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Computers in Biology and Medicine 136 (2021) 104677

Contents lists available at ScienceDirect

Computers in Biology and Medicine

journal homepage: www.elsevier.com/locate/compbiomed

Computational identification of repurposed drugs against viruses causing epidemics and pandemics via drug-target network analysis

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ARTICLE INFO

Keywords:
Virus
Pandemics
Epidemics
Drug repurposing
Antivirals
FDA approved

ABSTRACT

Viral epidemics and pandemics are considered public health emergencies. However, traditional and novel antiviral discovery approaches are unable to mitigate them in a timely manner. Notably, drug repurposing emerged as an alternative strategy to provide antiviral solutions in a timely and cost-effective manner. In the literature, many FDA-approved drugs have been repurposed to inhibit viruses, while a few among them have also entered clinical trials. Using experimental data, we identified repurposed drugs against 14 viruses responsible for causing epidemics and pandemics such as SARS-CoV-2, SARS, Middle East respiratory syndrome, influenza H1N1, Ebola, Zika, Nipah, chikungunya, and others. We developed a novel computational "*drug-target-drug*" approach that uses the drug-targets extracted for specific drugs, which are experimentally validated *in vitro* or *in vivo* for antiviral activity. Furthermore, these extracted drug-targets were used to fetch the novel FDA-approved drugs for each virus and prioritize them by calculating their confidence scores. Pathway analysis showed that the majority of the extracted targets are involved in cancer and signaling pathways. For SARS-CoV-2, our method identified 21 potential repurposed drugs, of which 7 (e.g., baricitinib, ramipril, chlorpromazine, enalaprilat, etc.) have already entered clinical trials. The prioritized drug candidates were further validated using a molecular docking approach. Therefore, we anticipate success during the experimental validation of our predicted FDA-approved repurposed drugs against 14 viruses. This study will assist the scientific community in hastening research aimed at the development of antiviral therapeutics.

1. Introduction

Viruses are responsible for causing various epidemics and pandemics worldwide [1,2]. Currently, the world is witnessing a major devastating pandemic of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes the disease known as COVID-19 [3]. With its high infectivity and mortality rates, it has infected over 180 million people and resulted in over 4 million deaths globally. The World Health Organization has reported 14 major epidemics and pandemics caused by viruses, such as SARS-CoV-2, Ebola, Zika, chikungunya, SARS, Middle East respiratory syndrome (MERS), and others (https://www.who.int/emergencies/diseases/en/). Despite the devastating consequences of viral infections, only a limited number of promising and approved drugs/vaccines are available [4,5]. Thus, the development of efficient antivirals would be highly beneficial to control viral diseases.

Drug discovery is a costly and time-consuming process. According to the U.S. Food and Drug Administration (FDA) guidelines, the development of new drugs generally consists of the following steps: preclinical testing, investigational new drug application, phases I to III, new drug application, and phase IV clinical trials [6]. The average time required for the development of new drugs (i.e., from target identification to marketing) is over 12 years [7], while the estimated total cost is over $1 billion (average of $2.6 billion) [8]. Furthermore, as per Eroom's law, the cost of developing a new drug doubles every 9 years [8,9]. In this regard, drug repurposing could represent a promising solution to tackle infectious agents such as viruses.

Drug repurposing identifies new uses for preexisting approved or investigational drugs for any disease [10,11]. The drug repurposing

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https://doi.org/10.1016/j.compbiomed.2021.104677
Received 20 July 2021; Accepted 20 July 2021
Available online 23 July 2021

strategy is advantageous and has a low risk of failure, shorter time frame, and reduced cost [12]. It reduces the cost to an average of $200–300 million [12]. In 1987, zidovudine was successfully repurposed as an anti-HIV drug (previously used as an anti-cancer drug) [13]. The ongoing SARS-CoV-2 pandemic further justifies the need to repurpose drugs as a rapid solution [14,15]. Many scientists worldwide are working on developing promising repurposed drug candidates against SARS-CoV-2 [16]. Drug repurposing also holds a promising solution against the emergence of various viral diseases caused by Zika, Ebola, influenza, Nipah, Japanese encephalitis, chikungunya, hepatitis, and many more viruses that pose serious global public health concerns [17–21]. Repurposed drugs may also bypass safety and toxicity testing and can directly be used under emergency pandemic situations [10,11].

Computational interventions can further reduce the cost of drug repurposing and can also allow researchers to monitor drug candidates and predict their effectiveness against various diseases within a short period [22] [–] [24]. A few computational approaches, such as molecular docking/simulation and quantitative structure-activity relationship methods, have already been utilized for the identification of repurposed drugs [25] [–] [31]. In the recent past, other strategies have also been adopted to identify repurposed drugs against SARS-CoV-2, such as transcriptomic signatures [32], the multi-omics approach [33], deep learning [34], protein interaction maps [35], network-controllability [36], protein-protein interaction [37], and assessing risk factors among patients [38].

In the present study, a data-driven approach has been used for the identification of repurposed drug candidates. In this method, we exploited drug candidates that were experimentally validated for their antiviral activities. The drug-targets of these molecules were used to predict new repurposed drugs with the same targets. The predicted repurposed drugs were further prioritized based on confidence scores. This novel "*drug-target-drug*" approach is used to predict promising repurposed drug candidates against 14 viruses responsible for causing epidemics and pandemics, including Lassa virus (LASV), Crimean-Congo hemorrhagic fever virus (CCHV), severe acute respiratory syndrome (SARS), MERS, novel coronavirus (SARS-CoV-2), Marburg virus (MARV), Ebola virus (EBOV), Zika virus (ZIKV), influenza virus (IAV/IBV), Hendra virus (HeV), Nipah virus (NiV), Rift Valley virus (RVFV), chikungunya virus (CHIKV), and variola virus (VARV).

2. Results

2.1. Identification of repurposed drugs using the "drug-target-drug" approach

We used the "*drug-target-drug*" approach to predict the efficiency of repurposed drugs (see **Methods** section). The best repurposed drug candidates identified using a Python-based pipeline show promising results against viruses known to cause epidemics and pandemics. The overall approach for the identification of repurposed drugs involves the manual curation of effective drugs followed by the extraction of their targets. Thereafter, these drug-targets are used to predict novel repurposed drugs based on their confidence scores. Confidence scores are calculated based on the ratio of the number of drug-targets mapped in

Table 1
Table depicting the topmost repurposed drugs of major pandemic/epidemic viruses along with information on their IC_{50} cutoffs, virus families, abbreviations, and repurposed drug categories.

Virus	Abbreviation	Family	Positive dataset (IC_{50}/EC_{50})	Negative dataset IC_{50}/EC_{50})	Repurposed Drugs category	Repurposed Drugs
Lassa virus	LASV	*Arenaviridae*	2.8 uM	50 uM	Antidepressant, Antiviral, Immunosuppressant	Isoprenaline, Loxapine, Mycophenolate mofetil, Ribavirin, Fostamatinib
Crimean-Congo hemorrhagic fever virus	CCHF	*Bunyaviridae*	4.3 uM	50 uM	Antidepressant, Antihyperprolactinemic	Loxapine, Cabergoline, Ziprasidone, Mianserin, Imipramine
Severe acute respiratory syndrome	SARS	*Coronaviridae*	5 uM	50 uM	Antidepressant, Antiviral, Immunosuppressant	Tramadol, Nicardipine, Fluphenazine, Felodipine, Artenimol
Middle East Respiratory Syndrome	MERS	*Coronaviridae*	1 uM	50 uM	Antineoplastic, Antiallergic	Clofarabine, Imexon, Trimethoprim, Pemetrexed, Fludarabine
Novel corona virus	SARS-CoV-2	*Coronaviridae*	1 uM	50 uM	Antineoplastic (lung, renal), Rheumatoid arthritis, Antidepressants, Immunosuppressant	Sorafenib, Baricitinib, Chlorpromazine, Mycophenolate mofetil, Baricitinib
Marburg virus	MARV	*Filoviridae*	5 uM	50 uM	Antidepressants, Rheumatoid arthritis, Antiallergic	Chlorhexidine, Citalopram, Adalimumab, Clemastine, Triprolidine
Ebola virus	EBOV	*Filoviridae*	0.7 uM	50 uM	Cardiovascular, Antihypertensive, Vasodilator, Anticancer (Renal)	Digoxin, Diazoxide, Bretylium, Almitrine, Lenvatinib
Zika virus	ZIKV	*Flaviviridae*	0.3 uM	50 uM	Anticancer, Immunosuppressants, Antiviral	Alvocidib, Mycophenolate mofetil, Ribavirin, Pemetrexed, Olmesartan
Influenza virus	IAV/IBV	*Orthomyxoviridae*	0.35 uM	50 uM	Antibiotic, Antiasthmatic, Anticancer, Antiepileptic, Immunomodulatory	Ceftriaxone, Carfilzomib, Nedocromil, Paclitaxel, Zonisamide
Hendra virus	HeV	*Paramyxoviridae*	9.75 uM	50 uM	Antidepressant, Antihypertension, Antitussive, Vasodilator, Antiasthmatic	Paroxetine, Pindolol, Methylephedrine, Mephentermine, Racepinephrine
Nipah virus	NiV	*Paramyxoviridae*	7.5 uM	50 uM	Antidepressant, Antihypertension, Antitussive, Vasodilator, Antiasthmatic	Paroxetine, Pindolol, Methylephedrine, Norepinephrine, Racepinephrine
Riftvalley virus	RVFV	*Phenuiviridae*	10 uM	50 uM	Anticancer, Anticoagulant	Regorafenib, Pimecrolimus, Erdafitinib, Cabozantinib, Heparin
Chikungunya virus	CHIKV	*Togaviridae*	1 uM	50 uM	Antidepressant, Anticancer, antiosteoporotic	Chlorpromazine, Imipramine, Alendronic acid, Olanzapine, Cabozantinib
Variola virus	VARV	*Poxviridae*	1 uM	50 uM	Anticancer, Anticonvulsant, Antibiotic, Antimycotic	Clotrimazole, Cyclophosphamide, Permethrin, Phenobarbital, Ritonavir

the repurposed drugs by the total number of targets mapped to experimentally validated drugs.

The predicted repurposed drugs against viruses fall under various categories such as antidepressants, immunosuppressants, and antiallergics. The details of 14 viruses including their families, cutoff thresholds, repurposed drug categories, and drugs are summarized in Table 1. For example, the identified repurposed drug candidates against SARS-CoV-2 belong to the antineoplastic (i.e., lung, renal), rheumatoid arthritis drug, antidepressant, immunosuppressant, and antihypertensive categories.

Furthermore, we explored repurposed drugs for all 14 viruses using the "*drug-target-drug*" approach (Fig. 1). SARS-CoV-2, SARS, and MERS viruses of the *Coronaviridae* family were checked. The analysis showed that SARS and MERS have two repurposed drugs in common (i.e., 3-phenyllactic acid and puromycin), while SARS-CoV-2 does not show any drugs in common with SARS and MERS. For SARS-CoV-2, the most promising predicted repurposed drug candidates are fostamatinib, chlorpromazine, mycophenolate mofetil, and etidronic acid (Fig. 2A). The identified repurposed drugs for SARS-CoV-2 were sorted according to "drug type" and represented as an alluvial plot (Fig. 3). Alluvial plots show the relationship among experimentally validated drugs, predicted repurposed drugs, and their respective drug categories. The best predicted repurposed drugs belong to the approved and investigational categories. Furthermore, we checked the predicted repurposed drugs in all three viruses of the *Coronaviridae* family and summarized them in the form of a heatmap with the scale of confidence score(s) (Fig. 2B). Notably, 3-phenyllactic acid and puromycin were common between SARS and MERS, with a high confidence score of 1.00. An analysis of the remaining 13 viruses is provided in Supplementary Figs. S1–S9.

Influenza virus belongs to the *Orthomyxoviridae* family, which was responsible for a severe pandemic in 2009. Our "*drug-target-drug*" approach identified repurposed drug candidates such as ceftriaxone, carfilzomib, nedocromil, paclitaxel, and fostamatinib, which had high confidence scores of 1.0. The repurposed drug candidates belong to the

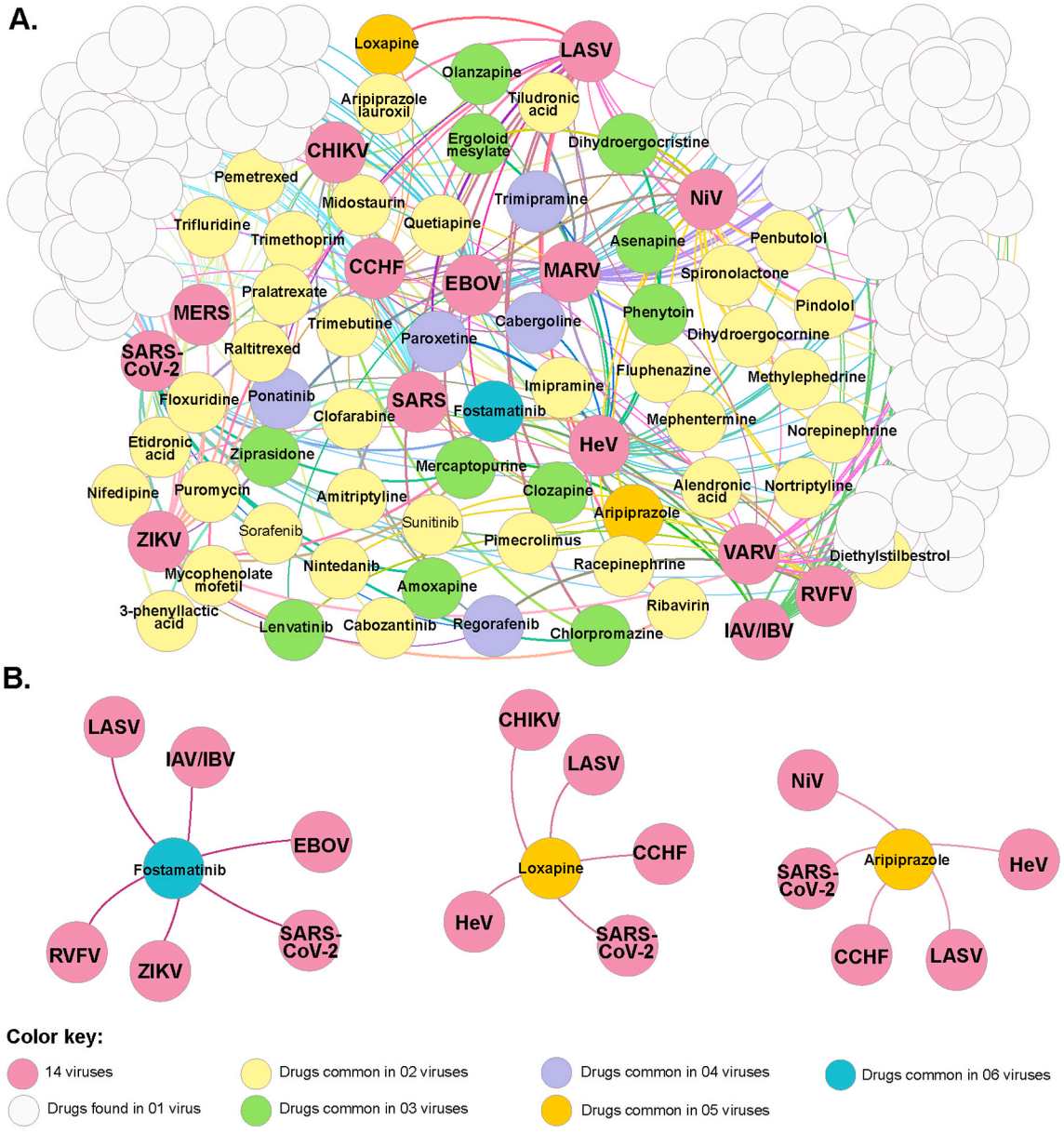

Fig. 1. The network displayed common repurposed drugs between different viruses using our pipeline. A) Correlations between the repurposed drugs identified using our "*drug-target-drug*" approach and 14 viruses causing epidemics/pandemics were visualized using complex networks. B) Interaction diagram of identified repurposed drugs found in common for more than five viruses.

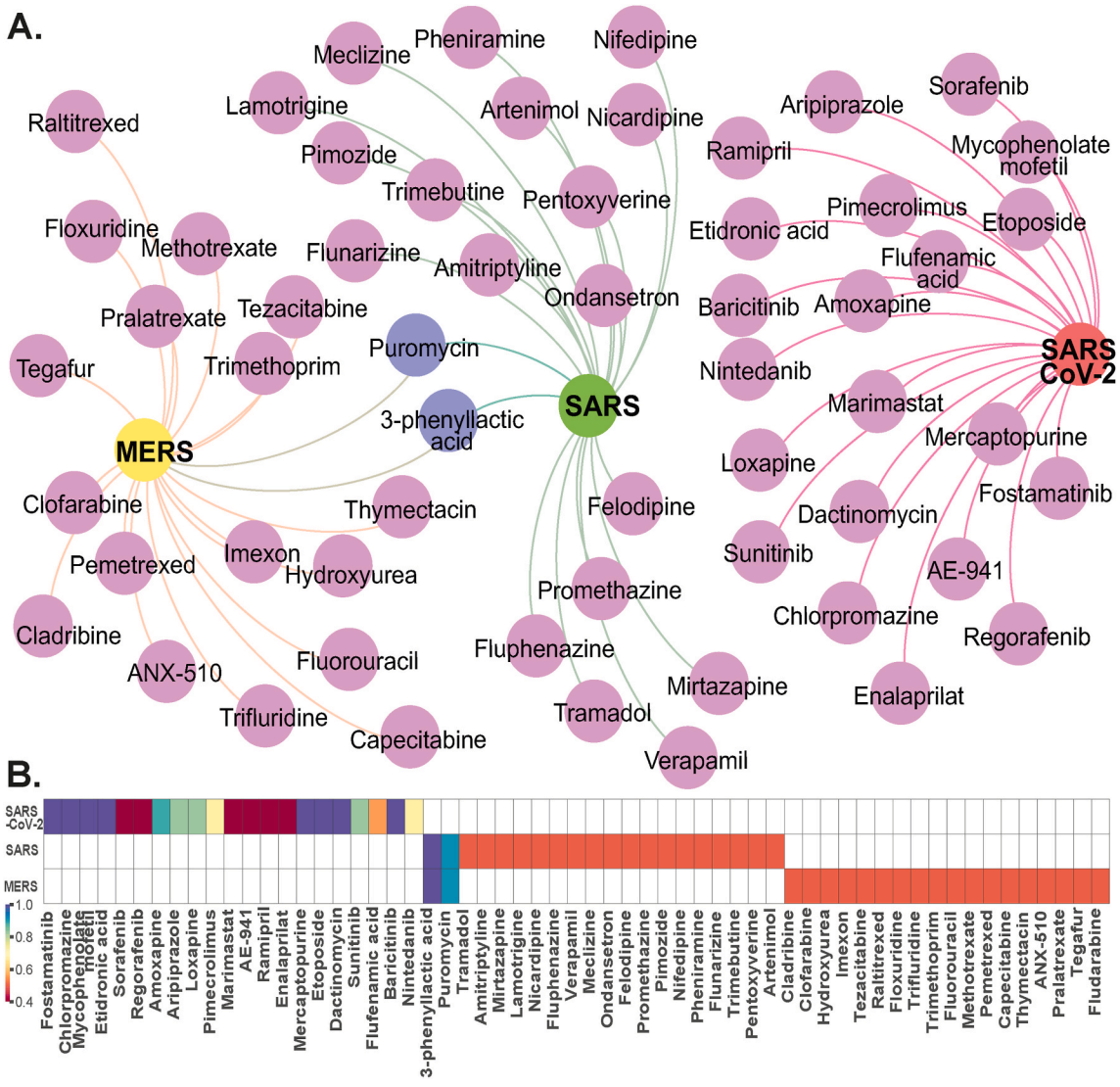

Fig. 2. Repurposed drug analysis for *Coronaviridae*. A) Network analysis of repurposed drugs, where nodes represent viruses belonging to the Coronaviridae family-like novel coronavirus-2019 (SARS-CoV-2), Severe acute respiratory syndrome (SARS) and Middle East Respiratory Syndrome (MERS) along with the repurposed drug candidates resulting from our "*drug-target-drug*" analysis. Edge line width represents the confidence score (thicker lines represent high confidence scores for repurposed drugs, while thinner lines represent comparatively lower confidence in repurposed drugs against a virus). B) Heatmap depicting the repurposed drug candidates resulting from our "*drug-target-drug*" analysis. The colors represent the confidence scores of individual repurposed drugs.

antibiotic, antiasthmatic, anti-cancer, antiepileptic, and immunomodulatory categories (Supplementary Fig. S4 and Supplementary Table S1).

The *Paramyxoviridae* family consists of two viruses (i.e., NiV and HeV) that are known to cause epidemics/pandemics. Both of these viruses had 16 repurposed drugs in common (i.e., mephentermine, racepinephrine, paroxetine, pindolol, ergoloid mesylate, dihydroergocornine, dihydroergocristine, methylephedrine, cabergoline, nortriptyline, trimipramine, aripiprazole, penbutolol, asenapine, norepinephrine, and racepinephrine) (Supplementary Table S1 and Supplementary Fig. S6). The identified repurposed drugs (i.e., NiV and HeV) are categorized as antidepressants, antihypertensives, antitussives, vasodilators, and antiasthmatics.

The EBOV and MARV (*Filoviridae* family) are known to cause epidemics/pandemics. The repurposed drug podofilox shows the highest confidence score of 1.00 for EBOV. However, for MARV, predicted drugs such as citalopram, benzatropine, ziprasidone, amitriptyline, and promazine show high confidence scores (Supplementary Table S1 and Supplementary Fig. S**3**). The antidepressant category of drugs is commonly repurposed against both viruses.

Among the top 20 repurposed drugs for ZIKV, drugs such as alvocidib, mycophenolate mofetil, ribavirin, pemetrexed, and olmesartan showed the most promising results (Supplementary Table S1 and Supplementary Fig. S9). These drugs are broadly categorized as anti-cancer drugs, immunosuppressants, and antivirals.

The mosquito-transmitted epidemic causing CHIKV can be targeted using predicted repurposed drugs such as chlorpromazine, imipramine, alendronic acid, olanzapine, and cabozantinib. Furthermore, these drugs are categorized as antidepressants, anti-cancer drugs, and anti-osteoporotics (Supplementary Table S1 and Supplementary Fig. S1).

The top 20 repurposed drug candidates against major epidemic-/pandemic-causing viruses identified from our pipeline are represented as network diagrams in Supplementary Figs. S1–S9 and in detailed tabulation format in Supplementary Table S1. We have also incorporated the information of the drug category as well as the classification of predicted repurposed drugs. The classification of identified drugs includes whether that drug is host-specific or pathogen-specific. The majority of these predicted drugs are host-specific (e.g., anti-cancer drugs, anti-diabetics, anticoagulants, anti-inflammatories, etc.). However, antibiotic, antifungal, antiviral, and antiparasitic drugs are considered pathogen-specific (as listed in Supplementary Table S1).

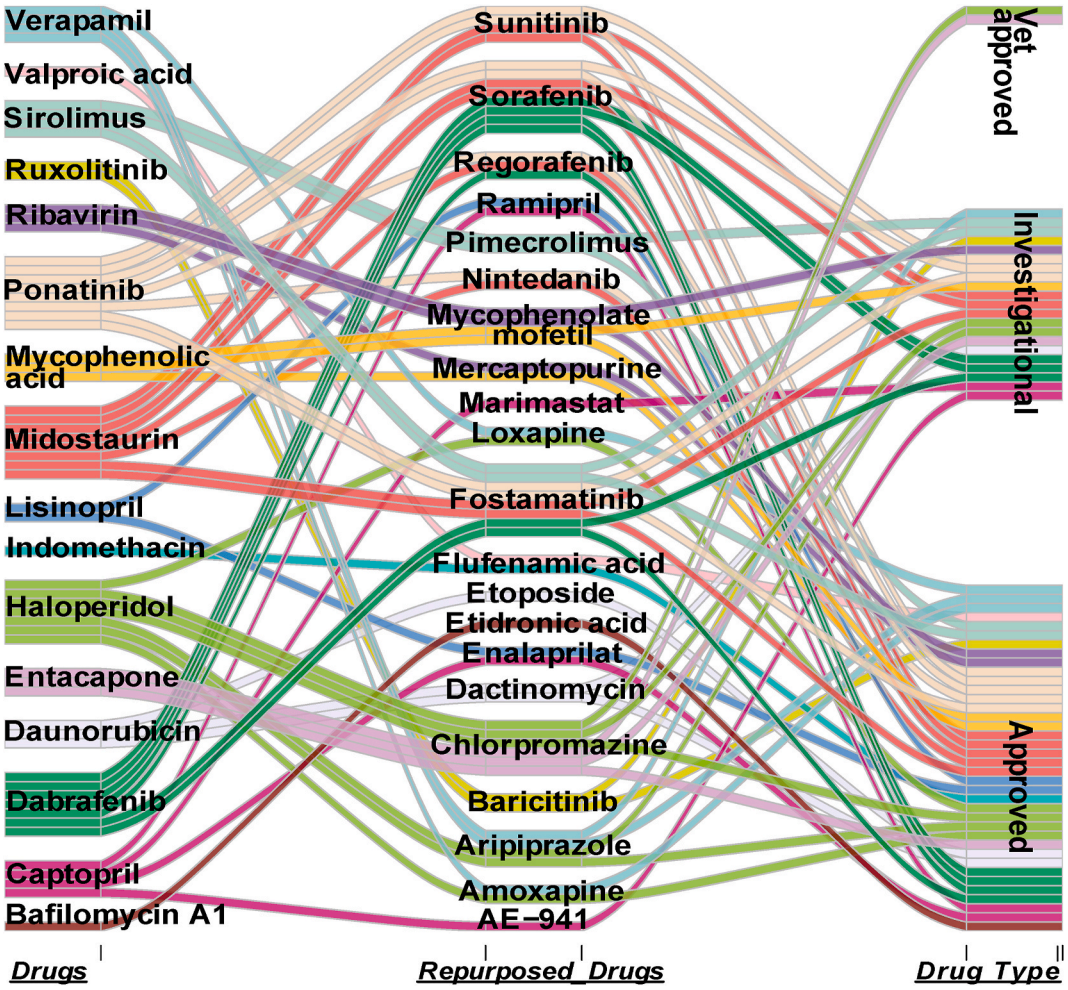

Fig. 3. The alluvial plot represents the correlation between experimentally validated drugs, promising repurposed drug candidates, and repurposed drug types for the treatment of SARS-CoV-2.

We checked the status of the predicted repurposed drugs in common among viruses and obtained 52 out of the 283 common drugs for at least two viruses (Fig. 4). Among these 52 drugs, fostamatinib (DB12010) and loxapine (DB00408) were commonly found between five viruses. Fostamatinib is predicted to be suitable for repurposing against LASV, IAV/IBV, RVFV, SARS-CoV-2, and ZIKV. Simultaneously, loxapine is predicted to be repurposed against CCHV, CHIKV, HeV, LASV, and SARS-CoV-2. The statuses of all 52 drugs are provided in Fig. 4.

2.2. Drug pathway analysis

We used a "*drug-target-pathway*" approach to identify KEGG pathways that were being targeted by existing drugs. Additionally, we used experimentally validated drugs to identify their drug-targets followed by the mapping of KEGG pathways. The top 10 pathways were selected for each of the 14 viruses (Fig. 5).

The "pathways in cancer" were found to be a majorly occurring drug-target for SARS-CoV-2, influenza, EBOV, and ZIKV. "Pathways in cancer" is a collection of several pathways whose genes are perturbed due to cancer. For SARS-CoV-2, we had 21 drugs with 124 genes. Overall, 21 out of 124 genes were mapped to the neuroactive ligand-receptor interaction pathway (hsa 04080), while 20 genes were found in the MAPK signaling pathway. For the influenza virus, 14 drugs were found to have 45 genes. Overall, 9 of these 45 genes belonged to the PI3K-Akt signaling pathway (hsa04151), while 7 genes coincided with the prostate cancer pathway. In the case of EBOV, 15 drugs targeted 58 genes. Of these genes, 14 were shared with the MAPK signaling pathway and 14 mapped to the Ras signaling pathway (hsa 04014). In the case of ZIKV, 13 drugs have 46 genes, of which 9 genes are involved in the PI3K-Akt signaling pathway (hsa04151) and 7 genes mapped to the Cushing syndrome pathway. Moreover, the "pathways in cancer" hsa 05200 pathway was a common target for eight of the viruses. This pathway was mapped onto 27, 9, 14, and 10 genes in the cases of SARS-CoV-2, influenza, EBOV, and ZIKV, respectively. Ten of the most common pathways for the other viruses are provided in Supplementary Table S2.

2.3. Gene ontology analysis

For the gene ontology (GO) analysis, gene Entrez IDs corresponding to the drugs were visualized with the enriched GO terms for the viruses. Fisher's exact test for GO term enrichment was performed using the topGO package in R. The enrichment of GO terms was visualized using R, and the statistical results of the test are provided in the supplementary material (Supplementary Figs. S10–S48 and Supplementary Table S3).

Enriched GO biological processes for SARS-CoV-2 were mostly predicted as regulatory processes for the transportation and localization of cellular components. In GO molecular functions, genes that acted as targets for drugs designed against SARS-CoV-2 were significantly involved in tyrosine kinase signaling activity (GO:0004713 and GO:0008227). We also identified many genes involved in ion channel transporter activities, especially sodium- and calcium-gated channels (GO:0005248 and GO:0005244). Ion channels are known to serve an

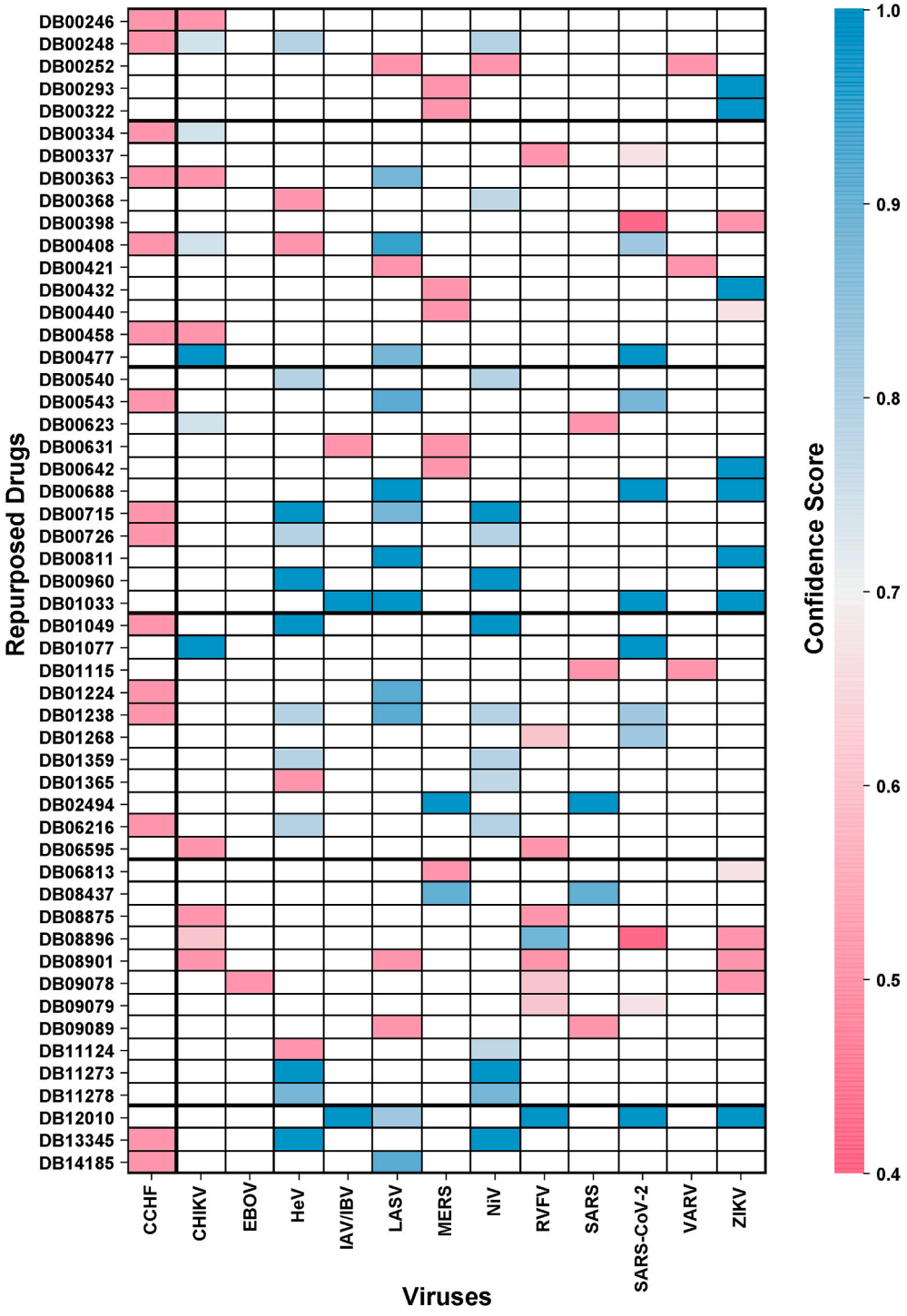

Fig. 4. Heatmap depicting the status of repurposed drugs predicted from our pipeline against the viruses responsible for causing epidemics/pandemics. The colors in the heatmap represent the confidence scores of individual repurposed drugs.

important role in the transmission of nerve impulses, and this result suggests that the "neuroactive ligand-receptor interaction pathway" may serve a critical role in virus infection. In the case of overrepresented GO cellular components, the majority of the components mapped to the plasma membrane. Since most of the cell signaling machinery is located in the plasma membrane (GO:0005886 and GO:0005887), we found the plasma membrane node to be highly significant (Supplementary Figs. S34–S36).

For the influenza virus, we primarily found that cell cycle-related GO terms (GO:0045,786 and GO:0044,772) were enriched within GO biological processes. Within GO molecular function terms, cyclin-dependent protein serine/threonine and kinase activity (GO:0004693 and GO:0097,472) were found to be significantly enriched. Other terms involved in binding functions were also found in higher numbers. Enriched GO cellular components were mainly protein kinase complexes (GO:0000307 and GO:1902911) or complexes involved in vesicular transport (GO:1903561 and GO:0031,982) (Supplementary Figs. S22–S24).

Signaling processes were the major biological processes enriched in the case of the EBOV. Generally, we found that the MAP kinase signaling

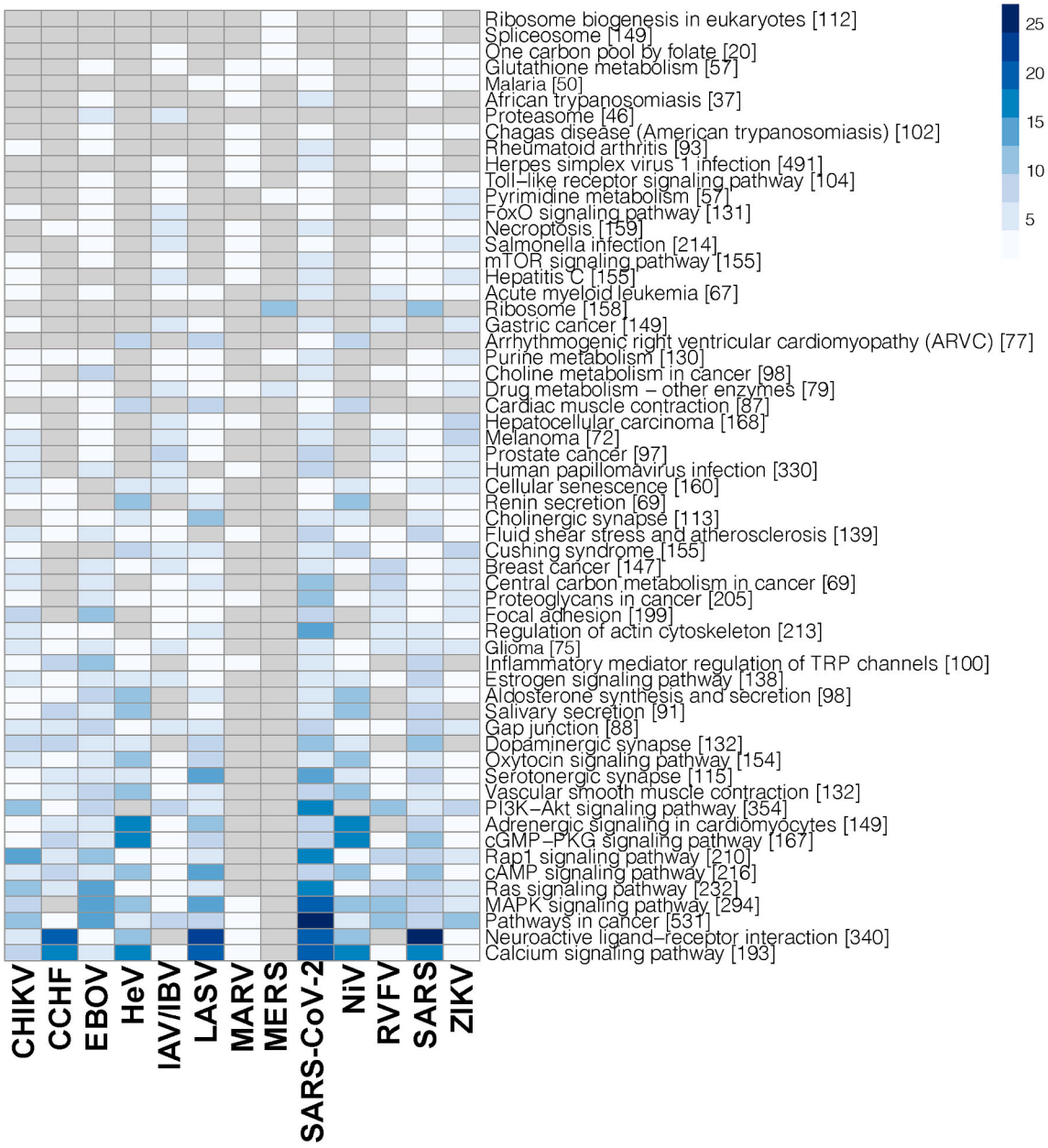

Fig. 5. Pathway heat map depicting the number of genes from the KEGG pathways (y-axis) that are involved as drug-targets against the epidemic/pandemic viruses (x-axis). Numbers within square brackets indicate the total number of genes in the pathway. Deep blue indicates a higher number of genes, whereas white indicates the lower involvement of genes.

pathway (GO:0000165) and Fc receptor signaling pathway (GO:0038,093) were involved as common drug-targets against EBOV. Among the GO molecular functions, protein kinase activity and nucleotide-binding (GO:0004672, GO:0004697, and GO:0000166) were more commonly enriched. Vesicle-related GO terms and the proteasome core complex were the GO cellular components targeted by drugs against EBOV (Supplementary Figs. S16–S18).

Furthermore, phosphate-related metabolic processes were enriched within GO biological processes for the ZIKV (GO:0006796 and GO:0006793). We observed a large number of binding-related molecular functions, such as nucleoside phosphate binding (GO:1901265), drug binding (GO:0008144), and anion binding (GO:0043,168) GO terms were more pronounced. Among GO cellular components, those involved in drug-targets for viral inhibition were cyclin-dependent protein kinases (GO:0000307) and certain lumen-related terms (GO:0031,983, GO:0034,774, and GO:0060,205) (Supplementary Figs. S46–S48).

2.4. Molecular docking

Molecular docking plays a significant role in understanding protein and ligand interactions. Additionally, it provides information about the bond length between atoms. In the present study, we selected 21 molecules against SARS-CoV-2, of which 17 were used for docking. These molecules were consecutively docked on the SARS-CoV-2 S-protein (PDB: 6LZG) to determine the best binding affinity (Kcal/mol). A comprehensive list of these molecules' binding affinities is presented in Table 2. Moreover, six molecules (i.e., etoposide, regorafenib, sorafenib, nintedanib, fostamatinib, and loxapine) were found to have binding energies ranging from −8.2 to −9.2 kcal/mol. Figs. 6 and 7 present the interacting residues of four molecules (i.e., etoposide, regorafenib, sorafenib, and nintedanib).

The interaction analysis shows that etoposide exhibits nine interactions, of which one interaction belongs to the N-terminal domain

Table 2
The ligand, binding affinity, root mean square deviation (RMSD) value (Å), interacting residues, bond length (Å), types of interactions, and interacting domain of the spike protein.

Drug_id	Drugs	Affinity (Kcal/mol)	*RMSD* (Å)	Interacting residues	Bond length(Å)	Interactions	Interacting domain
DB00773	Etoposide	−9.2	0	PHE-40	3.86	Conventional hydrogen bond	NTD/CTD (RBD)
				ASP-350	2.06	Carbon hydrogen bond	
				TYR-385	1.76	Pi-cation	
				PHE-390	4.39	Pi-sigma	
				ARG-393	3.41	Alkyl	
				ASN-394	2.43, 3.52	Pi-alkyl	
				HIS-401	2.94		
				ARG-514	2.76, 3.89, 4.13		
				TYR-515	4.47		
DB08896	Regorafenib	−9.1	0	LEU-95	3.94	Conventional hydrogen bond	NTD/CTD (RBD)
				GLN-102	2.40	Carbon hydrogen bond	
				TYR-202	5.64	Pi-Pi T-shaped	
				ASP-206	3.23, 4.82, 4.99	Halogen	
				ALA-396	3.31, 3.68	Pi-anion	
				SER-511	2.20, 2.48	Pi-sigma	
				ARG-514	2.29		
				LYS-562	3.04, 3.45		
				GLU-564	3.39		
				TRP-566	2.93		
DB00398	Sorafenib	−9	0	LEU-95	5.12	Conventional hydrogen bond	NTD/CTD (RBD)
				GLN-102	2.45	Carbon hydrogen bond	
				TYR-202	5.57	Pi-Pi T-shaped	
				ASP-206	3.19, 4.80	Halogen	
				ALA-396	3.06, 3.21	Pi-anion	
				ASP-509	3.78	Pi-alkyl	
				SER-511	2.16, 2.44	Alkyl	
				ARG-514	2.25		
				LYS-562	2.90, 4.49		
				GLU-564	3.43		
DB09079	Nintedanib	−8.7	0	GLN-102	2.87	Conventional hydrogen bond	NTD/CTD (RBD)
				ASP-509	3.45, 3.60	Carbon hydrogen bond	
				LYS-562	4.65	Pi-cation	
DB12010	Fostamatinib	−8.6	0	GLN-102	2.22, 2.63	Conventional hydrogen bond	NTD/CTD (RBD)
				TRP-203	4.59	Unfavorable positive-positive	
				ARG-514	2.04, 2.43	Pi-cation	
				LYS-562	2.52, 4.48, 4.99	Pi-alkyl	
DB00408	Loxapine	−8.2	0	PHE-40	4.84, 5.38	Carbon hydrogen bond	NTD/CTD (RBD)
				ALA-348	3.71	Pi-Pi stacked	
				ASP-350	3.52, 3.72	Pi-Pi T-shaped	
				PHE-390	4.76	Pi-alkyl	
				ARG-393	4.79		
DB01238	Aripiprazole	−8.1	0	ASP-350	2.39	Conventional hydrogen bond	NTD/CTD (RBD)
				GLY-352	3.65	Carbon hydrogen bond	
				HIS-378	5.47	Pi-cation	
				ARG-393	2.24, 3.70	Pi-anion	
				HIS-401	3.85, 5.12	Pi-sigma	
				GLU-402	3.73	Alkyl	
				ARG-514	3.62, 4.80	Pi-alkyl	
DB01268	Sunitinib	−8	0	PHE-40	4.87	Conventional hydrogen bond	NTD/CTD (RBD)
				LEU-73	4.27	Carbon hydrogen bond	
				ALA-99	3.18, 3.68	Pi-Sigma	
				LEU-391	2.43, 3.63	Pi-Pi stacked	
				ARG-393	2.22, 3.33, 4.69	Alkyl	
				ASN-394	2.60	Pi-alkyl	
DB00543	Amoxapine	−7.9	0	PHE-40	4.82,5.41	Carbon hydrogen	NTD/CTD (RBD)
				ASP-350	3.48, 3.67	Pi-Pi stacked	
				PHE-390	4.82	Pi-Pi T-shaped	
				ARG-393	4.82	Pi-alkyl	
DB11817	Baricitinib	−7.5	0	TYR-202	3.59, 5.30	Conventional hydrogen bond	NTD/CTD (RBD)
				GLY-205	3.69	Carbon hydrogen bond	
				ASP-206	3.62	Pi-Pi T-shaped	
				GLU-208	3.29		
				LYS-562	2.14, 3.76		
DB00178	Ramipril	−7.4	0	ALA-348	2.13	Conventional hydrogen bond	CTD (RBD)
				TRP-349	4.13, 4.75	Pi-sigma	
				ASP-350	2.85	Pi-Pi stacked	
				HIS-378	3.93		
DB02266	Flufenamic acid	−7.4	0	PHE-40	4.36, 4.81	Conventional hydrogen bond	NTD/CTD (RBD)
				ASP-350	3.10	Carbon hydrogen bond	
				PHE-390	2.60, 3.33, 4.3, 4.86	Halogen	
				ARG-393	2.77, 3.29, 3.29, 4.36	Pi-Pi stacked	
				ASN-394	1.84	Pi-Pi T-shaped	

(*continued on next page*)

Table 2 (*continued*)

Drug_id	Drugs	Affinity (Kcal/mol)	*RMSD* (Å)	Interacting residues	Bond length(Å)	Interactions	Interacting domain
						Alkyl	
						Pi-alkyl	
DB09477	Enalaprilat	−7.3	0	LEU-95	3.52	Conventional hydrogen bond	NTD/CTD (RBD)
				GLN-102	2.70	Pi-sigma	
				TYR-196	2.75	Pi-alkyl	
				TYR-202	2.81, 5.06		
				GLY-205	2.36		
				GLU-208	2.08		
				VAL-209	5.09		
				PRO-565	5.41		
DB00477	Chlorpromazine	−6.1	0	ASP-350	3.48		NTD/CTD (RBD)
				ASP-382	3.58, 3.62	Carbon hydrogen bond	
				PHE-390	4.74	Pi-Pi stacked	
				ARG-393	4.78	Pi-alkyl	
DB00786	Marimastat	−6.1	0	TYR-202	4.94	Conventional hydrogen bond	NTD/CTD (RBD)
				TRP-203	2.47	Carbon hydrogen bond	
				ASP-206	3.72, 2.66	Unfavorable positive-positive	
				GLU-398	2.73	Pi-cation	
				SER-511	1.21, 2.45	Pi-alkyl	
DB01033	Mercaptopurine	−5.7	0	HIS-34	2.50	Conventional hydrogen bond	NTD/CTD (RBD)
				GLU-37	3.58	Pi-cation	
				LYS-353	2.34, 3.60		
				ARG-403	2.30		
				GLY-496	2.44		
DB01077	Etidronic acid	−5.4	0		2.46	Conventional hydrogen bond	NTD/CTD (RBD)
				GLY-205	2.85, 2.94, 4.82	Carbon hydrogen bond	
				ASP-206	2.00	Attractive charge	
				GLU-208	2.79, 2.96, 4.20	Unfavorable positive-positive	
				LYS-562	2.11, 3.23, 3.48		
				TRP-566			

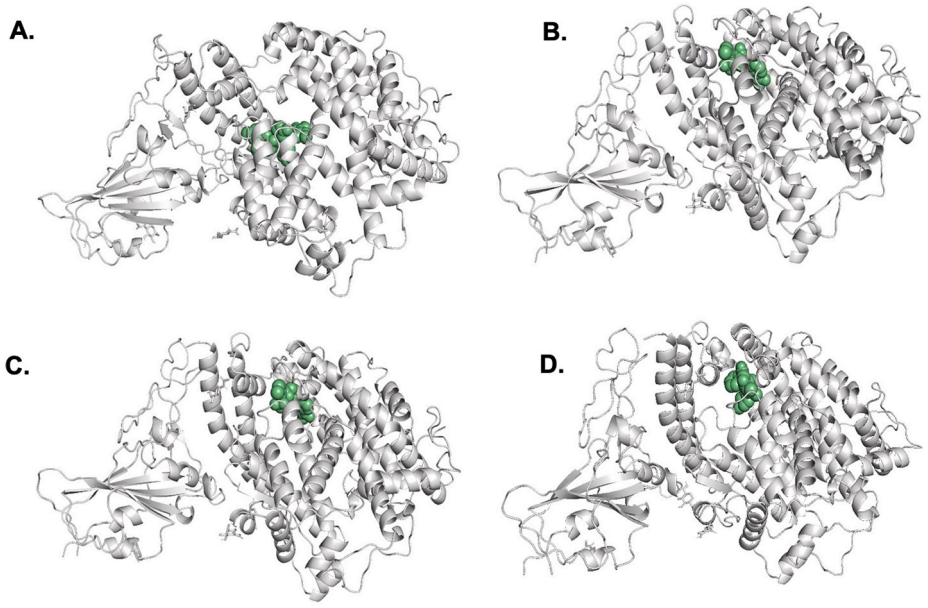

Fig. 6. The ligands A) etoposide, B) regorafenib, C) sorafenib, and D) nintedanib binding to the SARS-CoV-2 S-protein (the SARS-CoV-2 S-protein is shown in the ribbon diagram in gray color and the ligand molecule is shown in the green sphere).

(NTD) and eight interactions belong to the C-terminal domain (CTD) of the SARS-CoV-2 protein (PDB: 6LZG). The interactive residues are PHE-40, ASP-350, TYR-385, PHE-390, ARG- 393, ASN-394, HIS-401, ARG-514, and TYR-515. Moreover, two major types of interaction occur in these interacting residues (i.e., conventional hydrogen bond and carbon-hydrogen bonds) along with other types of interactions. The bond lengths between ligand and interacting residues are provided in Table 1. Regorafenib reveals 10 interactions, of which 4 were associated with NTD and 6 belonged to the CTD/receptor-binding domain (RBD). Furthermore, nintedanib showed one NTD and two CTD/RBD interactions. Additionally, fostamatinib and loxapine showed four and five interactions, respectively. For fostamatinib, two out of four interactions belong to the CTD/RBD. For loxapine, four out of five interactions belong to the CTD/RBD.

3. Discussion

Viruses are responsible for causing various pandemics/epidemics with high morbidity and mortality worldwide. However, designing effective antivirals remains a challenge for the scientific community.

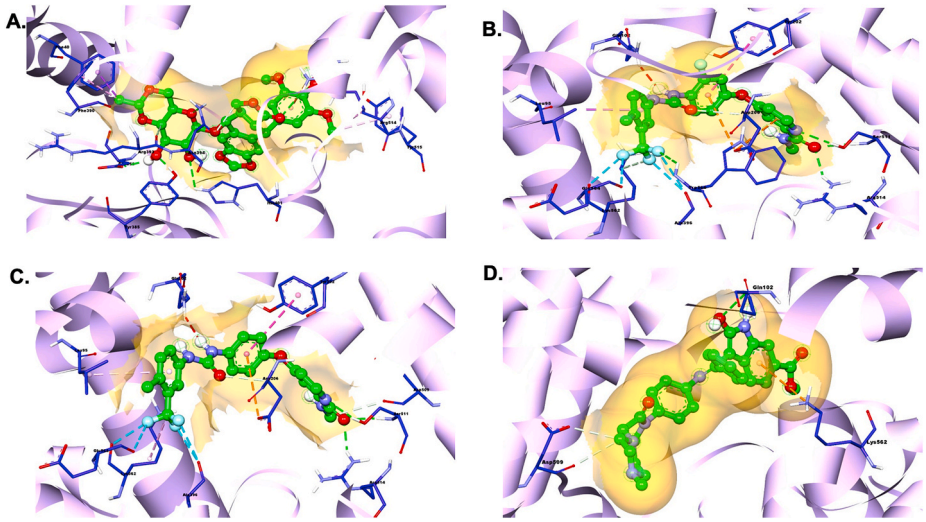

Fig. 7. The ligands A) etoposide, B) regorafenib, C) sorafenib, and D) nintedanib binding the SARS-CoV-2 S-protein (the SARS-CoV-2 S-protein is shown in cyan color, the interacting residues are shown in blue Color, and ligand molecules are shown as green balls and sticks).

Drug repurposing has emerged as a powerful tool that reduces time and cost [39]. In the current study, we provide a novel "*drug-target-drug*" approach to identify and prioritize promising repurposed drugs (see **Methods**). The overall analysis involved the collation of experimentally validated antiviral drugs from the literature followed by the extraction of their targets. Thereafter, these drug-targets were used for the identification of new and effective repurposed drugs against major human viruses.

The "*drug-target-drug*" approach is a novel strategy that was used in the present study to identify promising repurposed drug candidates against 14 viruses responsible for causing epidemics/pandemics. This study used experimentally validated and FDA-approved viral inhibitors as inputs. However, few published articles have used different approaches to identify repurposed drug candidates targeting SARS-CoV-2. O'Donovan et al. used transcriptomics signatures from the publicly available data of SARS-CoV-2 infected cell lines to identify 20 putative drugs for COVID-19 patients [32]. Moreover, Barh et al. used multi-omics (interactome, proteome, transcriptome, and bibliome) data to predict drug candidates against SARS-CoV-2 [33]. Additionally, Majumdar et al. identified effective chemical candidates against SARS-CoV-2 by incorporating the deep learning-based potential ligand prediction framework [34]. Cippa et al. predicted protective drugs against COVID-19 by examining the interplay between the risk factors and medications [38]. Furthermore, Gordon et al. identified the 66 druggable targets from 69 compounds in various phases of clinical trials for SARS-CoV-2 based on protein interaction maps [35]. Ackerman et al. showed eight prioritized drug-targets against SARS-CoV-2 using network-controllability [36]. Moreover, Stolfi et al. developed a target-based strategy to identify a drug against SARS-CoV-2 by analyzing protein-protein interactions [37]. However, none of the aforementioned approaches used experimentally validated repurposed drug candidates (tested for antiviral activity) as inputs. Therefore, the current study is different and more robust than the approaches reported in the literature.

We compared the drug-targets used in our study with other approaches for SARS-CoV-2 and found that 33 out of 114 targets were also identified in previous studies [34] [–] [37]. Overall, six of the targets mapped with those of Gordon et al. (i.e., P06280, P12268, P21964, P38606, Q92769, and Q99720) [35]. Our study also shows six targets in common with Stolfi et al. (i.e., P42345, P07948, P11362, P12931, P21964, and P05362) [37]. Furthermore, two targets were identified by Ackermann et al. (i.e., Q99720 and P12268) [36]. Moreover, Majumdar et al. used the kinase inhibitor bioactivity (KIBA) dataset to perform drug-target interaction prediction [34], which resulted in 25 targets that were also identified in the present study. Some studies did not use targets for the identification of repurposed drug candidates. For example, O'Donovan et al. used transcriptomics signatures [32], Barh et al. used multi-omics data [33], and Cippa et al. identified the risk profiles of the patients to identify protective drugs [38].

All of the reported approaches identified repurposed drug candidates for SARS-CoV-2. We compared our output (repurposed drugs) from recent studies and found many drug candidates in common (see Supplementary Fig. S49). Interestingly, we found that six drugs from our study were also predicted as potential repurposed drug candidates against SARS-CoV-2 in previous studies (e.g., fostamatinib, mycophenolate mofetil, sorafenib, regorafenib, etoposide, and nintedanib. This further validates the promising nature of our "*drug-target-drug*" pipeline. Among the aforementioned drugs, fostamatinib, regorafenib, and nintedanib were also predicted by Stolfi et al., while etoposide was also predicted by Barh et al., mycophenolate mofetil was identified by Ackermann et al., and sorafenib was also identified by O'Donovan et al. Thus, our "*drug-target-drug*" approach has some drug-targets and repurposed drugs in common with a few computational approaches. Notably, a few of the predicted repurposed drugs have also entered clinical trials. This demonstrates that our "*drug-target-drug*" approach is capable of identifying potential repurposed drug candidates for epidemic-/pandemic-causing viruses.

In light of the SARS-CoV-2 pandemic, we have predicted promising repurposed drug candidates in the antineoplastic (lung, renal, and hepatic), rheumatoid arthritis drug, antidepressant, and immunosuppressant categories. For example, fostamatinib, chlorpromazine, baricitinib, ramipril, enalaprilat, nintedanib, and etoposide are already in various phases of clinical trials for COVID-19 patients. Chlorpromazine had a high confidence score (1.0) and was also experimentally validated by Weston et al. (IC_{50} = 3.14 μM) [40]. During our analysis, we identified certain drugs (e.g., ramipril and enalaprilat) as potential repurposed drugs against COVID-19 patients. The effectiveness of ramipril and enalaprilat was confirmed by their targets (i.e., angiotensin-converting enzyme (ACE) or angiotensin II receptor blocker (ARB), which already showed promising results in treating COVID-19 patients [41] [–] [43]. Reports have highlighted the potential use of ACE2, which is also the target of drugs approved for use in COVID-19 patients (e.g., chloroquine and hydroxychloroquine) [44]. Our approach also predicted drugs for use in COVID-19 patients (e.g., sorafenib, AE-941, and sunitinib) that were previously used to treat renal disorders. These drugs could be promising repurposed drug candidates in COVID-19 patients since

reports suggest major kidney functionality complications [45,46]. However, our method also predicted that drugs used in hepatocellular carcinoma and immune thrombocytopenic purpura (ITP) (i.e., regorafenib and fostamatinib) will be effective in COVID-19 patients. These drugs could be used for various clinical indications in COVID-19 patients, such as non-functionality of the liver [46] and blood-related disorders [47]. However, we also predicted that baricitinib (usually given to rheumatoid arthritis patients) will be effective for COVID-19 patients. Various reports further confirmed the effective reuse of rheumatoid arthritis drugs in COVID-19 patients. JAK/STAT is involved in the cytokine production of macrophages and the differentiation, survival, and activation of neutrophils. These genes are highly expressed during SARS-CoV-2 infection. Furthermore, drugs such as ruxolitinib—which target these pathways—have been predicted to be effective against SARS-CoV-2 [48]. Tumor necrosis factor-α (TNF-α) is a cytokine that helps in the pathogenesis of SARS-CoV-2 infection [49] in acute respiratory distress syndrome (ARDS) patients [50].

We also predicted the potential reuse of nedocromil—a well-known antiasthmatic drug—against influenza infection. The presence of asthma has further confirmed its use as a clinical indication among influenza patients during the 2008–2009 flu pandemic. Furthermore, our "*drug-target-drug*" approach identified the potential for the anti-cancer drugs gemcitabine and paclitaxel to cure influenza patients. Interestingly, some anti-cancer drugs showed promising results in treating influenza patients [39]. Furthermore, we found a few gene targets that are involved in viral pathogenesis. For example, Chavas et al. reported that human cytosolic sialidase Neu 2 interacts with the sialidase of the influenza virus and is targeted by drugs such as oseltamivir and zanamivir [51]. Through an RNAi screening study, Zhang et al. revealed that the anti-cancer drug flavopiridol targets cyclin-dependent kinase 4 (CDK4), which is involved in leukocyte migration and lung injury. Notably, they observed significant improvement in edema among H5N1-infected mouse lung tissues [52]. We predicted that paclitaxel (also known as Taxol) is effective against the influenza virus. Taxol is primarily used to treat Kaposi's sarcoma and lung cancer. Roberts et al. have shown that the addition of the microtubule stabilizer paclitaxel (Taxol) significantly reduces the spread of influenza A virus infection in cell lines [53]. A few studies have also suggested the non-cancer repurposed use of paclitaxel at low concentrations to treat skin disorders, renal and hepatic fibrosis, inflammation, axon regeneration, limb salvage, and coronary artery restenosis [54].

The EBOV caused a major epidemic between 2014 and 2016. We identified that drugs categorized as cardiovascular drugs, antihypertensives, vasodilators, and anti-cancer drugs can be repurposed for EBOV patients. We predicted the use of deslanoside and digitoxin, which are well-known cardiovascular drugs that could be effectively repurposed against EBOV. Previously, some studies also reported the promising use of cardiovascular drugs to treat EBOV infections [55]. We also identified lenvatinib and diethylstilbestrol as anti-cancer drugs that could be repurposed to tackle EBOV. Various reports have shown the effective use of anti-cancer drugs against Ebola hemorrhagic fever [56]. There are several repurposed drug-targets in the EBOV. García-Dorival et al. showed that the ATP1A1 enzyme is inhibited in Ebola virus-infected cells, which results in decreasing virus progeny [57]. Also, the dihydroorotate dehydrogenase (DHODH) target results in the inhibition of the Ebola virus-induced minigenome (MG) assay [58].

Epidemics caused by ZIKV occurred during the 2015–2016 period in Brazil as well as areas of North and South America [59]. Our "*drug--target-drug*" approach predicted anti-cancer, antiviral, and immunosuppressant drugs as repurposed candidates for ZIKV infections. From our *in silico* analysis, we identified certain anti-cancer drugs (e.g., alvocidib, sorafenib, regorafenib, and lenvatinib) as promising candidates for treating ZIKV infection. Previous reports showed that the anti-cancer drug methotrexate is effective against ZIKV infection [60]. We also found that repurposed drugs such as ribavirin and trifluridine showed promising results in tackling ZIKV infection [61,62]. Additionally, we found that the immunosuppressant drug mycophenolate mofetil is effective against ZIKV patients with high efficiency. Notably, the DHFR gene plays a vital role in inhibiting ZIKV replication [60]. Beck et al. showed that methotrexate inhibits the DHFR pathway against ZIKV in cell lines such as Vero and human neural stem cells (hNSCs). Similarly, RNase L gene function is also activated in Zika infection, which degrades genomic RNA [63].

Apart from the aforementioned viruses responsible for causing epidemics and pandemics, we also identified the most promising drug-targets for the remaining 10 viruses, which have not been previously used for treating viral infections. Among all of the identified repurposed drugs, fostamatinib has been used as a highly promising broad-spectrum drug against SARS-CoV-2, EBOV, IAV/IBV, ZIKA, LASV, and RVFV. Fostamatinib is an orphan drug and has been primarily used to treat rheumatoid arthritis and ITP [47,64]. Likewise, aripiprazole—an antipsychotic drug—has been identified as a common drug against SARS-CoV-2, LASV, CCHF, HeV, and NiV. Furthermore, the antipsychotic drug loxapine was found to be effective against five viruses (i.e., SARS-CoV-2, LASV, CCHF, HeV, and CHIKV). Interestingly, the literature shows psychotic disorder as a clinical indication for all of these viruses [65] [–] [67]. Nayak et al. showed that chikungunya infection results in TNF production in the host macrophages [68]. Likewise, fatty acid synthase (FASN) has been reported as a proviral for CHIKV via nsP1 palmitoylation [69].

Most of the enriched GO terms belonged to the cell cycle and signaling pathways. Cell cycle processes are essential for the survival of viruses within hosts and are the preferred targets of most viruses. Notably, cellular and viral kinases (involved in the cell cycle) may prove to be viable targets for the prophylactic and therapeutic treatment of viral infections. Cyclin-dependent kinases regulate the state of cellular growth and replication. These were also found to be significantly enriched among GO terms, which indicates that they could be preferred as drug-targets. The plasma membrane is a reservoir for nearly all signaling receptors and is also the primary route of viral invasion into host cells. Thus, targeting the plasma membrane could help the immune system perform apoptosis of the infected cells and prevent the spread of viral infections.

The "*drug-target-pathway*" analysis showed that some pathways are crucial for the survival of viruses. For example, the "pathways in cancer" are mapped with the majority of the genes involved in cytokine-cytokine receptor. This is one of the main reasons why immunosuppressants can be repurposed as antivirals. Signaling pathways are essential for viral infection and replication. Due to their small genome size, viruses need to hijack the host cell machinery for their survival and proliferation. Manipulating certain signaling pathways (e.g., PI3K-Akt, MAPK, and JAK-STAT) is a technique used by viruses to prolong viral replication and evade the host's immune response. Drugs targeting these pathways could be repurposed to provide an effective countermeasure against viral infection.

We found that the targets were mapped with various drugs categorized as anti-inflammatories, anti-cancer drugs, and anticoagulants (e.g., sorafenib, imatinib, duvelisib, and acalabrutinib). Some of these drugs are known anti-tumor tyrosine kinase inhibitors that have been shown to possess antiviral and anti-inflammatory properties against SARS-CoV-2 [70,71]. IL-6 inhibitors such as tocilizumab and siltuximab are approved for cancer treatment by the US FDA. These IL-6 inhibitors are also considered effective against the cytokine storm associated with a SARS-CoV-2 infection and have entered clinical trials [71]. Furthermore, prednisolone, dexamethasone, and hydrocortisone are popular anti-inflammatory and immunosuppressive drugs that have shown promising results during *in vitro* validations in SARS-CoV-2-infected cell lines. Additionally, NF-kB inhibitors such as baicalin, amygdalin, and mulberroside A reduce NF-κB expression and are used as anti-tumor drugs. These anti-inflammatory drugs are predicted to have a regulatory effect on the expression of pro-inflammatory genes and would be effective against the cytokine storm caused by SARS-CoV-2 [72].

Dinaciclib is a small molecule and multi-cyclin-dependent kinase inhibitor that represents one of the major regulators of the cell cycle [73]. Kinase inhibitors such as dinaciclib have shown promising results in both *in vitro* and *in vivo* testing against H7N9 IAV as well as other IAV strains [74]. Additionally, toremifene and clomiphene are selective estrogen reuptake modulators that have been effective in the treatment of breast cancer. These drugs were found to have antiviral activity due to their ability to inhibit EBOV entry by more than 90 % [75]. Furthermore, Temoporfin—a photosensitizer drug originally used for the treatment of squamous cell carcinoma of the head and neck—has been shown to obstruct ZIKV replication by inhibiting the interactions between viral NS2B and NS3 proteins [76].

Protein-ligand interaction plays a very crucial role in various cellular processes. Molecular docking and dynamics are significant methods used to predict the best binding affinity between ligands and proteins [77]. In this study, 17 out of 21 molecules were sequentially docked on the SARS-CoV-2 S-protein complex with the ACE-2 receptor. We found six ligand molecules with a high binding affinity (i.e., etoposide, regorafenib, sorafenib, nintedanib, fostamatinib, and loxapine) against the SARS-Cov-2 S-protein complex with ACE-2. Etoposide and regorafenib have a binding affinity (−9.2 and −9.1 kcal/mol, respectively) and exhibit a large amount of interaction with the CTD/RBD domain of the SARS-CoV-2 S-protein complex with ACE-2. Moreover, these results correspond to a previous study reporting docking scores of −7.9 kcal/mol for etoposide against SARS-CoV-2 Spike-RBD [78]. Awad et al. mentioned a binding energy of −8.2 kcal/mol for regorafenib against SARS-CoV-2 Spike-RBD [79]. Furthermore, the IC_{50}/EC_{50} values of these 21 drugs were confirmed by one of our recently published artificial intelligence (AI)-based pipelines known as "*anti-Corona*" [80]. Overall, 17 out of 21 drugs were predicted to have IC_{50}/EC_{50} values $\leq$ 1 μM, corresponding to approximately 81 % accuracy. Moreover, all of the 21 drugs were predicted to have IC_{50}/EC_{50} values $\leq$ 5 μM.

Through the "*drug-target-drug*" computational approach, the current study identified promising repurposed drugs against 14 viruses responsible for causing epidemics and pandemics. Although several other computational approaches (e.g., molecular simulation, RNAseq, and drug networks) have been used for drug repurposing, the data-driven "*drug-target-drug*" approach has not been exploited to date [15,81,82]. The strength of this algorithm is that we focused on the identification of repurposed drug candidates that have been experimentally validated. An important step that makes this a robust technique is the exclusion of drugs obtained through the negative dataset from the identified repurposed drugs of the positive dataset, which has not been previously performed [15]. Furthermore, the calculation of confidence scores makes this a more promising approach. The repurposed drugs identified for SARS-CoV-2 using our approach were further validated by molecular docking analysis and supported by our recently published AI-based computational method "*anti-Corona*" [80]. The advantage of the study is that some of the predicted repurposed drugs are in various phases of clinical trials (e.g., baricitinib, ramipril, chlorpromazine, enalaprilat). Thus, the predicted repurposed drug candidates could be potential antivirals. The identified drug candidates fall within the approved drug category, which could easily go through to testing trials. Therefore, a massive repertoire of drugs remains unexplored. As such, our study is critical since it has prioritized the repositioned drug candidates. This analysis can help speed up the discovery of effective antivirals. Furthermore, this approach could also be applied to identify repurposed drugs for cancer, diabetes, bacterial infection, and many other diseases.

3.1. Limitations of the study

The main limitation of this algorithm is that it only focused on drugs whose targets are already known in the literature. Thus, other drugs are excluded. However, the implementation of machine learning algorithms would further speed up research by considering drugs with known and unknown targets.

4. Material and methods

The overall methodology used in the present study is provided in Figs. 8 and 9. It involves data extraction, the identification of repurposed drugs, and the prioritization of filtered repurposed drug candidates. We also performed drug-target pathway analysis, GO analysis, and the visualization of experimentally validated drugs effective against 14 viruses known to cause epidemics and pandemics.

4.1. Data extraction

The data preparation involved the following steps:

1. Data mining was performed for the drugs experimentally tested for *in vitro* or *in vivo* antiviral activity against 14 viruses that cause epidemics and pandemics. Experimental data on the virus inhibition efficiency (IC_{50}/EC_{50}) of drugs were manually curated from the literature.
2. The selection of drugs tested for antiviral activities (for the positive and negative datasets) was based on the IC_{50}/EC_{50} values. Drugs with IC_{50}/EC_{50} values $<$ 10 μM were included in the positive dataset [15], while drugs with $>$50 μM IC_{50}/EC_{50} were included in the negative dataset.
3. Overall, the drugs used to analyze the 14 viruses were as follows: SARS-CoV-2 (22^{p21+n1}), LASV (07^{p7+n0}), CCHV (04^{p2+n2}), SARS (13^{p7+n6}), MERS (08^{p4+n4}), MARV (07^{p4+n3}), EBOV(23^{p15+n8}), ZIKV (16^{p13+n3}), IAV/IBV ($24^{p14+n10}$), HeV (13^{p5+n8}), NiV (14^{p5+n9}), RVFV (05^{p1+n4}), CHIKV ($25^{p13+n12}$), and VARV (01^{p1+n0}). The distribution of the positive and negative datasets for drugs tested against individual viruses is shown in superscript.
4. The details of the drugs, viruses, antiviral activity, drug-targets (from the DrugBank database), and PubMed IDs are provided on GitHub (https://github.com/manojk-imtech/viralrep/blob/master/data.zip) and in Supplementary Table S4.

4.2. Identification of repurposed drugs

Following data extraction, novel and promising repurposed drugs were identified via the "*drug-target-drug*" approach (Fig. 8), which was conducted as follows:

1. The targets of the drugs in the positive and negative datasets for all 14 viruses were extracted from the DrugBank database using Python script.
2. We identified new drugs with the same targets as repurposed candidates for individual viruses using the respective input datasets via a Python-based pipeline (https://github.com/manojk-imtech/viralrep).
3. Various filters were set to obtain promising repurposed drug candidates (excluding the repurposed drugs from the positive dataset, which were extracted using the negative dataset).

4.3. Prioritization of repurposed drug candidates

The aforementioned filtered repurposed candidates were then prioritized based on their confidence scores, as follows:

1. Confidence scores were calculated based on the number of drug-targets. For example, for SARS-CoV-2, the experimentally validated drug dabrafenib (DB08912) was reported to have five targets (P15056, P04049, P57059, Q8NG66, and P53667). We identified 13 drugs from the DrugBank database that possess the same targets as the 13 fostamatinib (DB12010) drugs with the same five targets. Thus, the confidence score for fostamatinib was calculated as 1.0

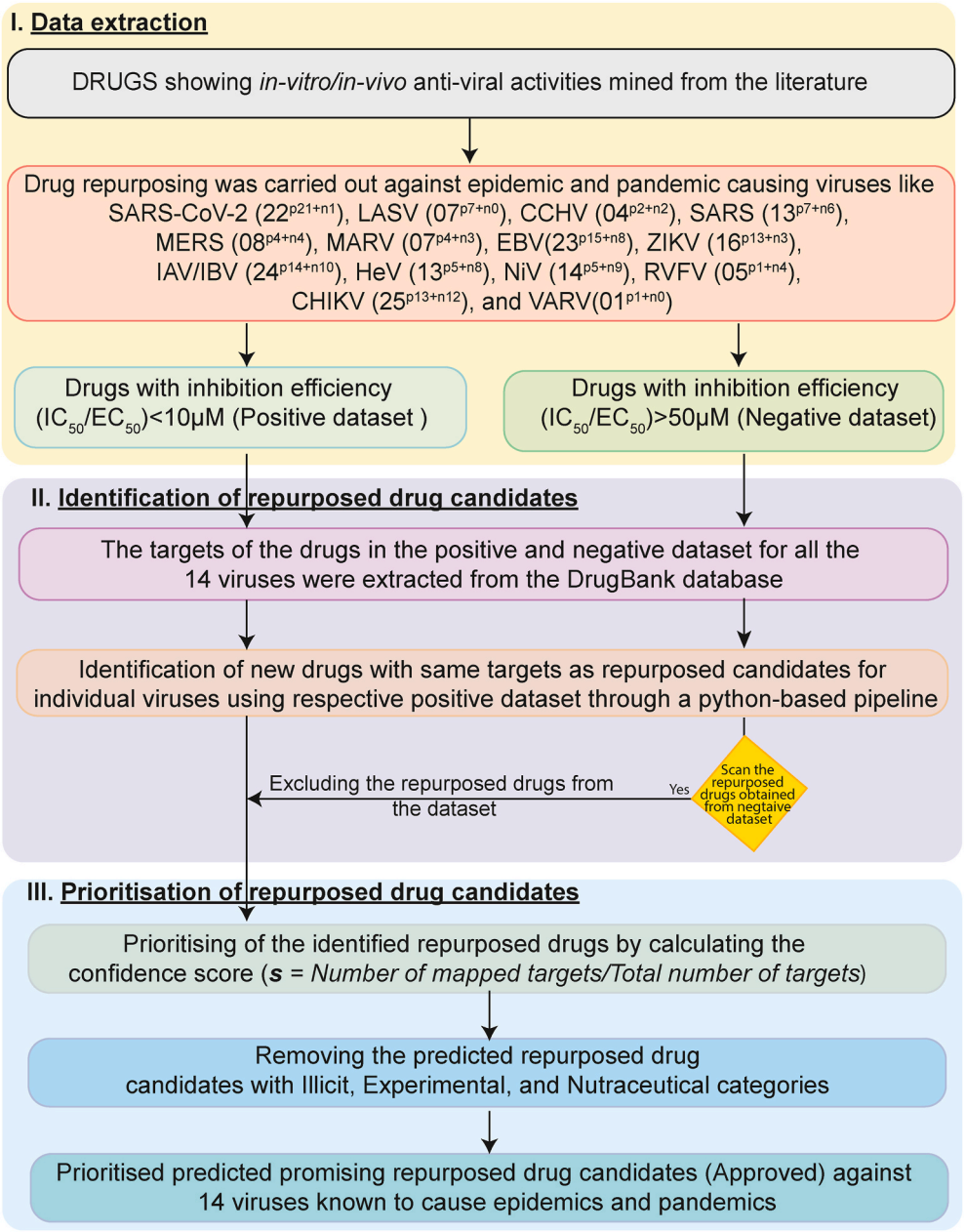

Fig. 8. The overall methodology undertaken for identifying repurposed drugs.

(*confidence score, s = number of mapped targets/Total number of targets*). However, sorafenib (DB00398) mapped with two out of five experimentally validated targets of dabrafenib. Thus, we calculated its confidence score as 0.4 (Fig. 9).

2. The highest confidence score (s = 1) suggests the highest efficacy of a novel predicted repurposed drug candidate.
3. Finally, we retained drugs from the "Approved" category and removed those from the "Withdrawn", "Illicit", and "Nutraceutical" categories (as per the DrugBank database).

4.4. Drug-target and pathway analysis

Drug-targets are important entities that are usually protein molecules in the body. A drug-target is associated with a disease against which a drug candidate shows a significant therapeutic effect. We identified the drug-targets for all experimentally validated drugs using DrugBank [83]. The drug versus drug-target associations were depicted in the form of highly enriched networks.

The "*drug-target-pathway*" analysis (pathway-level) was performed using experimentally validated drugs extracted from the literature and their corresponding drug-targets for each of the 14 viruses. The gene Entrez IDs of each target were extracted for further analysis. These gene IDs were then mapped onto KEGG pathways using the KEGGREST package in R/Bioconductor [84]. The frequency of each of the pathways per virus was calculated, and the top 10 pathways for each of the viruses were then explored.

4.5. Gene ontology analysis

Gene ontology analysis [85] is a common method used to annotate genes and gene products for identifying genes that are overrepresented in terms of molecular function (MF), biological process (BP), and cellular component (CC) attributes [86]. For the GO analysis, we used the targets of experimentally validated drugs extracted from the

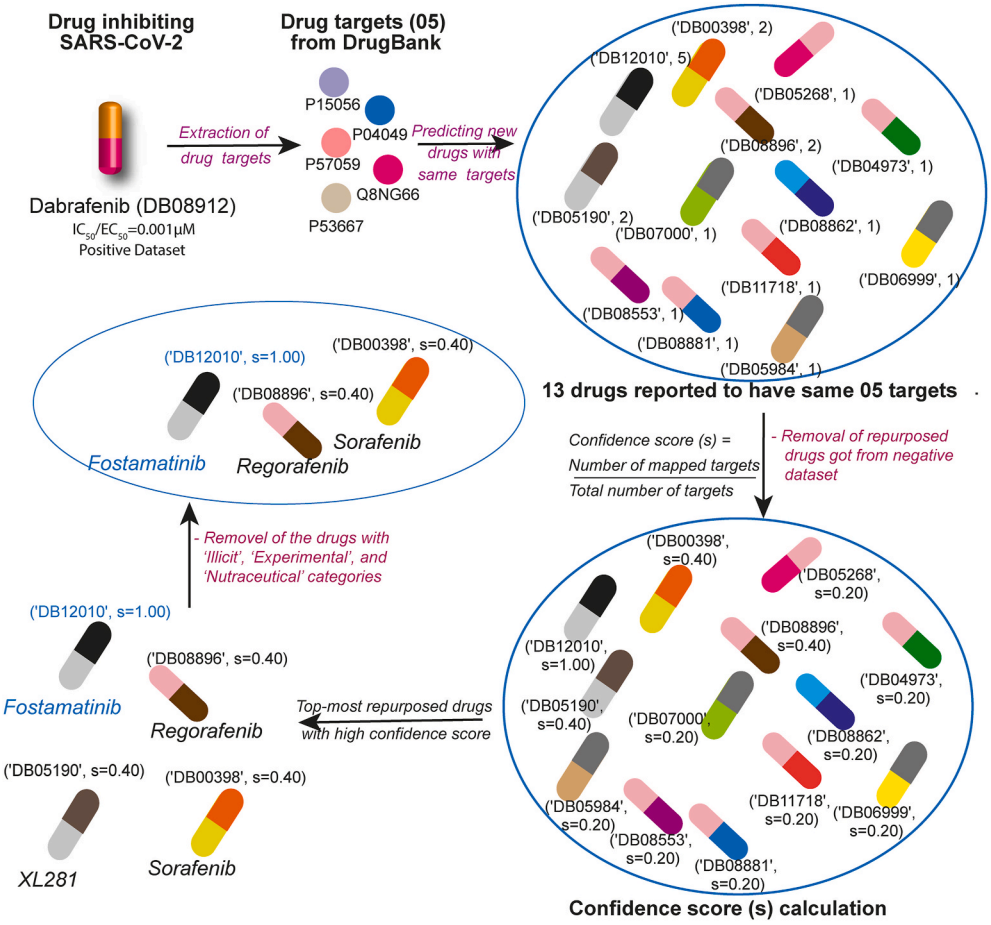

Fig. 9. Diagrammatic representation of the "*drug-target-drug*" pipeline used for the identification of repurposed drugs. The positive (IC_{50}/EC_{50} < 10 μM) and negative (IC_{50}/EC_{50} > 50 μM) data sets extracted from the literature were submitted to Github (https://github.com/manojk-imtech/viralrep/blob/master/data.zip). The targets for each drug were extracted from the DrugBank database. Furthermore, all of the drugs with identified protein targets were predicted using a Python-based pipeline. However, the checkpoint of any negative repurposed drug is present in a positive repurposed drug. In the same case, the negative repurposed drug is removed from the list of positive repurposed drug candidates. Calculation of confidence score for every repurposed drug: s = number of mapped targets/Total number of targets. Removal of Withdrawn, Illicit, and Nutraceutical category drugs from the predicted drugs.

literature for 14 viruses known to cause epidemics and pandemics. To visualize the enrichment of GO terms (BP, MF, and CC), we used topGO [87] (an R/Bioconductor package). The Gene Entrez IDs of all drug-targets were extracted and used as inputs to create a topGO object. Fisher's exact test was performed on the objects using the runTest function within the topGO package to assess the overrepresentation of GO terms with statistical significance.

4.6. Molecular docking

Protein and ligand molecules were customized using the AutoDock tool [88]. Furthermore, the molecular structures of proteins and ligands were saved in PDBQT file format. To perform docking between the protein (SARS-CoV-2 S-protein complex with ACE-2 receptor PDB: 6LZG) and ligand molecules, AutoDock Vina (*v*1.1.2) was used with the default parameters [89]. A grid box was generated using the default settings and nine of the best docking poses were generated between protein and ligand molecules. To determine the best docking pose, the exhaustiveness parameter was set to 10. Pymol and discovery studio visualizer were used to visualize the interacting residues between the protein and ligand molecules.

4.7. Data visualization

All of the results were made user-friendly using various Python or R packages. Network visualization was performed using Gephi software 0.9.2 (https://gephi.org/). The alluvial plots were constructed using the R package (https://github.com/mbojan/alluvial). The heatmaps and GO plots were prepared using R packages.

Authors' contributions

MK conceived the idea and helped in the interpretation, analysis, and overall supervision. AR, AT, AMB, and SC performed data collection and curation. AR, AMB, and SC performed data analysis. AR, AT, AMB, and SC worked on the visualization of data. AR, AMB, SC, and MK wrote the manuscript.

Code availability

The codes used in this study are available athttps://github.com/manojk-imtech/viralrep.

Funding

This work was supported by grants from the CSIR-Institute of Microbial Technology, Council of Scientific and Industrial Research (CSIR) (OLP0501, OLP0143, and MLP0024).

Declaration of competing interest

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

Acknowledgments

We acknowledge the infrastructure support from the Department of Biotechnology, Government of India (GAP0001).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.compbiomed.2021.104677.

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