Computational approaches for drug repositioning and repurposing to combat SARS-CoV-2 infection

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12.1 Introduction: COVID-19: challenges and issues

The RNA virus severe acute syndrome-Coronavirus-2 (SARS-CoV-2) causes Coronavirus disease-2019 (COVID-19), an acute respiratory condition. The deadly infection has spread exponentially since its first outbreak in Wuhan, China, to more than 180 countries around the world. The World Health Organization (WHO) designated it a global health concern on January 30, 2020, and it was recognized as a pandemic on March 11, 2020. The COVID-19 pandemic's condition is constantly changing (Wang & Guan, 2021). Coronavirus disease was first discovered in domestic chickens as an acute respiratory infection in the 1930s. However, the human Coronavirus was discovered in the 1960s in the United States and the United Kingdom. Severe acute respiratory syndrome Coronavirus (SARS-CoV) and Middle East respiratory syndrome Coronavirus (MERS-CoV) are two types of Coronaviruses that have been identified. SARS and MERS have evolved into the novel Coronavirus (nCoV). These are almost identical to SARS-CoV-2 strains and are pathogenic to humans. Coronaviruses are responsible for serious and lethal respiratory tract infections in humans (Cooke & Shapiro, 2003; Sahoo et al., 2021).

Although many vaccines are now available, combating the COVID-19 pandemic remains extremely difficult due to the virus's evolving mutant strains, the challenges of producing and distributing vaccines, and other factors (Kim et al., 2021). Small molecule

drug study, especially drug repurposing, is another option for finding quick treatments (Wang & Guan, 2021). The process of finding new therapeutic applications for old/available/existing medicines is drug repurposing or repositioning. It's a novel way to find new potential pharmacological/therapeutic targets for existing drugs. Traditional drug development and discovery is a time-consuming, labor-intensive, costly, and highly risky endeavor. Drug repositioning is a novel strategy for drug discovery that has the potential to be used instead of conventional drug discovery programs because it reduces the high monetary cost, the length of time it takes to produce a drug, and the possibility of failure (Rudrapal et al., 2020). The conventional drug discovery programs have a failure rate of approximately 45% due to safety or toxicity concerns, as well as saving up to 5−7 years in an overall time of drug development process (Chong & Sullivan, 2007). To rationally identify/develop new uses for drug molecules, drug repositioning incorporates experimental or activity-based and in silico-guided or computational-based strategies. It is supposed to be a novel technique in which existing medicines that are safe in people are redirected to treat rare, complicated, and ignored diseases with a valid target molecule (Kwarteng et al., 2021; Rudrapal et al., 2020).

Drug repurposing will produce new treatments at a faster pace than the novel drug invention if the safety profiles of the repurposed medicines have been assessed for a different disease in the context of drug production and even faster when drugs are licensed for other diseases and safety surveillance data are available for post-marketing (Ashburn & Thor, 2004; Li et al., 2021; Pushpakom et al., 2018). Through relying on the pharmacodynamic, pharmacokinetic, and toxicity profiles of the medications being repurposed that are already known, one can significantly improve the speed of response to a disease with unmet clinical needs, particularly for an infectious disease where a medication that has been proved safe can be tested right away. In February 2020, at the start of the pandemic, more than ten repurposed drugs were in clinical trials for COVID-19. Remdesivir (clinical trial No. NCT04257656), which was designed primarily to cure Ebola and has shown to suppress replicates in a wide variety of viruses, including coronaviruses, is one of them. In contrast, chloroquine (clinical trial no. ChiCTR2000029975) was authorized earlier for autoimmune disease and malaria that acts as an inhibitor of human endosomal acidification fusion, and it can aid in the interruption of the lifecycle of virus (Harrison, 2020).

12.2 Conventional drug discovery versus drug repurposing

According to one report, pharmaceutical firms invested US$2.6 billion in the year 2015 to develop a new chemical compound licensed by the US Food and Drug Administration (US FDA) (Avorn, 2015). The vast number of compounds being examined in preclinical stages and the enormous number of randomized controlled trials that fail to achieve therapeutic outcomes or have toxicity-related issues are driving up drug production costs. Considering the increasing failure rates, high prices, and slow speed of novel drug development, maximizing the effectiveness of existing drugs, and reducing side effects in drug testing is a smart option. "The most fruitful basis for the discovery of a new drug is to start with an old drug," said Nobel Laureate and pharmacologist Sir James Black (Chong & Sullivan, 2007).

Drug repurposing, also known as drug reprofiling, re-tasking, or repositioning, is a technique for discovering new applications for licensed or investigational drugs. Repurposed medicines could deliver treatment to patients much more quickly and at a reduced price than developing new drugs since the efficacy of these medications has already been evaluated in clinical testing for other ailments (Zhou, Hou, Shen, Huang, et al., 2020). Various research and academic institutions have promoted the concept that reviewing repositories of existing drugs with different tests could discover new indications, thereby discovering that medicines engineered for one disease could be effective in another. The repurposing of remdesivir for the management of COVID-19 is the latest and most significant example (Beigel et al., 2020).

In contrast to conventional drug discovery methods, drug repositioning has many benefits. When compared to conventional drug development programs, there is a substantial decrease in the amount of time consumed on research and development programs. In the conventional method, it takes around 10−16 years to produce a new drug, while around 3 and 12 years is required for drug repurposing (Aggarwal et al., 2021; Cha et al., 2018). A repositioned drug goes straight to preclinical studies, minimizing overall time, cost, and risk. According to surveys, repurposed drugs take 3−12 years to receive FDA approval, and the cost is almost reduced to half the amount that is required for new drug approval (Rudrapal et al., 2020). Fig. 12.1 depicts
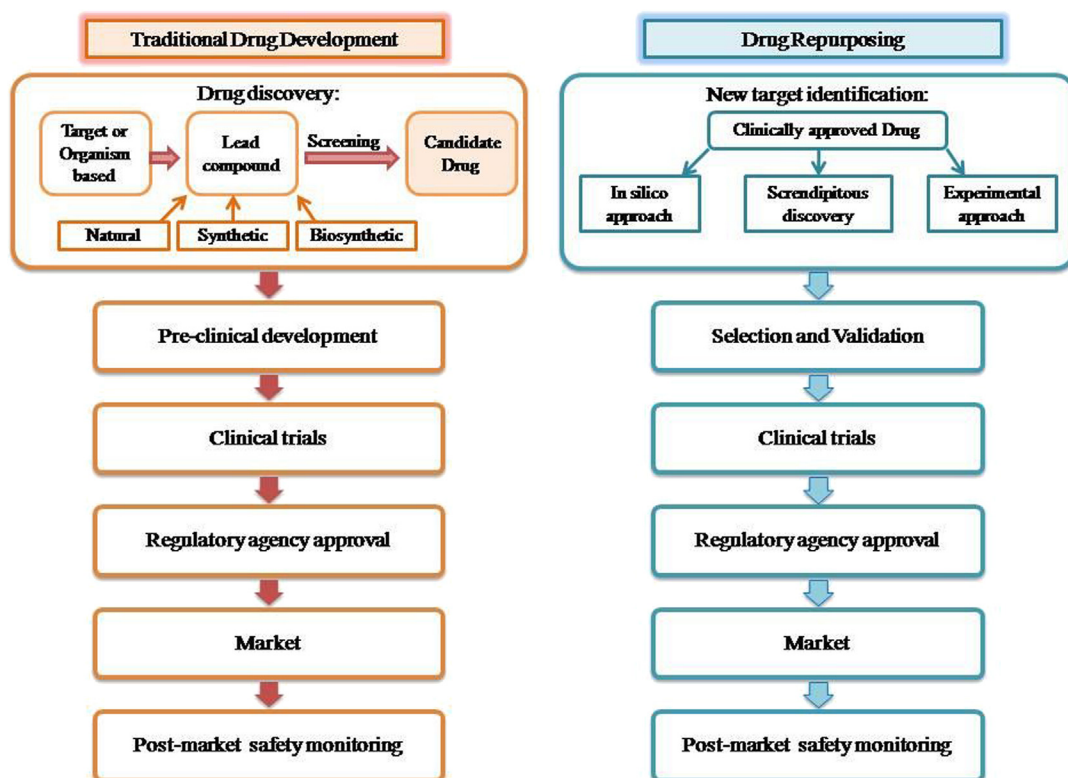

FIGURE 12.1 Traditional drug discovery versus drug repurposing.

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to Mitigate SARS-CoV-2 Infection

the workflow for conventional drug development and drug repurposing. Drug repositioning approaches primarily concentrate on the development of medicines for evolving infectious diseases that are hard to cure and overlooked diseases, while traditional drug discovery techniques mainly contribute to the development of medications to treat chronic health conditions (Li et al., 2016).

12.3 Strategies and approaches of drug repurposing

The drug-repurposing method is focused on using analytical methods such as homology modeling and molecular similarity to virtually screen drug libraries for appropriate drugs and their binding interactions with target proteins (Sliwoski et al., 2013). To assess the binding affinities and drug−receptor interactions, binding free energy calculations and molecular docking are used (Leelananda & Lindert, 2016). In silico approaches, as well as artificial intelligence (AI) technology, ligand-based drug design and structure-based drug design have recently been used to pace up the drug-repurposing phase (Ashburn & Thor, 2004).

12.4 Computational tools used for drug repurposing

Since this approach is usually more economical, drug repurposing is considered the most promising technique for discovering new clinical applications for already licensed or existing medicines (Peyvandipour et al., 2018). With the technological advancements including metabolomics, proteomics, genomics, transcriptomics, there are a plethora of prospects to discover drugs by combining all of the abovementioned approaches. Scientists now have the most up-to-date tools and data to investigate new unexplored modes of action/pathways based on target proteins/genes and/or unique biomarkers linked to disease development (Naylor et al., 2015; Naylor & Schonfeld, 2014). Numerous computational approaches for accelerating and simplifying the repurposing procedure have already been devised. Fig. 12.2 lists some of the most prominent databases utilized in drug repositioning analyses (Rudrapal et al., 2020). These databases deliver important insights into the three-dimensional structures of drugs and their binding sites.

12.5 Drug-repurposing strategies for COVID-19

The computational drug-repurposing strategies used on COVID-19 can be divided into three types (Dotolo et al., 2021), as presented in Fig. 12.3.

12.5.1 Network-based approaches

Network-based techniques are vital and commonly utilized in medication repurposing because of their ability to combine multiple data sources (Zhou, Wang, et al., 2020; Fan et al., 2020). Networks can be used to model molecular interactions in living organisms, primarily due to developments in bioinformatics techniques and high-throughput technologies
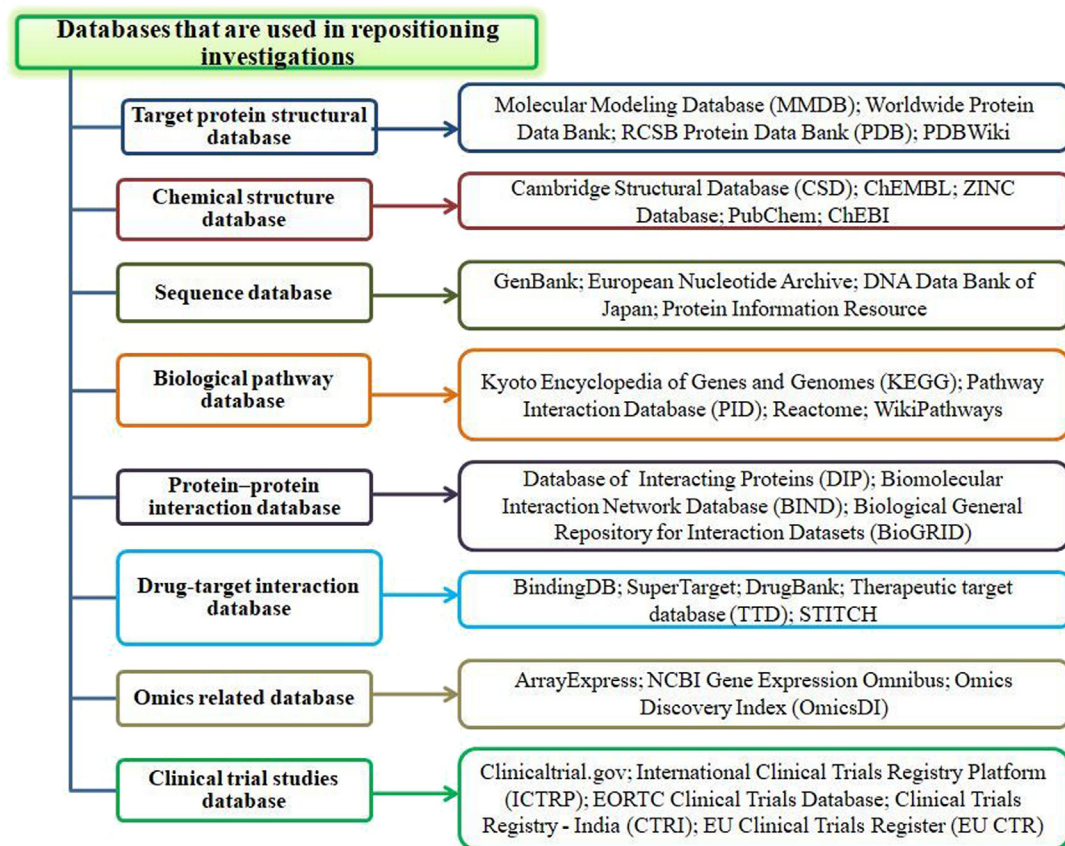
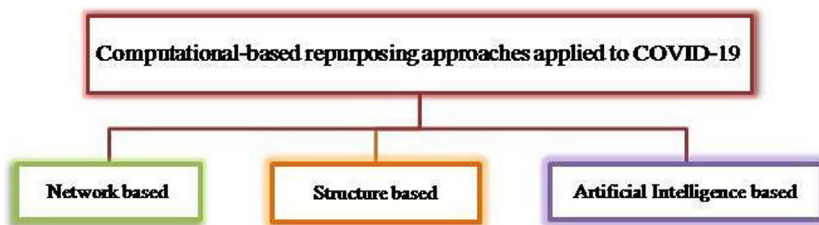**FIGURE 12.2**   Databases used in repositioning studies.

FIGURE 12.3   Drug-repurposing approaches applied to Coronavirus disease-2019.

(Fakhraei et al., 2014). Drugs, diseases, and target genes are represented by network nodes, whereas interactions or interconnections between nodes are represented by edges in these models (Chen et al., 2015; Re & Valentini, 2013). The pattern thus obtained may make a

structure-guided pharmaceutical and diagnostic research easier, with the possibility of discovering new molecular targets. Drug—drug networks, drug—target networks, protein interaction networks, and drug—disease networks have all been shown to be effective in identifying new options for drug development or repositioning (Li & Lu, 2013).

Network-based propagation and network-based clustering approaches are the two kinds of network-based methodologies investigated and applied to COVID-19 (Tu et al., 2020). To find novel drug—disease or drug—target interactions, network-based clustering methods have been reported (Barlow et al., 2020). These methods use clustering algorithms to locate numerous modules (drug—target, drug—drug, or drug—disease) based on the topology structure of networks. Another popular aspect of network-based technique is network-based propagation. A pan-human Coronavirus (HCoV) protein subnetwork was created by collecting and pooling HCoV-associated host proteins from the literature. Under the human protein interactome model, network proximity between HCoV-associated proteins and therapeutic targets was estimated for screening possible repositioning medicines for HCoVs. By utilizing a network-based technique, certain essential patterns beneficial for annotating the proteins that are functionally related with HCoVs and are situated inside the comprehensive human interactome network could be evaluated. Moreover, due to shared protein—protein interactions established by the human interactome, they can mimic the proteins that act as drug targets for a particular disease, and they might even become effective target options for emerging antiviral infections (Messina et al., 2020; Sadegh et al., 2020).

Wong et al. (2021) utilized the pre-existing ΔORF6 mutant of SARS-CoV as a surrogate for SARS-CoV-2, since both lack the moiety responsible for interferon antagonistic effects. They investigated at the gene expression profile of Calu-3, a human lung cell line infected with the SARS-CoV ΔORF6. Their transcriptomics-driven drug discovery strategy resulted in a candidate list of commercial medications (licensed for other applications) that might be employed in an empirical targeted application for SARS-CoV-2 infection (as shown in Fig. 12.4). They identified 55 genes and 238 ligands to repurpose already available drugs for COVID-19 therapy by studying periodic profiles of upregulated genes in ΔORF6-infected Calu-3 cells. Ritonavir, tofacitinib, dexamethasone, baricitinib, ciclesonide, formoterol, budesonide, and naproxen are among the eight drugs currently in clinical trials. A total of 16 pharmacological groups from the Anatomical Therapeutic Chemical Classification System that can reduce SARS-CoV-2 infection symptoms and hence be repurposed for SARS-CoV-2 treatment were also identified. As a result, the findings support the notion that studying transcriptome data from virus-infected cells can offer significant information for prospective therapies, which can then be used to identify possible medication for repurposing drugs. Owing to the lack of omics-level data from SARS-CoV-2-infected lung tissue, the surrogate transcriptomic-driven drug discovery framework has selected the range of suggested drug candidates for preclinical assessment, to be taken into consideration for scientific clinical application, and to allow access to newer therapeutic opportunities for the treatment of COVID-19.

Similarly, various other scientists have also contributed to the network-based drug repositioning for COVID-19 (Li et al., 2021; Zhou et al., 2020; Gysi et al., 2021; Meng et al., 2021; Fiscon et al., 2021).
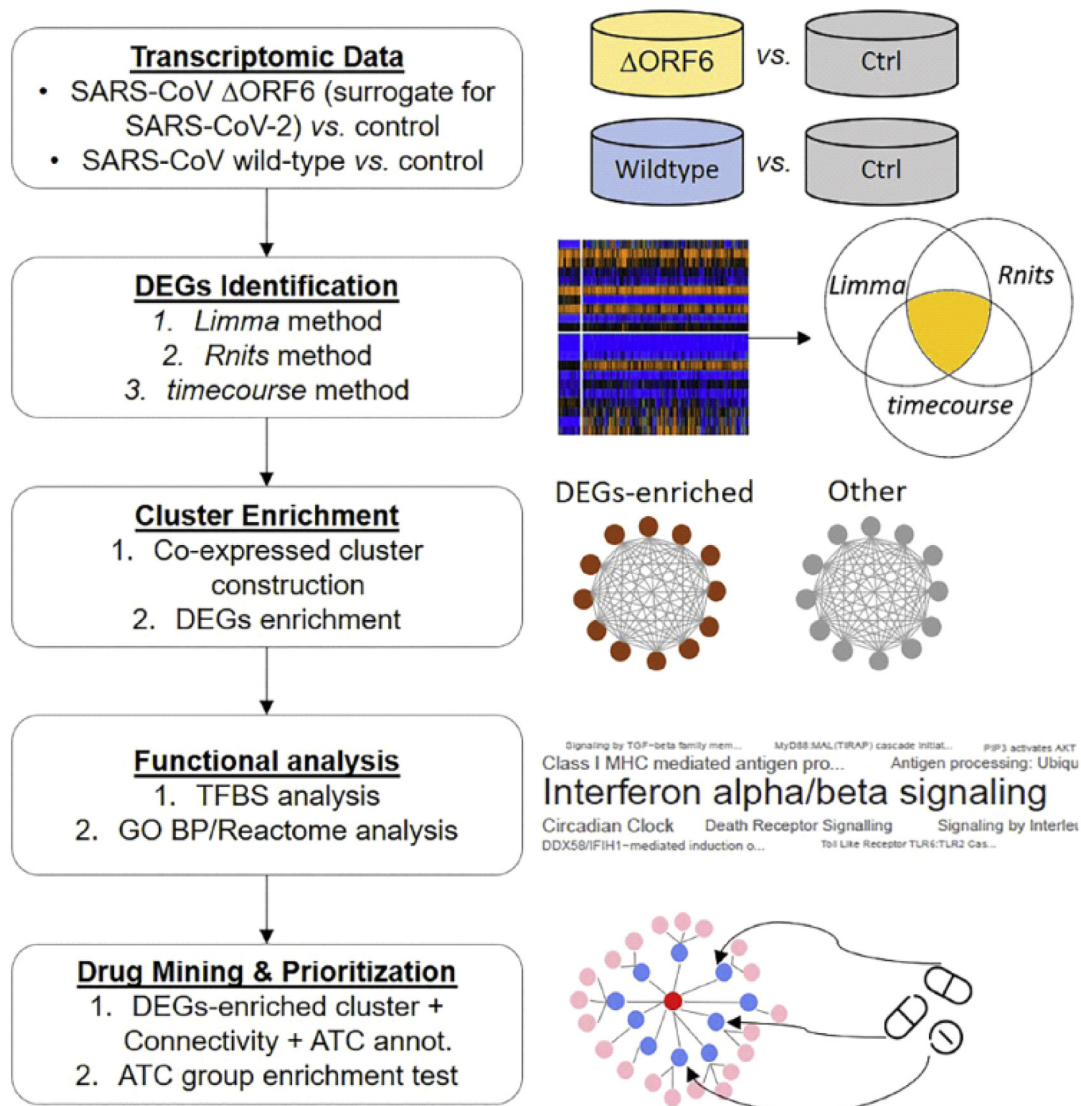
FIGURE 12.4   Flowchart of transcriptomic-driven network discovers pathophysiology of human coronavirus and contributes to drug repositioning for severe acute respiratory syndrome-Coronavirus-2 infection. *Source: Reproduced by permission of Wong, H.S.-C., Guo, C.-L., Lin, G.-H., Lee, K.-Y., Okada, Y., & Chang, W.-C. (2021). Transcriptome network analyses in human coronavirus infections suggest a rational use of immunomodulatory drugs for COVID-19 therapy. Genomics, 113(2), 564–575.* https://doi.org/10.1016/j.ygeno.2020.12.041.

12.5.2 Structure-based approaches

Smaller chemical substances that can bind macromolecular targets with established or expected three-dimensional structures can be identified through virtual screening. It

enables the screening of millions of components in a short amount of time, lowering the expenses of identifying hits for new drug development and also finding new targets for existing medications. This method is mostly based on molecular docking that was originally created to comprehend how a chemical compound interacts with a biological analog but is now widely utilized for a variety of activities, including drug repurposing (Kumar & Kumar, 2019; Pinzi & Rastelli, 2019).

The structures of many target viral proteins, including spike protein, papain-like protease, helicase protein, RNA-dependent RNA polymerase (RdRp), and 3-chymotrypsin-like (3CL) protease [also known as main protease (Mpro)], were predicted using homology modeling approaches (Cavasotto, 2011). These approaches were then utilized to conduct virtual screenings of active compounds, which included both approved clinic drugs and phytochemicals. After the isolation of the SARS-CoV-2 virus particles virus and sequencing of the genome, the structural biology community launched an extraordinary massive attempt to fix the structures of the most significant proteins that play a vital role in viral infection, its replication, and dispersal. Protein Data Bank (Berman et al., 2003) launched a page devoted to COVID-19-related data, and on February 5, 2020, the first structure, SARS-CoV-2 Mpro was reported in complex with an inhibitor found by computer-aided drug design, resolved at 2.16 Å resolution (Jin et al., 2020). Ever since, more than 500 structures of SARS-CoV-2 proteins have been described and made accessible to the research world, either alone or in combination with ligands and/or target proteins. The publication of these findings has sparked a flood of computational studies attempting to predict the ability of approved drugs to either inhibit the function of the virus or impair the virus's ability to recognize and associate with host cells, both of which are needed for its penetration and replication. To improve the reliability of the docking performance, the virtual screening of drug databases was carried out using various docking methods, often accompanied by additional computational techniques such as molecular dynamics simulations and the estimation of the free energy related to the interaction of the top hits with the specified target protein (Alonso et al., 2006). In certain cases, the findings were not experimentally validated. The molecular structures of chemical compounds in a docking-ready format were typically the starting point for screening in common databases with at least a section dedicated to approved drugs. Fig. 12.2 lists some examples of common, publicly accessible databases.

In a virtual screening investigation using FDA authorized drug dataset, Kandeel and Al-Nazawi (2020) studied the targeting of the first resolved COVID-19 crystal structure (main protease). A close phylogenetic relationship was observed between COVID-19 Mpro and SARS-CoV, which was found to be distinct from MERS-CoV. When COVID-19/SARS and COVID-19/MERS-CoV sequences were compared, the identity percent was 96.061% and 51.61%, respectively. The data for 20 drugs were compared to curcumin and presented as a relative value (a previously approved SARS Mpro inhibitor). The docking score for curcumin was 334, indicating the presence of a wide range of expected more strong binding agents. In the virtual screening investigation, the twenty drugs employed and their respective relative docking score (RDS) were Ribavirin (antiviral drug) (RDS 2.01), Bemegride (CNS stimulant) (RDS 1.83), Chromocarb (vasoprotective) (RDS 2.08), Aminophylline (bronchodilator) (RDS 1.92), Zonisamide (anticonvulsant) (RDS 1.76), Amiloride hydrochloride (diuretic) (RDS 1.76), (+,−)-Octopamine HCl (adrenergic agonist) (RDS 1.76), Telbivudine (anti-hepatitis B virus) (RDS 2.00), Triflusal (cardiovascular drug) (RDS 1.87), Tioxolone (antiacne agent) (RDS 1.78),

Pyrazinamide (antituberculosis agents) (RDS 1.80), Aminosalicylate sodium (antituberculosis agents) (RDS 1.80), Temozolomide (anticancer) (RDS 1.79), Methazolamide (employed to treat glaucoma) (RDS 1.78), Nicotinamide (vitamin) (RDS 1.91), Vitamin B12 (RDS 1.99), Propylthiouracil (antithyroid agent) (RDS 1.77), Cysteamine HCl (nephropathic cystinosis) (RDS 1.77) and Methoxamine hydrochloride (alpha-adrenergic agonist) (RDS 1.77). The predominant imperators for binding were hydrogen and hydrophobic binding interactions, as per a detailed scan of the binding mechanism of these drugs with SARS-CoV-2 Mpro (as shown in Fig. 12.5). Telbivudine binds to the SARS-CoV-2 Mpro via hydrogen bond interactions with the S49 and Q189 amino acid residues. Additionally, ribavirin interacts with SARS-CoV-2 Mpro by creating hydrogen bonds with backbone amino acid residue T25 and side-chain amino acid residue Q189. For COVID treatment, ribavirin, nicotinamide, vitamin B12, and telbivudine might be combined. This strategy repositions safe medications that are already on the market and licensed for use in COVID treatment.

In another research work, Singh et al. (2020) depicted a schematic workflow of structure-based virtual screening of drugs over the serine protease domain of TMPRSS2 (Fig. 12.6). Since TMPRSS2 lacks an experimental structure, comparative modeling was performed. The research for druggable pockets on the surface of the three-dimensional models clearly indicated that the catalytic site and one key, potentially crucial active exosite should be screened. Two drug collections were employed, and two docking engines were implemented on the two chosen TMPRSS2 three-dimensional models. By analyzing the structure and considering various binding scores obtained with three distinct scoring functions, consensus scoring results, and other rescoring strategies, a database of putative catalytic site inhibitors and compounds that could bind to the exosite of the TMPRSS2 serine protease domain and modulate the catalytic site and/or interfere with substrate binding or protein partner binding was compiled.

Some other researchers who investigated structure-based strategies for drug repositioning by targeting main protease (Mpro) are as follows: Al-Khafaji et al. (2021), Bharadwaj et al. (2020), Gimeno et al. (2020), Jiménez-Alberto et al. (2020), Liu et al. (2020), etc. Similarly, several researchers working in this field also explored the repurposing of drugs by targeting other viral proteins such as spike protein, RdRp, and TMPRSS2 (Choudhury et al., 2020; de Oliveira et al., 2020; Durdaği, 2020).

12.5.3 Artificial intelligence-based approaches

In the 1950s, AI pioneers predicted that computers would be able to hear, reason, and think like humans—a proof-of-concept known as general AI (Turing, 1950). Significant advances in AI have resulted from substantial growth in computational power and memory storage, as well as an enormous amount of data and the implementation of sophisticated technology. AI has been used in drug research and development by pharmaceutical firms (Fleming, 2018). Since drugs that target one disease could target another via a shared functional protein—protein interaction network, therefore analyzing the relationship between drug targets and human disorders can offer insights for potential drug repurposing (Cheng et al., 2018). For instance, the replication of SARS-CoV-2 needs cellular components of the host [which includes furin, transmembrane serine protease 2 (TMPRSS2), and angiotensin I converting enzyme 2 (ACE2)] (as illustrated in Fig. 12.7) (Zhou, Wang, et al., 2020). The
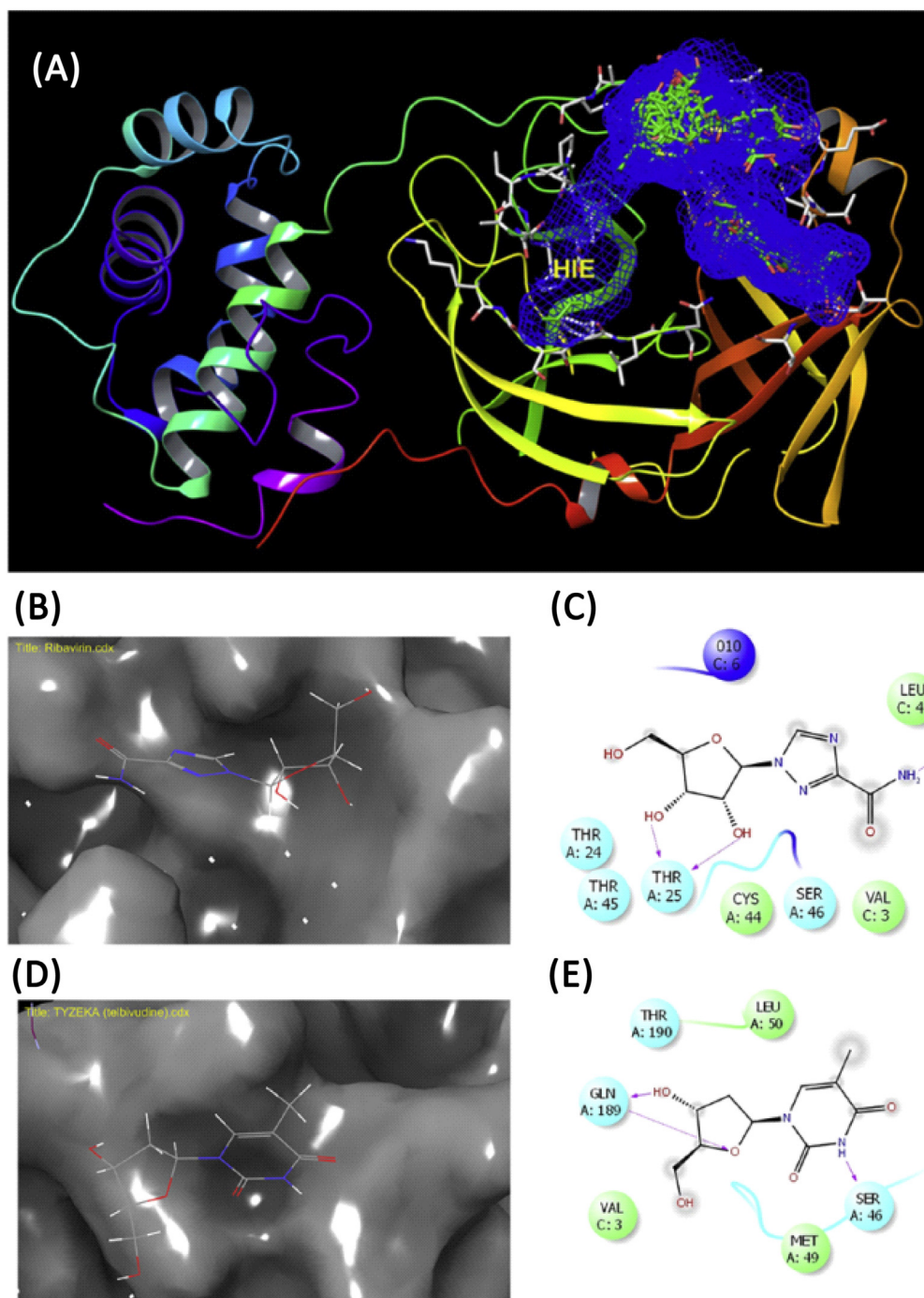
FIGURE 12.5 Virtual screening and docking of Food and Drug Administration drugs with COVID-19 Mpro. (A) The top 40 compounds docked into the Mpro binding site. (B) The docking site of ribavirin. (C) The ligand interactions of ribavirin with Mpro. (D) The site of docking of telbivudine. (E) The ligand interactions of telbivudine with Mpro. Hydrogen bonds are shown in purple arrows, hydrophobic interactions in gray circles.
Source: *Reproduced by permission of Kandeel, M., & Al-Nazawi, M. (2020). Virtual screening and repurposing of FDA approved drugs against COVID-19 main protease.* Life Sciences, 251, 117627. *https://doi.org/10.1016/j.lfs.2020.117627.*
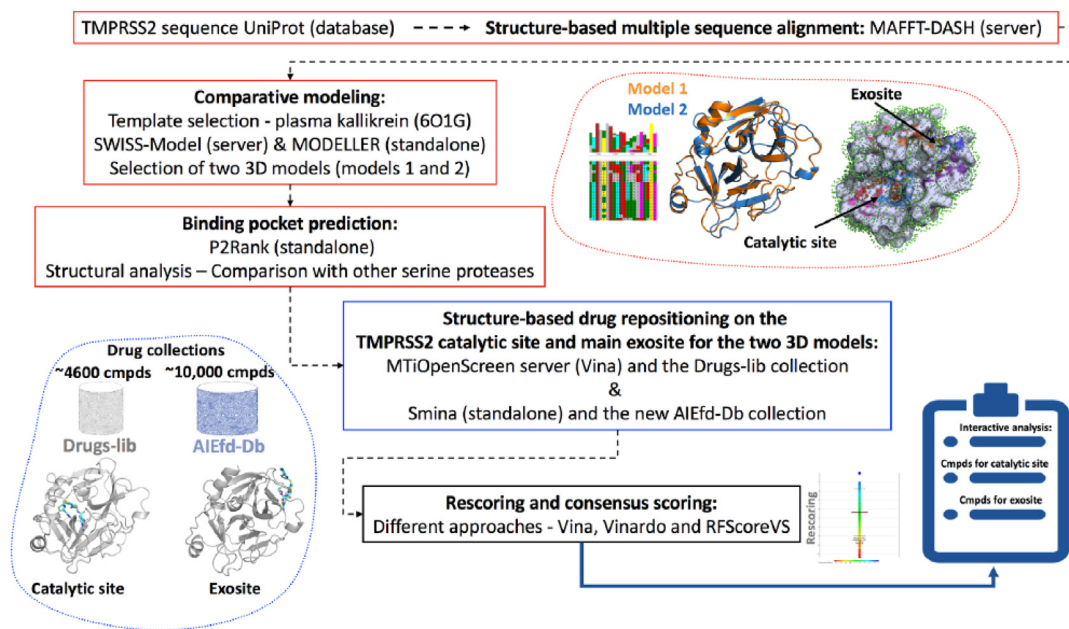
FIGURE 12.6 Structure-based virtual screening workflow investigated by Singh et al. (2020). Source: *Reproduced by permission of Singh, N., Decroly, E., Khatib, A. M., & Villoutreix, B. O. (2020). Structure-based drug repositioning over the human TMPRSS2 protease domain: Search for chemical probes able to repress SARS-CoV-2 Spike protein cleavages.* European Journal of Pharmaceutical Sciences, 153. *https://doi.org/10.1016/j.ejps.2020.105495.*

SARS-CoV-2 interactome presents a potential paradigm for efficient drug repurposing for COVID-19. Using affinity purification mass spectrometry, a SARS-CoV-2 virus—host interactome was constructed, containing 332 high-confidence protein—protein interactions between 26 viral proteins and human proteins. In the SARS-CoV-2—host interactome, 69 therapeutic compounds were prioritized for targeting host proteins (Gordon et al., 2020). Two types of drugs were tested for antiviral activity: sigma-1 and sigma-2 receptor regulators (i.e., haloperidol) and mRNA translation inhibitors (such as zotatifin).

Another research concluded 16 repurposed drug candidates for potential therapy of COVID-19 using a network-based methodology that assesses the interaction between the virus—host interactome and therapeutic targets in the human interactome network (Zhou, Hou, Shen, Huang, et al., 2020). This discovery necessitates a comprehensive approach that includes AI and network medicine, and it prompts the query of not just which protocols to investigate, but also which elements to examine, and how to combine the disciplines more widely. To anticipate drug—target interactions, a hybrid technique combining graph neural networks and RNNs was devised (Yingkai Gao et al., 2018). Beck et al. also created the Molecule Transformer-Drug—Target Interaction model, which is a hybrid CNN and RNN model that predicts whether any currently available antiviral medicines will function in SARS-CoV-2 (Beck et al., 2020). Several recognized antiviral medications, including dolutegravir, ritonavir, efavirenz, remdesivir, and atazanavir were computationally evaluated as promising treatments for SARS-CoV-2 infection. Morselli Gysi et al. (Gysi et al., 2021)
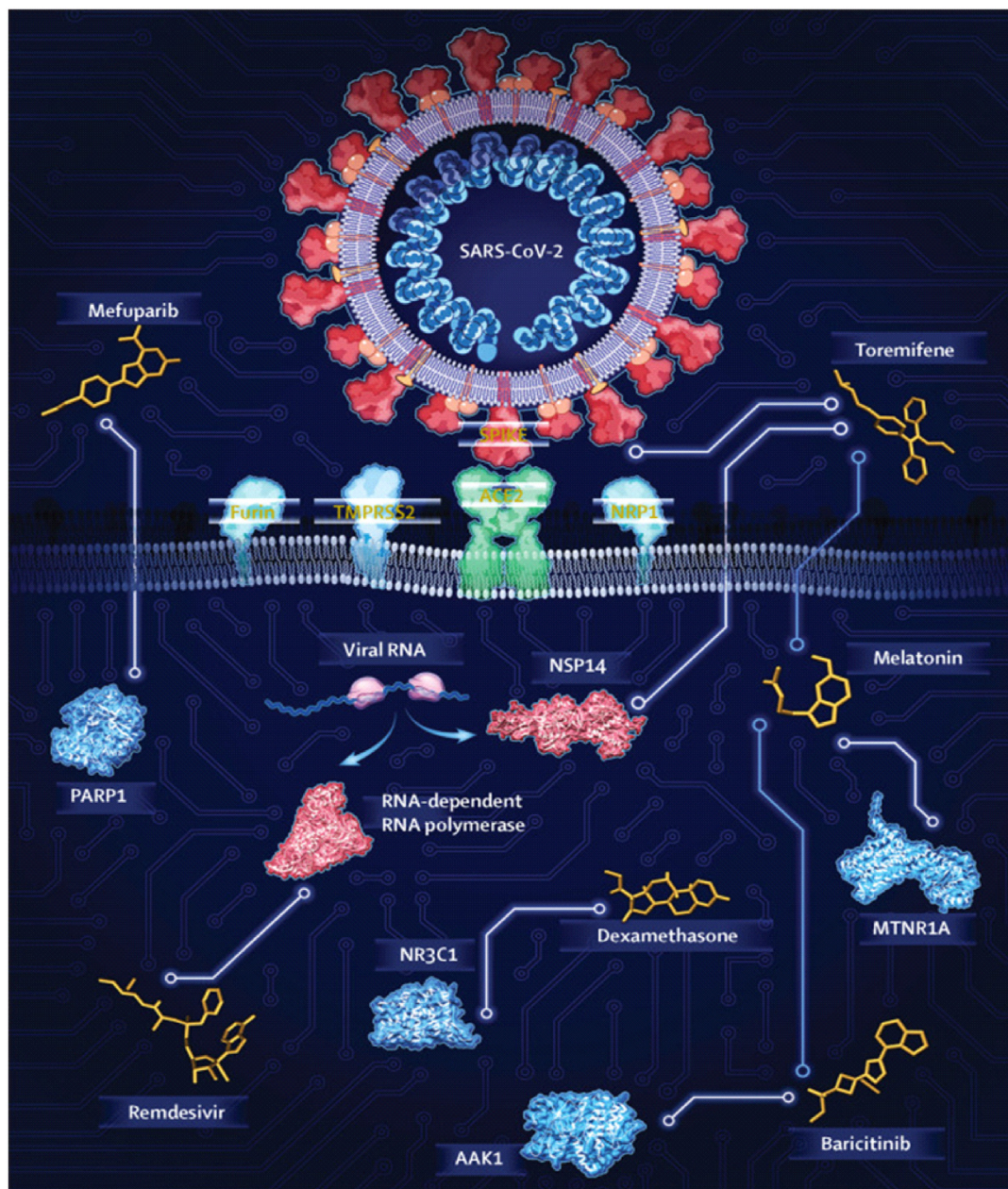
FIGURE 12.7 Overview of artificial intelligence-assisted drug repurposing for Coronavirus disease-2019. *AAK1*, AP2-associated protein kinase 1; *ACE2*, angiotensin I converting enzyme 2; *AI*, artificial intelligence; *MTNR1A*, melatonin receptor 1A; *NR3C1*, nuclear receptor subfamily 3 group C member 1; *NRP1*, neuropilin 1; *NSP14*, nonstructural protein 14; *PARP1*, poly-ADP-ribose polymerase 1; *TMPRSS2*, transmembrane serine protease 2. Source*: Reproduced by permission of Zhou et al. (2020).*

conducted a case study on SARS-CoV-2, which revealed 81 prospective repurposing drugs using an approach based on graph neural networks. BenevolentAI's knowledge graph is a vast repository of organized health records, including various links derived from the research literature via AI (Richardson et al., 2020). By inhibiting AP2-associated protein kinase 1 encoded by AAK1 (Fig. 12.7), BenevolentAI hypothesized that baricitinib, a drug recommended for the treatment of rheumatoid arthritis, might be a possible drug for COVID-19 therapy. A group used a vast scientific corpus of 24 million PubMed literature to create a detailed COVID-19 information graph (dubbed CoV-KGE), which comprised 15 million edges across 39 kinds of associations linking drugs, genes, proteins, pathways, diseases, and protein and gene expressions (Zeng et al., 2020).

12.6 Drugs proposed by computational methods that are under clinical trials

The computational analysis for prioritizing previous FDA-approved drugs for repurposing to manage COVID-19 has been put in a lot of effort. The PubChem repository and FDA drug database were used to select the potential drugs that are proposed by computational means and are under different phases of clinical trial. Table 12.1 summarizes the various agents, their classification, targets, and comments of the clinical trials for the management of COVID-19 (Pandey et al., 2008; Tarighi et al., 2021).

12.7 Future prospects and conclusion

Drug repurposing is a research area of developing drugs that have grown in significance in recent years as a result of the ability to reduce the length of clinical trials and discover a new clinical application of an old drug. The discovery of drug molecules with unknown therapeutic indications has resulted from more thorough and deliberate drug repositioning. Drug repositioning, in comparison to conventional drug discovery, provides significant savings, decreased chances of failure, relatively short research time, and extremely low financial risk, and thus is increasingly gaining market opportunity. The need for medications to combat the COVID-19 epidemic has pushed this type of research forward in recent months. Computational techniques have played an important role in the hunt for effective weapons against the SARS-CoV-2 virus among the drugs currently accessible. However, experimental procedures (including cell-based assays, animal study, clinical testing, and target protein-based screening) that provide clear scientific proof of linkages between drugs and disease conditions are more robust and convincing than computational approaches. With the technological advancement such as transcriptomics, proteomics, metabolomics, genomics, and the accessibility of massive databases resources such as drug omics data, disease omics data, and so on, there are a plethora of possibilities to explore drugs by combining all of the abovementioned strategies. In drug repurposing, however, possibilities are frequently accompanied by numerous obstacles. A fundamental problem in repurposing is identifying a new therapeutic application for an established medication. Drug repurposing is a complicated procedure covering a combination of aspects including expertise, marketing strategies, patents, and financing and commercial needs.

TABLE 12.1   Repurposed drugs for Coronavirus disease-2019 under clinical trials.

Agent	Classification	Target	Approved for	Comments for COVID-19	Clinical trials (based on Clinicaltrials.gov and ctri.nic.in)
Darunavir (Prezista)	Antiviral	Protease inhibitor: inhibiting Gag-Pol polyprotein cleavage	HIV	Positive effects in combination with other antivirals	(NCT04252274)
Favipiravir (Avigan)	Antiviral	RdRp inhibitor	Influenza	Symptoms reduction	(NCT04336904) (NCT04358549) (NCT04349241)
Remdesivir (Veklury)	Antiviral	RdRp inhibitor	Investigational drug	Authorized emergency use	(NCT04365725) (NCT04323761) (NCT04302766) (NCT04410354)
Ribavirin (Virazole)	Antiviral	Viral protein synthesis inhibitor	Hepatitis C, Respiratory Syncytial Virus.	Effective as an addon therapy	(NCT04392427) (NCT04356677)
Nafamostat mesylate	Antiviral	Serine protease inhibitor	Chronic pancreatitis, Anticoagulant in Japan	Improve patient's conditions effectively	(NCT04352400) (NCT04473053)
Bevacizumab	Monoclonal antibody	Anti-VEGF	Cancer	Second line treatment	(NCT01351415) (NCT01239732)
Anakinra	Interleukin antagonist	Recombinant IL-1 receptor antagonist	Rheumatoid arthritis	Effective compared to standard care	(NCT03265132) (NCT04443881) (NCT03002974)
Interferons (α, β, λ)	Biological response modifier	Hindering the viral replication, the viral load reduction	Cancers, Autoimmune diseases, Hepatitis B and C	Significant reduction in viral replication and titer in combination with other therapies.	(NCT04350671) (NCT04343976)
Losartan (Cozaar)	Angiotensin II receptor antagonists	Angiotensin II receptor blockade	Heart failure, hypertension	Attenuates lung injuries	(NCT04335123) (NCT04312009) (NCT04311177)
Corticosteroids	Adrenal Cortex hormones	Antiinflammation and antifibrotic agent	Natural corticosteroids, Inflammation, Autoimmune conditions, Allergy symptoms.	Can be used in specific clinical conditions.	(NCT04344288) (NCT04345445) (NCT04359511) (NCT04355247)
Ivermectin	Anthelmintic	IMP α/β1-mediated nuclear import inhibitor	Parasitic infections	Effective in in vitro examinations and safe	(NCT04381884) (NCT04360356) (NCT04405843)
Nitazoxanide	Antiviral and antiparasitic	Antiprotozoal agent	Treatment of various Helminthic, Protozoal	Antiviral potential against MERS-CoV and other coronaviruses in in vitro	(NCT04435314) (NCT04552483) (NCT04463264)

(*Continued*)

TABLE 12.1 (Continued)

Agent	Classification	Target	Approved for	Comments for COVID-19	Clinical trials (based on Clinicaltrials.gov and ctri.nic.in)
Thalidomide (Thalomid)	Immunomodulatory agent	TNF-α suppressor	Leprosy, Multiple myeloma	Patient's conditions improvement effectively	(NCT04273529) (NCT04273581)
Heparin (LMWH)	Anticoagulant	Antithrombin	Prophylaxis treatment for venous thrombosis, pulmonary embolism, and peripheral arterial embolism	Effective in combination with other therapies	(NCT00182403) (NCT00049777) (NCT03378466)
2-deoxy-D-glucose (2-DG)[a]	Anticancer, Antiviral	Targets glucose metabolism to deplete cancer cell energy; Inhibition of viral replication	Investigational drug	Effective in combination with other therapies	CTRI/2020/06/025664

[a]*http://ctri.nic.in/Clinicaltrials.*

Modified from Tarighi, P., Eftekhari, S., Chizari, M., Sabernavaei, M., Jafari, D., & Mirzabeigi, P. (2021). A review of potential suggested drugs for coronavirus disease (COVID-19) treatment. European Journal of Pharmacology, 895, 173890. https://doi.org/10.1016/j.ejphar.2021.173890.

Several of these research findings do not appear to be very compelling. Few trials on the same target concentrate on the same medications, and even fewer provide irrefutable evidence of an impact, with nearly none providing validation of experiments. Moreover, numerous studies anticipate the efficacy of medications that have not yet been shown beneficial in clinical studies. To evaluate the safety and efficacy of a drug for repositioning, direct contact between key parties are required to utilize and examine available data and create strategies for the development of newer clinical evidences. The primary objective of such collaborative work ought to be to ensure clarity of investigations and to design experiments so that the evaluated results can be analyzed. In addition, for the maintenance of significant outcomes of repurposed drugs, deeper insights and a combination of strategies between experimental and computational techniques are essential for better drug repurposing.

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Disclosure of interest

The authors declare no financial or other conflicts of interest.

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