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Problem Solving Protocol

DrugRepV: a compendium of repurposed drugs and chemicals targeting epidemic and pandemic viruses

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Abstract

Viruses are responsible for causing various epidemics and pandemics with a high mortality rate e.g. ongoing SARS-CoronaVirus-2 crisis. The discovery of novel antivirals remains a challenge but drug repurposing is emerging as a potential solution to develop antivirals in a cost-effective manner. In this regard, we collated the information of repurposed drugs tested for antiviral activity from literature and presented it in the form of a user-friendly web server named 'DrugRepV'. The database contains 8485 entries (3448 unique) with biological, chemical, clinical and structural information of 23 viruses responsible to cause epidemics/pandemics. The database harbors browse and search options to explore the repurposed drug entries. The data can be explored by some important fields like drugs, viruses, drug targets, clinical trials, assays, etc. For summarizing the data, we provide overall statistics of the repurposed candidates. To make the database more informative, it is hyperlinked to various external repositories like DrugBank, PubChem, NCBI-Taxonomy, Clinicaltrials.gov, World Health Organization and many more. 'DrugRepV' database (https://bioinfo.imtech.res.in/manojk/drugrepv/) would be highly useful to the research community working to develop antivirals.

Key words: viruses; drug repurposing; pandemics/epidemics; web server; SARS-CoV-2

Introduction

Identification of the promising antiviral agents always remains a challenge. The development of antivirals started more than 50 years ago [1]. In 1967, the description of DNA dependent RNA polymerase for pox virus was the first viral enzyme to be discovered, which led to the discovery of antiviral drugs [2]. The major concerns in the development of a novel drug are high costs, time, mutation rates, etc. [3]. However, the periodic emergence of viral epidemics and pandemics, poses serious challenges for the speedy development of novel and effective antivirals [4]. Thus, there is a need for parallel drug discovery rate as per the emergence and reemergence of viral infections [5]. Since the last decade, the drug repurposing approach shows promising results in the identification of antivirals.

Drug repurposing (drug repositioning or retasking or reprofiling) is the investigation of existing approved or investigational drugs for new medical indications [6]. The drug repurposing strategy is highly advantageous, as it has lower failure rate because it has been already tested safe in the preclinical trials; reduced time frame as most of the preclinical trials and safety assessment were already tested; and economical due to skipped clinical trial phases [7]. The first successful repurposed antiviral drug is zidovudine for human immunodeficiency virus (HIV) whose original indication was anticancer [8]. Numerous drugs like hydroxychloroquine, remdesivir, dexamethasone, etc. have

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been tested as potential candidates to fight COVID-19 [9, 10]. For Zika virus (ZIKV), the drugs like ribavirin and sofosbuvir were previously used to treat Hepatitis C virus (HCV) infections [11]. The *Coronaviridae* family viruses like severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) have been treated with Chlorpromazine, an antipsychotic drug [12]. For the dengue virus (DENV), the prochlorperazine (a previously used antiemetic drug) has been successfully repurposed [13]. Thus, drug repurposing emerged as a fast and successful approach, as a solution to target various viral diseases.

Till date, no comprehensive manually curated database dedicated for the viruses has not been reported in the literature. However, few databases are available consisting of other information for general repurposed drugs. The RepoDrug database provides information about the repurposing of only approved drugs from only Clinicaltrial.gov and DrugCentral [14]. The PROMISCUOUS database consisted of the drug-protein interaction of repurposing drug data [15]. However, we have developed a 'DrugRepV' database with various characteristics, which make it unique from the rest of the databases. Thus, in the current scenario of the virus pandemic, this database would be very helpful for the researchers to speed up the research to identify promising repurposed drug candidates.

The computational interventions can further reduce the cost and time of the drug repurposing that facilitates researchers to monitor drug candidates and test for the variety of diseases within a short period of time [16–18]. In this endeavor, we have developed 'DrugRepV', the first dedicated one-stop solution for the repurposed drugs against epidemics and pandemics viruses like SARS Coronavirus-2 (SARS-CoV-2), ZIKV, Ebola (EBV), DENV, Nipah (NiV), influenza (IFV), chikungunya (CHIKV), Lassa virus (LASV), Crimean-Congo hemorrhagic fever virus (CCHV), enterovirus (EV), HIV, SARS, MERS, Hendra virus (HeV), Japanese encephalitis virus (JEV), Marburg virus (MARV), Measles virus (MV), polio virus (PV), Rift Valley fever virus (RVFV), Vaccinia virus (VACV), Variola virus (VARV), West Nile virus (WNV) and Yellow fever virus (YFV). DrugRepV is a complete package of repurposed drugs against viruses. It contains information of biological, chemical, clinical and structural details of each repurposed drug.

Material and methods

Data collation

We build the search query '(((virus) OR viral)) AND (((repurpos*) OR reposition*))' in the advanced search option of the PubMed database and got 1210 papers. Then, we filter out papers for only those viruses that are listed as epidemic/pandemic diseases by World Health Organization (WHO) (https://www.who.int/emergencies/diseases/en/). These 23 viruses are SARS-CoV-2, ZIKV, EBV, DENV, NiV, IFV, CHIKV, HIV, SARS, MERS, CCHV, EV, HeV, JEV, LASV, MARV, MV, PV, RVFV, VACV, VARV, WNV and YFV. This leads to the shortlisting of 986 articles. Further, we started scanning the 986 articles for relevant data but still there are articles, which do not have the required information as per our database instead describing other aspects like a drug synthesis, in silico studies, etc. In addition, we also excluded reviews, non-journal papers, books, documents, etc. Finally, we extracted 8485 entries for 23 viruses from the 351 research articles having the relevant data for the development of the DrugRepV resource.

Database enrichment

The database was made highly informative by cross-linking each entry with their respective biological, chemical, structural and clinical information from various repositories.

Biological information

It includes the information manually extracted from the articles like primary indication, secondary indication, assay used, the concentration of the antiviral agent, type of inhibition, cytotoxicity and many more.

Chemical information

The details like IUPAC, canonical and isomeric SMILES, molecular weight, molecular formula, InChl, common name and synonyms were extracted from various sources like PubChem, ChEMBL, DrugBank and ChemSpider. However, various chemicals were drawn using Chemicalize or Marvin Sketch from scratch followed by the extraction of all other information. All the entries are hyperlinked to PubChem, ChEMBL and DrugBank for making the database more informative [19, 20].

Structural information

The structural details are an important component of the chemical agents. Thus, we calculated the 2D and 3D sdf format for every agent. Further, both the 2D and 3D structures were displayed on the web server using mol2ps (http://merian.pch.univie.ac.at/~nhaider/cheminf/mol2ps.html) and Jmol from JavaScript-based molecular viewer (JSmol) (http://jmol.sourceforge.net/), respectively.

Clinical information

It incorporates details like the category of drug, clinical trials phases, hyperlink to clinicaltrails.gov, WHO and Centers for Disease Control and Prevention (CDC) websites, etc.

Database statistics

We have summarized the important fields of the database in the form of various user-friendly plots. The fields like antiviral agents, viruses, drug target, disease category of antiviral agents, taxonomy and drug categories are displayed. We also provided the network-based statistics of the highly effective antivirals according to the families. The summarized plots and networks would be helpful for getting valuable insight into the repurposed drugs against viral diseases.

Web server development

The DrugRepV web server is designed in a user-friendly manner. It contains browse, search, statistics, manual, frequently asked questions and contact web pages. The manual/help page is well documented to address queries of the users and explain the usage of each component of the server. The DrugRepV web server was made functional using the LAMPP package. The front end is developed using PHP, Javascript, CSS, XML, etc., whereas the backend is comprehended using MySQL, Python, Perl, etc. [19, 21, 22].

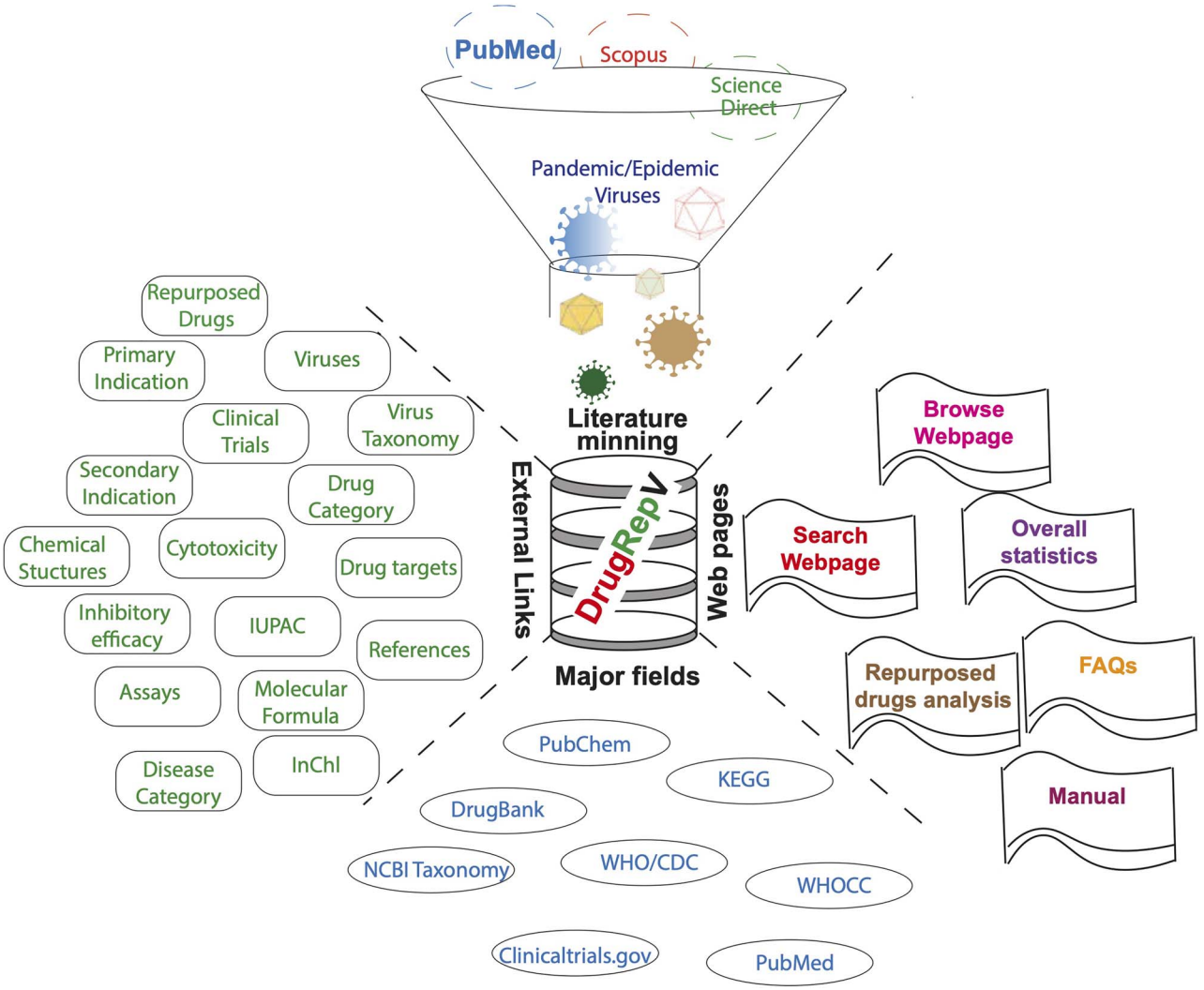

Figure 1. DrugRepV architecture.

Results

Database architecture

DrugRepV is a comprehensive repository with 8485 entries, which include multi-variant information like biological, chemical, clinical and structural. The web server includes extensive browse and search options. The overall architecture of DrugRepV is shown in Figure 1.

Repurposed drugs analysis

We have compiled the antiviral drugs of 23 viruses responsible to cause pandemic/epidemic from literature. Further, we analyzed the data to check the trend of the research done in antiviral discovery for viruses. We scanned the important fields like antiviral drugs, viruses, drug targets, drug categories and taxonomy. Further, we also perform the network-based analysis for the virus families.

Repurposed drugs

Among all the experimentally validated antiviral drugs we found that ribavirin utilized in majorly and consisted of 102 entries. Further, other drugs like chloroquine, favipiravir, mycophenolic acid, dolutegravir, raltegravir, elvitegravir and bictegravir have been checked in 92, 90, 89, 60, 60, 59 and 58 cases, respectively (Figure 2A). However, we also provided the summarized tabulated view of the repurposed drugs from the DrugRepV database. The table includes the information of the repurposed drug, primary indication, secondary indication, inhibition efficiency and references (Table 1).

Viruses

We have analyzed the viruses, against which the drugs have been repurposed. We found that most tested viruses are ZIKV, CHIKV, DENV, EBV, HIV, IFV, MERS, SARS and SARS-CoV-2 with 1475, 1371, 900, 868, 790, 422, 401, 380 and 342 cases (Figure 2B).

Drug targets

All the drug entries recorded in the literature were used to extract the targets. Topmost targets are P35367 (histamine H1 receptor); P35348 (alpha-1A adrenergic receptor); Q7ZJM1 (integrase); P14416 (D(2) dopamine receptor); P20839

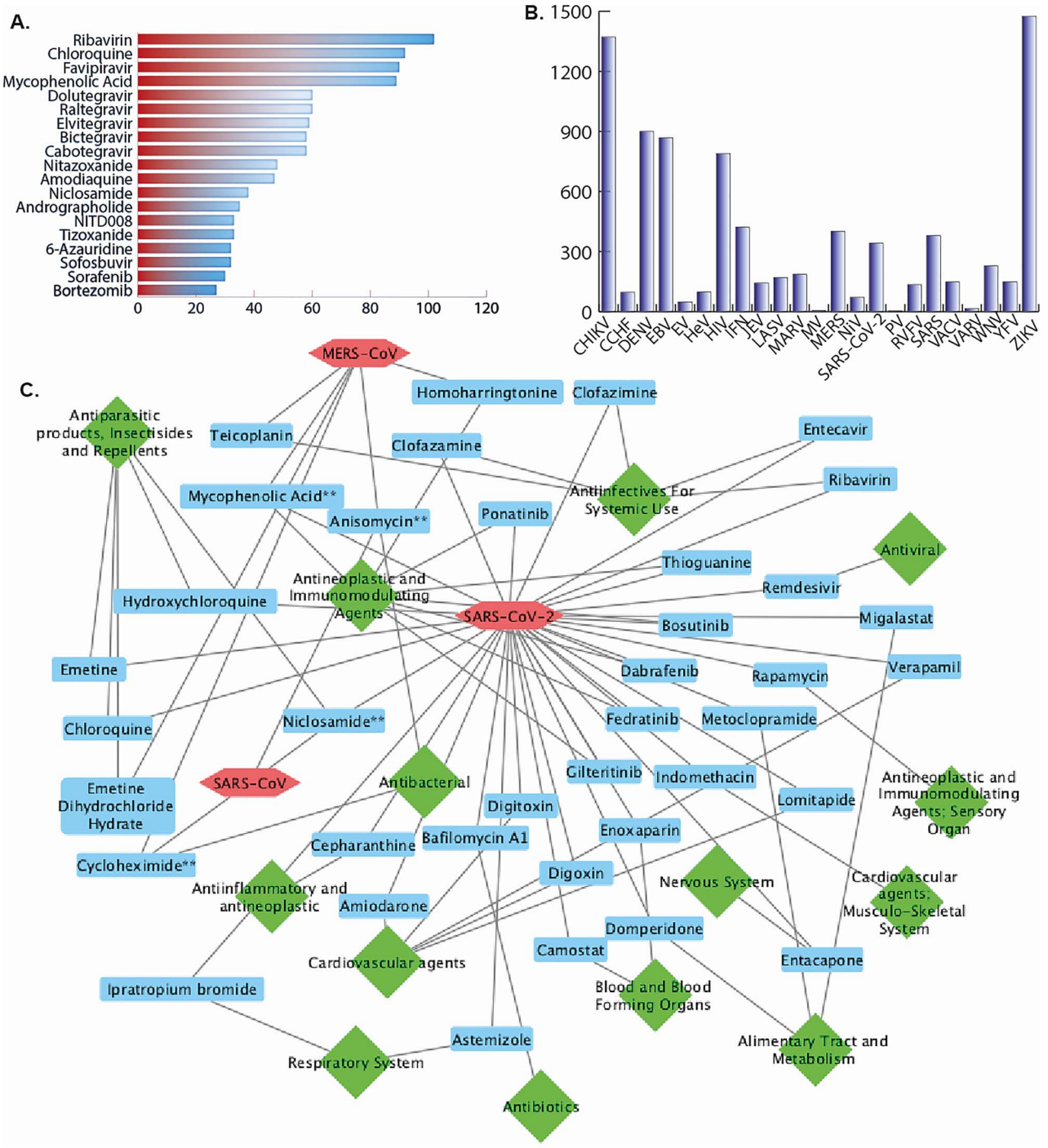

Figure 2. Data statistics of DrugRepV (A) repurposed drugs, (B) viruses, (C) interaction network showing the highly efficient repurposed drugs having < 1 μM IC_{50}/EC_{50} among coronaviruses namely SARS, MERS and SARS-CoV-2. Hexagon shape (pastel red color) represents the virus, rectangle shape (light blue color) displays repurposed 'drug' and diamond shape (green color) shows drug-categories. Drugs tested for two viruses are denoted with ** sign.

(inosine-5′-monophosphate dehydrogenase 1); P12268 (inosine-5-monophosphate dehydrogenase 2); P28223 (5-hydroxytryptamine receptor 2A) and P35368 (slpha-1B adrenergic receptor) in 269; 251; 237; 228; 225; 217; 211 and 209 cases, respectively. Diagram showing the frequently used drug targets in repurposed antiviral drugs is shown in Supplementary Figure S1B.

Drug category

The drugs which have been entered in our database were grouped into several drug categories. The majority of the drugs were categorized as 'antiinfectives for systemic use' in 884 entries. However, other drugs fall in categories like 'antineoplastic and immunomodulating agents'; 'antiparasitic

Table 1. Table showing the information of majorly used antiviral drugs with the information of primary indication, secondary indication, inhibition efficiency' and references

Repurposed drugs	Primary indication	Repurposed indication	Inhibition efficacy	References
Ribavirin	HCV	CHIKV	EC50 = 2.5 ± 0.3 μM	[23]
		CCHV	IC50 = 0.04 ± 0.01 mM	[24]
		DENV	EC50 = 7.7 ± 0.6 μM	[25]
		EBV	EC50 = 60.1 μM	[26]
		MERS	EC50 = 9.99 ± 2.97 μM	[27]
		SARS-CoV-2	EC50 = 26.739 μg/ml	[28]
		SARS	EC50= >100 μM	[29]
		ZIKV	EC50 = 12 ± 6.6 μM	[30]
Chloroquine	Malaria	SARS-CoV-2	EC50 = 5.47 μM	[31]
		SARS	EC50 = 3.3 μM	[32]
		MERS	EC50 = 3.0 μM	[32]
		EBV	EC50 = 16 μM	[33]
		CHIKV	EC50 = 10 ± 5 μM	[34]
Favipiravir	IFV	ZIKV	EC50 = 22 ± 15 μM	[30]
		RVFV	EC50 = 5 μg/ml	[35]
		SARS-CoV-2	EC50 = 61.88 μM	[36]
		NiV	EC50 = 14.57 μM	[37]
Mycophenolic Acid	Organ rejection (immunosuppressants)	SARS-CoV-2	IC50 = 20 nM	[38]
		WNV	IC50= > 100 μg/ml	[39]
		MERS	EC50 = 0.17 ± 0.03 μM	[40]
		EBV	IC50 = 0.96 μg/ml	[41]
		LASV	IC50 = 0.34 μg/ml	[41]
Nitazoxanide	Diarrhea	IFV	EC50 = 1 μM	[42]
		ZIKV	Log Reduction= > 100 fold	[43]
		SARS-CoV-2	EC50 = 2.12 μM	[44]
		MERS	IC50 = 0.92 μg/ml	[45]
		CHIKV	EC50 = 3.01 ± 0.61 μM	[46]
Amodiaquine	Malaria	SARS-CoV-2	EC50 = 1832.7 mg/ml	[28]
		ZIKV	EC50 = 3.07 ± 0.36 μM	[47]
		MARV	IC50 = 2.3 μM	[48]
		DENV	EC50 = 7.41 ± 1.09 μM	[49]

products, insecticides and repellents'; 'nervous system'; 'cardiovascular system' and 'antiviral' with 688; 465; 461; 366 and 317, respectively. Frequently used drug categories are depicted as pie charts in Supplementary Figure S1C.

Taxonomy

The 23 viruses in the database were also explored on the basis of the taxonomy. Majorly explored viruses are from the *Flaviviridae* family with 2895 entries. Further, the viruses from *Togaviridae*, *Coronaviridae*, *Filoviridae*, *Reteroviridae* and *Orthomyxoviridae* family have 1371, 1123, 1054, 790 and 422 entries, respectively. The distribution of taxonomy is shown in Supplementary Figure S1A.

Network-based analysis

We constructed the network of the highly efficient drugs ($IC_{50}/EC_{50} < 1$ μM) from the families of the 23 viruses. The network-based analysis of the *Coronaviridae* family viruses like SARS-CoV-2, SARS and MERS is shown in Figure 2C. To build a network, we have used drug, virus and drug categories as input in the Cytoscape software. We have used different shapes and colors to represent the virus (hexagon shape having Pastel Red color), drug (rectangle shape with light blue color) and drug-categories (diamond shape with green color). Further, we have used a single color for edges. We have developed graphs for those drugs whose efficacy (IC50/EC50) is less than 1 μM and excluded those whose drug category information is not given. Drugs tested for two or three viruses are denoted with ** and *** signs, respectively. For example, anisomycin and cycloheximide drugs are found in SARS and MERS. Mycophenolic acid is found in MERS and SARS-CoV-2. Niclosamide drug is found in SARS-CoV-2 and SARS as shown in Figure 2C. However, the network of the virus families like *Filoviridae, Flaviviridae, Orthomyxoviridae, Retroviridae* and *Togaviridae* are shown in Supplementary Figures S2–S6.

Web server

DrugRepV web server is the first dedicated repository for repurposed antivirals. It contains browse and search options for the exploration of data. To make the database more user-friendly, we provide help and frequently asked questions on web pages. To summarize the important fields of the data, we provide statistics web pages for the fields like drugs, drug categories, drug targets, viruses and disease categories. Freely available at: https://bioinfo.imtech.res.in/manojk/drugrepv/.

Browse

The database can be explored by the 'browse' option. The data can be browsed by fields like viruses, chemicals, drugs, drug targets, disease categories, clinical trials and PubMed. The 'browse' is displayed in two web pages. The first page

provides information on a few important fields like DrugRepV IDs, drug name, drug type, primary indication, secondary indication, virus strain, pathways, assay, activity, clinical status and references. In the second page, each entry is expanded as biological, chemical, structural and clinical information. The diagrammatic representation of the 'browse' option is shown in Supplementary Figure S7.

The 'biological information' contains primary indication (disease and disease category), secondary indication (approaches, methods, model system, mode of viral infection, time and duration of drug delivery, drug concentration, inhibition type and references). The 'chemical information' consisted of IUPAC name, SMILES (canonical and isomeric), molecular formula, molecular weight, InChl, common names and Synonyms. The 'structural information' provides 2D and 3D structure of each drug. The 'clinical information' has clinical trial phases and links to clinicaltrials.gov.

Search

The 'search' page is used to explore the desired query. The entries can be searched by DrugRepV_ID, drug Name, the primary target, the secondary target, assay, diseased category and PubMed ID. The biological, chemical, structural and clinical information of each entry is being displayed for the query.

Hyperlinking with external databases

To make our database highly informative, we have hyperlinked it with various resources. Chemical information is linked to PubChem and ChemSpider, whereas the DrugBank provides the details of each drug. Further, for clinical status the entries are linked to Clinicaltrails.gov. The NCBI-Taxonomy browser was used for retrieving the taxonomy of viruses. However, WHO and CDC databases were linked to get more information about viruses. Finally, the PubMed repository was used for references.

Webpages

The DrugRepV database is made on the apache server in a Linux environment. The front end is linked to the server PHP, Javascript, Perl and HTML, whereas the back end the database was linked via MySQL (relational database).

Discussion

Viruses are responsible for various pandemics/epidemics with very high mortality rates. The designing of an effective antiviral remains a challenge for the scientific community. For the same, drug repurposing emerged as a powerful tool, which reduces both time and cost for developing successful antivirals [50, 51]. In the current study, we provide all the experimentally validated repurposed antivirals in the form of a repository named 'DrugRepV'. On analyzing the viruses against which drugs were repurposed, we found that attempts were made almost against all the major viruses. But the repositioning seems to be utilized extensively against viruses responsible to cause epidemics and pandemics like SARS-CoV-2, SARS, MERS, ZIKV, DENV, EBV, CHIKV, IFV, etc. [50, 52–54].

Existing antiviral drugs are a preferred choice for repurposing against other viruses [55]. In this endeavor, the antiviral drugs ribavirin, Favipiravir and many more were repositioned against viruses [37, 56]. Ribavirin initially used to treat HCV [57], and viral haemorrhagic fevers has now been tested for ZIKV, RVFV, CHIKV, CCHV, MARV, NiV, MERS, IFV, EBV, LASV, DENV, SARS-CoV-2, HIV and WNV. It shows the good inhibition efficacy (IC_{50}/EC_{50}) of 0.02 μM and 0.1 μM for DENV and SARS-CoV-2, respectively. The Favipiravir with the trade name Fabiflu was used to treat IFV [58]. Later, it is checked for antiviral activity against NiV, IFV, ZIKV, CHIKV, DENV, HeV, MARV, CCHV, EBV, SARS-CoV-2, LASV, RVFV and YFV. Among them the Favipiravir shows high inhibition efficiency (IC_{50}/EC_{50}) of 1.03 μM and 1.9 μM against CCHV and CHIKV correspondingly. The Sofosbuvir drug with the trade name Sovaldi was originally used as an anti-HCV drug. However, it is also showing promising results against CHIKV, YFV and ZIKV with the inhibition efficiency (IC_{50}/EC_{50}) of <5 μM. Furthermore, the antiparasitic drug Chloroquine (antimalarial) also proved effective against SARS-CoV-2, SARS, MERS, EBV, CHIKV, etc. [31, 32]. However, Mycophenolic acid, an immunosuppressant, shows promising results against various epidemics and pandemics causing viruses like SARS-CoV-2, SARS, MERS, etc. [38, 39].

The understanding of the drug targets is important to increase the efficiency of drug repurposing approach. Thus, we identified the target of all the drugs reported in our database. Among all the drug targets, the histamine H1 receptors, Alpha-1A adrenergic receptor and integrase have been extensively used. The histamine (H1, H2, H3 and H4) and alpha-1A adrenergic receptors are a class of GPCRs. The H1 expressed in peripheral tissues and the central nervous system, and it is responsible for modulating the allergic responses. It has also been found effective for filoviruses like EBV and Marburg [59]. Various antivirals are shown to target the alpha-1A adrenergic receptors among viruses [60]. However, the integrase is a viral enzyme, which integrates the retroviral DNA in the host genome. Therefore, it is one of the most popular targets for the promising antiviral drugs [61].

The DrugRepV database is the first manually curated repository for repurposed drugs tested for their antiviral activities. There are a few databases available in the literature describing repurposed drugs candidates e.g. 'Drug Repurposing Hub' and 'RepoDB' [62]. The Drug Repurposing Hub database comprises hand curated and annotated repurposed drugs, which are categorized as FDA-approved, clinical trials and preclinical drugs [63]. It has 6798 unique entries and 670 drug indications for various diseases like cancer, diabetes, microbial infections, etc. But it contains only 60 entries as antivirals. The RepoDB database contains 6677 approved drugs against various diseases [14]. It contains data extracted from the DrugCentral and ClinicalTrials.gov. However, the RepoDB database has only 15 entries of the drugs repurposed against viruses. Therefore, with 8485 entries DrugRepV serves as a comprehensive resource of experimentally validated drugs repurposed as antivirals.

The DrugRepV database would be of immense importance for the researchers working in the field of antiviral drug discovery. As the development of the novel drug candidate is a time-consuming process. Thus, drug repurposing proves to be a successful strategy to get effective drug candidates. For example, for SARS-CoV-2 causing the recent pandemic also our database contains about 342 repurposed drug entries tested for *in vitro* or *in vivo* antiviral activities. It has about 183 unique repurposed drugs and of which 144 have efficacy in terms of IC_{50}/EC_{50} value. We searched these repurposed drugs in the ClinicalTrials.gov database to know whether these drugs with <1uM IC_{50}/EC_{50} value have clinical potential. We found several repurposed drugs candidates incorporated in our database have entered various stages of clinical trials for SARS-CoV-2 e.g. ritonavir, ivermectin, nitazoxanide, baricitinib, remdesivir, favipiravir, etc. This demonstrates the utility of our 'DrugRepV' resource for

SARS-CoV-2. We anticipate high success rates for other viruses also on further exploitation of the repurposed candidates with better IC_{50}/EC_{50} efficacies. As the discovery of the novel drug candidates is a time consuming and costly process, thus, this database would provide insights to speed up the antiviral drug for COVID-19 using repurposing approaches [64].

We performed the initial network-based analysis for the viruses responsible to cause epidemics and pandemics as shown in Figure 2C and Supplementary Figures S2–S6. From the network analysis, we can opt for the shared drugs between more than one virus, as promising targets as antiviral drugs. The DrugRepV data have further implications in identifying and prioritizing the new repurposed candidates using numerous approaches. For example, we can infer new repurposed candidates through detailed network analysis combining drug and target data. Moreover, the molecular docking studies can be performed on the basis of antiviral drugs and their efficacies. Likewise, the machine learning algorithms (support vector machine, random forest, artificial neural network, deep learning, etc.) based predictive methods could be developed to identify potential repurposed drug candidates. Further, the extension of this work would be the compilation of the repurposed drugs against diseases like cancer, bacteria, diabetes and many more.

DrugRepV is the first comprehensive one-stop platform for all the drugs and chemicals repurposed against viruses. This initiative would prove to be a successful step for speeding up the discovery of effective antivirals. The repository comprehends all the information from various external resources, which further make this database a complete package. The frontends of the DrugRepV are designed in a highly user-friendly manner, which can be easily accessible. We anticipate that this dedicated and comprehensive resource would help the researcher in antiviral drug development.

Key Points

- 'DrugRepV' is the first dedicated repurposed drug repository for 23 viruses causing epidemics and pandemics.
- It harbors 8485 repurposed drugs with biological, chemical, structural and clinical information.
- The user-friendly 'DrugRepV' web server can be browsed and searched in multivariate ways to get information of repurposed drugs against viruses.
- The database would be really helpful to speed up the research for developing effective antivirals against various epidemics/pandemics e.g. SARS-CoV-2

Supplementary data

Supplementary data are available online at *Briefings in Bioinformatics*.

Availability

The DrugRepV resource is an open access web server and available at https://bioinfo.imtech.res.in/manojk/drugrepv/. We will update the resource regularly at half yearly or when enough data are available.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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