737793.

Kneller, D. W., Phillips, G., O'Neill, H. M., Jedrzejczak, R., Stols, L., Langan, P., Joachimiak, A., Coates, L., & Kovalevsky, A. (2020). Structural plasticity of SARS-CoV-2 3CL Mpro active site cavity revealed by room temperature X-ray crystallography. *Nat Commun.*, *11*(1), 3202. Available from https://doi.org/10.1038/s41467-020-16954-7, PMID: 32581217; PMCID: PMC7314768.

Koes, D. R., & Camacho, C. J. (2012). ZINCPharmer: pharmacophore search of the ZINC database. *Nucleic Acids Research*, *40*(Web Server issue), W409–W414. Available from https://doi.org/10.1093/nar/gks378.

Lai, C. C., Shih, T. P., Ko, W. C., Tang, H. J., & Hsueh, P. R. (2020). Severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): The epidemic and the challenges. *International Journal of Antimicrobial Agents*, *55*(3). Available from https://doi.org/10.1016/j.ijantimicag.2020.105924.

Laver, T., Nozell, S. E., & Benveniste, E. N. (2008). IFN-β-mediated inhibition of IL-8 expression requires the ISGF3 components Stat1, Stat2, and IRF-9. *Journal of Interferon and Cytokine Research*, *28*(1), 13–23. Available from https://doi.org/10.1089/jir.2007.0062.

Letunic, I., & Bork, P. (2018). 20 years of the SMART protein domain annotation resource. *Nucleic Acids Research*, *46*(1), D493–D496. Available from https://doi.org/10.1093/nar/gkx922.

Lian, N., Xie, H., Lin, S., Huang, J., Zhao, J., & Lin, Q. (2020). Umifenovir treatment is not associated with improved outcomes in patients with coronavirus disease 2019: A retrospective study. *Clinical Microbiology and Infection*, *26*(7), 917–921. Available from https://doi.org/10.1016/j.cmi.2020.04.026.

Lim, M. A., & Pranata, R. (2020). Worrying situation regarding the use of dexamethasone for COVID-19. *Therapeutic Advances in Respiratory Disease*, 14. Available from https://doi.org/10.1177/1753466620942131.

Lin, X., Li, X., & Lin, X. (2020). A review on applications of computational methods in drug screening and design. *Molecules (Basel, Switzerland)*, *25*(6). Available from https://doi.org/10.3390/molecules25061375.

Lu, H. (2020). Drug treatment options for the 2019-new coronavirus (2019-nCoV) *Biosci Trends*. *14*, 69–71.

Lyu, J., Wang, S., Balius, T. E., Singh, I., Levit, A., Moroz, Y. S., O'Meara, M. J., Che, T., Algaa, E., Tolmachova, K., Tolmachev, A. A., Shoichet, B. K., Roth, B. L., & Irwin, J. J. (2019). Ultra-large library docking for discovering new chemotypes. *Nature*, *566*(7743), 224–229. Available from https://doi.org/10.1038/s41586-019-0917-9.

Mahdian, S., Zarrabi, M., Moini, A., Shahhoseini, M., & Movahedi, M. (2022). In silico evidence for prednisone and progesterone efficacy in recurrent implantation failure treatment. *J Mol Model*, *28*(4), 105.

Martin, R., Löchel, H. F., Welzel, M., Hattab, G., Hauschild, A.-C., & Heider, D. (2020). CORDITE: The curated CORona Drug InTERactions database for SARS-CoV-2. *IScience*, *23*(7), 101297. Available from https://doi.org/10.1016/j.isci.2020.101297.

Martin, T. C. S., & Vinetz, J. M. (2018). Asymptomatic *Plasmodium vivax* parasitaemia in the low-transmission setting: The role for a population-based transmission-blocking vaccine for malaria elimination. *Malaria Journal*, *17*(1), 89. Available from https://doi.org/10.1186/s12936-018-2243-3.

Mavian, C., Pond, S. K., Marini, S., Magalis, B. R., Vandamme, A. M., Dellicour, S., Scarpino, S. V., Houldcroft, C., Villabona-Arenas, J., Paisie, T. K., Trovão, N. S., Boucher, C., Zhang, Y., Scheuermann, R. H., Gascuel, O., Lam, T. T. Y., Suchard, M. A., Abecasis, A., Wilkinson, E., & Salemi, M. (2020). Sampling bias and incorrect rooting make phylogenetic network tracing of SARS-COV-2 infections unreliable. *Proceedings of the National Academy of Sciences of the United States of America*, *117*(23), 12522–12523. Available from https://doi.org/10.1073/pnas.2007295117.

Michalska, K., Kim, Y., Jedrzejczak, R., Maltseva, N. I., Stols, L., Endres, M., & Joachimiak, A. (2020). Crystal structures of SARS-CoV-2 ADP-ribose phosphatase: from the apo form to ligand complexes. *IUCrJ.*, *7*(Pt 5), 814–824. Available from https://doi.org/10.1107/S2052252520009653, PMID: 32939273; PMCID: PMC7467174.

Moore, N., Carleton, B., Blin, P., Bosco-Levy, P., & Droz, C. (2020). Does Ibuprofen worsen COVID-19? *Drug Safety*, *43*(7), 611–614. Available from https://doi.org/10.1007/s40264-020-00953-0.

Moschini, L., Loffi, M., Regazzoni, V., et al. (2021). Effects on QT interval of hydroxychloroquine associated with ritonavir/darunavir or azithromycin in patients with SARS-CoV-2 infection. *Heart Vessels*, *36*, 115–120. Available from https://doi.org/10.1007/s00380-020-01671-4.

Murugan, N.A., Kumar, S., Jeyakanthan, J. et al. (2020). Searching for target specific and multi targeting organics for Covid-19 in the Drugbank database with a double scoring approach (Vol. 10). https://doi.org/10.1038/s41598-020-75762.

Naksuk, N., Lazar, S., & Peeraphatdit, T. (B.) (2020). Cardiac safety of off-label COVID-19 drug therapy: A review and proposed monitoring protocol. *European Heart Journal: Acute Cardiovascular Care*, *9*(3), 215–221. Available from https://doi.org/10.1177/2048872620922784.

Osborne, V., Davies, M., Lane, S., Evans, A., Denyer, J., Dhanda, S., Roy, D., & Shakir, S. (2020). Lopinavir-Ritonavir in the treatment of COVID-19: A dynamic systematic benefit-risk assessment. *Drug Safety*, *43*(8), 809–821. Available from https://doi.org/10.1007/s40264-020-00966-9.

Osiluk 2020 https://www.rcsb.org/structure/6w9c

Ou, X., Liu, Y., Lei, X., Li, P., Mi, D., Ren, L., Guo, L., Guo, R., Chen, T., Hu, J., Xiang, Z., Mu, Z., Chen, X., Chen, J., Hu, K., Jin, Q., Wang, J., & Qian, Z. (2020). Characterization of spike glycoprotein of SARS-CoV-2 on virus entry and its immune cross-reactivity with SARS-CoV. *Nature Communications*, *11*(1). Available from https://doi.org/10.1038/s41467-020-15562-9.

Pang, J., Xu, F., Aondio, G., Li, Y., Fumagalli, A., Lu, M., Valmadre, G., Wei, J., Bian, Y., Canesi, M., Damiani, G., Zhang, Y., Yu, D., Chen, J., Ji, X., Sui, W., Wang, B., Wu, S., Kovacs, A., & Cao, Y. (2021). Efficacy and tolerability of bevacizumab in patients with severe Covid-19. *Nature Communications*, *12*(1). Available from https://doi.org/10.1038/s41467-021-21085-8.

Raybould, M. I. J., Kovaltsuk, A., Marks, C., Deane, C. M., & Wren, J. (2021). CoV-AbDab: The coronavirus antibody database. *Bioinformatics (Oxford, England)*, *37*(5), 734–735. Available from https://doi.org/10.1093/bioinformatics/btaa739.

Roques, P., Thiberville, S. D., Dupuis-Maguiraga, L., Lum, F. M., Labadie, K., Martinon, F., Gras, G., Lebon, P., Ng, L. F. P., de Lamballerie, X., & Le Grand, R. (2018). Paradoxical effect of chloroquine treatment in enhancing chikungunya virus infection. *Viruses*, *10*(5). Available from https://doi.org/10.3390/v10050268.

Rosas-Lemus, M., Minasov, G., Shuvalova, L., Inniss, N. L., Kiryukhina, O., Brunzelle, J., & Satchell, K. J. F. (2020). High-resolution structures of the SARS-CoV-2 2′-O-methyltransferase reveal strategies for structure-based inhibitor design. *Sci Signal*, *13*(651), eabe1202. Available from https://doi.org/10.1126/scisignal.abe1202.

Russell, C. D., Millar, J. E., & Baillie, J. K. (2020). Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. *The Lancet*, *395*(10223), 473–475. Available from https://doi.org/10.1016/S0140-6736(20)30317-2.

Rut, W., Lv, Z., Zmudzinski, M., Patchett, S., Nayak, D., Snipas, S. J., El Oualid, F., Huang, T. T., Bekes, M., Drag, M., & Olsen, S. K. (2020). Activity profiling and crystal structures of inhibitor-bound SARS-CoV-2 papain-like protease: A framework for anti-COVID-19 drug design. *Sci Adv*, *6*(42), eabd4596. Available from https://doi.org/10.1126/sciadv.abd4596.

Sadegh, S., Matschinske, J., Blumenthal, D. B., Galindez, G., Kacprowski, T., List, M., Nasirigerdeh, R., Oubounyt, M., Pichlmair, A., Rose, T. D., Salgado-Albarrán, M., Späth, J., Stukalov, A., Wenke, N. K., Yuan, K., Pauling, J. K., & Baumbach, J. (2020). Exploring the SARS-CoV-2 virus-host-drug interactome for drug repurposing. *Nature Communications*. Available from https://doi.org/10.1038/s41467-020-17189-2.

Shah, S., Das, S., Jain, A., Misra, D. P., & Negi, V. S. (2020). A systematic review of the prophylactic role of chloroquine and hydroxychloroquine in coronavirus disease-19 (COVID-19). *International Journal of Rheumatic Diseases*, *23*(5), 613–619. Available from https://doi.org/10.1111/1756-185X.13842.

Sharun, K., Tiwari, R., Dhama, J., & Dhama, K. (2020). Dexamethasone to combat cytokine storm in COVID-19: Clinical trials and preliminary evidence. *International Journal of Surgery*, *82*, 179–181. Available from https://doi.org/10.1016/j.ijsu.2020.08.038.

Shenoy, V., Qi, Y., Katovich, M. J., & Raizada, M. K. (2011). ACE2, a promising therapeutic target for pulmonary hypertension. *Current Opinion in Pharmacology*, *11*(2), 150–155. Available from https://doi.org/10.1016/j.coph.2010.12.002.

Shi, Y., Zhang, X., Mu, K., Peng, C., Zhu, Z., Wang, X., Yang, Y., Xu, Z., & Zhu, W. (2020). D3Targets-2019-nCoV: A webserver for predicting drug targets and for multi-target and multi-site based virtual screening against COVID-19. *Acta Pharmaceutica Sinica. B*, *10*(7), 1239–1248. Available from https://doi.org/10.1016/j.apsb.2020.04.006.

Shu, Y., & McCauley, J. (2017). GISAID: Global initiative on sharing all influenza data – From vision to reality. *Eurosurveillance*, *22*(13). Available from https://doi.org/10.2807/1560-7917.ES.2017.22.13.30494.

Siegel, D., Hui, H. C., Doerffler, E., Clarke, M. O., Chun, K., Zhang, L., Neville, S., Carra, E., Lew, W., Ross, B., Wang, Q., Wolfe, L., Jordan, R., Soloveva, V., Knox, J., Perry, J., Perron, M., Stray, K. M., Barauskas, O., & Mackman, R. L. (2017). Discovery and synthesis of a phosphoramidate prodrug of a Pyrrolo[2,1-f][triazin-4-amino] adenine C-nucleoside (GS-5734) for the treatment of ebola and emerging viruses. *Journal of Medicinal Chemistry*, *60*(5), 1648–1661. Available from https://doi.org/10.1021/acs.jmedchem.6b01594.

Singer, J., Gifford, R., Cotton, M., & Robertson, D. (2020). CoV-GLUE: A web application for tracking SARS-CoV-2 genomic variation. *Preprints*. Available from https://doi.org/10.20944/preprints202006.0225.v1, 2020.

Soler, M. J., Barrios, C., Oliva, R., & Batlle, D. (2008). Pharmacologic modulation of ACE2 expression. *Current Hypertension Reports*, *10*(5), 410–414. Available from https://doi.org/10.1007/s11906-008-0076-0.

Soremekun, O. S., Omolabi, K. F., Adewumi, A. T., & Soliman, M. E. S. (2021). Exploring the effect of ritonavir and TMC-310911 on SARS-CoV-2 and SARS-CoV main proteases: Potential from a molecular perspective. *Future Science OA*, *7*(1). Available from https://doi.org/10.2144/fsoa-2020-0079.

Tchesnokov, E. P., Feng, J. Y., Porter, D. P., & Götte, M. (2019). Mechanism of Inhibition of Ebola Virus RNA-Dependent RNA Polymerase by Remdesivir. *Viruses.*, *11*(4), 326. Available from https://doi.org/10.3390/v11040326.

Tempestilli, M., Caputi, P., Avataneo, V., Notari, S., Forini, O., Scorzolini, L., Marchioni, L., Bartoli, T. A., Castilletti, C., Lalle, E., Capobianchi, M. R., Nicastri, E., D'Avolio, A., Ippolito, G., & Agrati, C. (2020). Pharmacokinetics of remdesivir and GS-441524 in two critically ill patients who recovered from COVID-19. *Journal of Antimicrobial Chemotherapy*, *75*(10), 2977–2980. Available from https://doi.org/10.1093/jac/dkaa239.

Theoharides, T.C., & Conti, P. (2020). Dexamethasone for COVID-19? Not so fast. *Journal of Biological Regulators And Homeostattic Agents*, 34(3). https://doi.org/10.23812/20-EDITORIAL_1-5.

Tran, D. H., Sugamata, R., Hirose, T., Suzuki, S., Noguchi, Y., Sugawara, A., Ito, F., Yamamoto, T., Kawachi, S., Akagawa, K. S., Ōmura, S., Sunazuka, T., Ito, N., Mimaki, M., & Suzuki, K. (2019). Azithromycin, a 15-membered macrolide antibiotic, inhibits influenza A(H1N1)pdm09 virus infection by interfering with virus internalization process. *Journal of Antibiotics*, *72*(10), 759–768. Available from https://doi.org/10.1038/s41429-019-0204-x.

Trott, O., & Olson, A. J. (2010). AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. *Journal of computational chemistry*, *31*(2), 455–461.

Ugurel, O. M., Ata, O., & Turgut-Balik, D. (2020). An updated analysis of variations in SARS-CoV-2 genome. *Turkish Journal of Biology*, *44*(1), 157–167. Available from https://doi.org/10.3906/biy-2005-111.

Usha, T., Sukhralia, S., Pareek, C., et al. (2022). *Prediction of drug target interaction—a helping hand in drug repurposing Editor Khan,* ISBN 978-0-323-91171-6 Publisher Elesvire.

Usha, T., Dhivya, S., Goyal, A., Kumar, C., & Middha, S. (2017). Recent updates on computer-aided drug discovery: Time for a paradigm shift. *Current Topics in Medicinal Chemistry*, *17*(30), 3296–3307. Available from https://doi.org/10.2174/1568026618666180101163651.

Usha, T., Middha, S. K., Kukanur, A. A., Shravani, R. V., Anupama, M. N., Harshitha, N., Rahamath, A., Kukanuri, S. S., & Goyal, A. K. (2020). Drug repurposing approaches: Existing leads for novel threats and drug targets. *Current Protein & Peptide Science*, *22*(3), 251–271. Available from https://doi.org/10.2174/1389203721666200921152853.

Verma, N., Qu, X., Trozzi, F., Elsaied, M., Karki, N., Tao, Y., Zoltowski, B., Larson, E. C., & Kraka, E. (2021). SSnet: A deep learning approach for protein-ligand interaction prediction. *International Journal of Molecular Sciences*, *22*(3), 1392. Available from https://doi.org/10.3390/ijms22031392.

Vita, R., Mahajan, S., Overton, J. A., Dhanda, S. K., Martini, S., Cantrell, J. R., Wheeler, D. K., Sette, A., & Peters, B. (2019). The immune epitope database (IEDB): 2018 update. *Nucleic Acids Research*, *47*(1), D339–D343. Available from https://doi.org/10.1093/nar/gky1006.

Wan, Y., Shang, J., Graham, R., Baric, R. S., & Li, F. (2020). Receptor recognition by the novel Coronavirus from Wuhan: An analysis based on decade-long structural studies of SARS coronavirus. *Journal of Virology*, *94*(7). Available from https://doi.org/10.1128/JVI.00127-20.

Wang, Q., Zhang, Y., Wu, L., Niu, S., Song, C., Zhang, Z., Lu, G., Qiao, C., Hu, Y., Yuen, K.-Y., Wang, Q., Zhou, H., Yan, J., & Qi, J. (2020). Structural and functional basis of SARS-CoV-2 entry by using human ACE2. *Cell*, *181*(4), 894–904. Available from https://doi.org/10.1016/j.cell.2020.03.045, e9.

Waterhouse, A., Bertoni, M., Bienert, S., Studer, G., Tauriello, G., Gumienny, R., Heer, F. T., de Beer, T. A. P., Rempfer, C., Bordoli, L., Lepore, R., & Schwede, T. (2018). SWISS-MODEL: Homology modelling of protein structures and complexes. *Nucleic Acids Research*, W296–W303. Available from https://doi.org/10.1093/nar/gky427.

Weinreich, D. M., Sivapalasingam, S., Norton, T., Ali, S., Gao, H., Bhore, R., Musser, B. J., Soo, Y., Rofail, D., Im, J., Perry, C., Pan, C., Hosain, R., Mahmood, A., Davis, J. D., Turner, K. C., Hooper, A. T., Hamilton, J. D., Baum, A., & Yancopoulos, G. D. (2021). REGN-COV2, a neutralizing antibody cocktail, in outpatients with Covid-19. *New England Journal of Medicine*, *384*(3), 238–251. Available from https://doi.org/10.1056/NEJMoa2035002.

Westover, J. B., Mathis, A., Taylor, R., Wandersee, L., Bailey, K. W., Sefing, E. J., Hickerson, B. T., Jung, K. H., Sheridan, W. P., & Gowen, B. B. (2018). Galidesivir limits Rift Valley fever virus infection and disease in Syrian golden hamsters. *Antiviral Res.*, *156*, 38–45. Available from https://doi.org/10.1016/j.antiviral.2018.05.013, Epub 2018 Jun 1.

Wilamowski, M., Hammel, M., Leite, W., Zhang, Q., Kim, Y., Weiss, K. L., Jedrzejczak, R., Rosenberg, D. J., Fan, Y., Wower, J., Bierma, J. C., Sarker, A. H., Tsutakawa, S. E., Pingali, S. V., O'Neill, H. M., Joachimiak, A., & Hura, G. L. (2021). Transient and stabilized complexes of Nsp7, Nsp8, and Nsp12 in SARS-CoV-2 replication. *Biophys J.*, *120*(15), 3152–3165. Available from https://doi.org/10.1016/j.bpj.2021.06.006.

Wishart, D. S., Feunang, Y. D., Guo, A. C., Lo, E. J., Marcu, A., Grant, J. R., Sajed, T., Johnson, D., Li, C., Sayeeda, Z., Assempour, N., Iynkkaran, I., Liu, Y., Maciejewski, A., Gale, N., Wilson, A., Chin, L., Cummings, R., Le, D., & Wilson, M. (2018). DrugBank 5.0: A major update to the DrugBank database for 2018. *Nucleic Acids Research*, D1074–D1082. Available from https://doi.org/10.1093/nar/gkx1037.

Xu, X., Chen, P., Wang, J., Feng, J., Zhou, H., Li, X., Zhong, W., & Hao, P. (2020). Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its spike protein for risk of human transmission. *Science China Life Sciences*, *63*(3), 457–460. Available from https://doi.org/10.1007/s11427-020-1637-5.

Yan, R., Zhang, Y., Li, Y., Xia, L., Guo, Y., & Zhou, Q. (2020). Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2. *Science.*, *367*(6485), 1444–1448. Available from https://doi.org/10.1126/science.abb2762, Epub 2020 Mar 4 PMID: 32132184; PMCID: PMC7164635.

Yang, J., & Zhang, Y. (2015). I-TASSER server: New development for protein structure and function predictions. *Nucleic Acids Research*, W174–W181. Available from https://doi.org/10.1093/nar/gkv342.

Yin, W., Mao, C., Luan, X., Shen, D. D., Shen, Q., Su, H., Wang, X., Zhou, F., Zhao, W., Gao, M., Chang, S., Xie, Y. C., Tian, G., Jiang, H. W., Tao, S. C., Shen, J., Jiang, Y., Jiang, H., Xu, Y., Zhang, S., Zhang, Y., & Xu, H. E. (2020). Structural basis for inhibition of the RNA-dependent RNA polymerase from SARS-CoV-2 by remdesivir. *Science.*, *368*(6498), 1499–1504. Available from https://doi.org/10.1126/science.abc1560.

Yuan, M., et al. (2020). A highly conserved cryptic epitope in the receptor-binding domains of SARS-CoV-2 and SARS-CoV. *Science*. Available from https://doi.org/10.1126/science.abb7269, Nelson C. (n.d.). Available from https://www.rcsb.org/structure/6w37.

Zeng, S., Meng, X., Huang, Q., Lei, N., Zeng, L., Jiang, X., & Guo, X. (2019). Spiramycin and azithromycin, safe for administration to children, exert antiviral activity against enterovirus A71 in vitro and in vivo. *International Journal of Antimicrobial Agents*, *53*(4), 362–369. Available from https://doi.org/10.1016/j.ijantimicag.2018.12.009.

Zhang, L., Lin, D., Sun, X., Curth, U., Drosten, C., Sauerhering, L., Becker, S., Rox, K., & Hilgenfeld, R. (2020). Crystal structure of SARS-CoV-2 main protease provides a basis for design of improved a-ketoamide inhibitors. *Science (New York, N.Y.)*, *368*(6489), 409–412. Available from https://doi.org/10.1126/science.abb3405.

Zhou, D., Dai, S. M., & Tong, Q. (2020). COVID-19: A recommendation to examine the effect of hydroxychloroquine in preventing infection and progression. *Journal of Antimicrobial Chemotherapy*, *75*(7), 1667–1670. Available from https://doi.org/10.1093/jac/dkaa114.

Zhou, N., Bao, J., & Ning, Y. (2021). H2V: A database of human genes and proteins that respond to SARS-CoV-2, SARS-CoV, and MERS-CoV infection. *BMC Bioinformatics*, *22*(1), 18. Available from https://doi.org/10.1186/s12859-020-03935-2.

Zhou, P., Yang, X. L., Wang, X. G., Hu, B., Zhang, L., Zhang, W., Si, H. R., Zhu, Y., Li, B., Huang, C. L., Chen, H. D., Chen, J., Luo, Y., Guo, H., Jiang, R. D., Liu, M. Q., Chen, Y., Shen, X. R., Wang, X., & Shi, Z. L. (2020). A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature*, *579*(7798), 270–273. Available from https://doi.org/10.1038/s41586-020-2012-7.