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Review

Drug databases and their contributions to drug repurposing

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ABSTRACT

Drug repurposing is an interesting field in the drug discovery scope because of reducing time and cost. It is also considered as an appropriate method for finding medications for orphan and rare diseases. Hence, many researchers have proposed novel methods based on databases which contain different information. Thus, a suitable organization of data which facilitates the repurposing applications and provides a tool or a web service can be beneficial. In this review, we categorize drug databases and discuss their advantages and disadvantages. Surprisingly, to the best of our knowledge, the importance and potential of databases in drug repurposing are yet to be emphasized. Indeed, the available databases can be divided into several groups based on data content, and different classes can be applied to find a new application of the existing drugs. Furthermore, we propose some suggestions for making databases more effective and popular in this field.

1. Introduction

A drug is a substance that is designed to obviate/cure a particular disease/symptom, alleviate pain, or modify an anomaly of the body [1]. Given the usefulness of drugs, many companies and researchers carry out tremendous effort to design various drugs with different applications. However, drug design is a process which is laborious and time-consuming and needs galactic investment. Furthermore, only a few numbers of drug design projects are completed, and most of them fail during different rigorous development phases [2]. Having considered such challenges, many researchers and companies seek novel methods such as drug repurposing or repositioning for better management of diseases [3]. In drug repurposing methods, hidden therapeutic capabilities of drugs are discovered using diverse approaches, including computational manners [4], clinical experiments [5], and other in vitro approaches [6]. As some famous instances, Viagra and Thalidomide can be epitomized on the basis that they had been designed to reduce pulmonary arterial hypertension [7] and nervousness [8], while their applications have further been developed to cure erectile dysfunction and leprosy, respectively.

With the advancement of computer sciences, drug repositioning methods have been improved, and researches have also been accelerated. By applying information technology, several efficient drug repurposing methods have been proposed, including molecular modeling [9] and data mining [10] approaches. For instance, molecular docking methods have been exploited to investigate how a drug and a target can bind to each other and how much the energy exists among them [11]. To this end, different software applications have been developed based on various needs and techniques [12]. In the data-mining methods, hidden relationships between drugs and targets are discovered [13]. As a result, the acquired information is used for the discovery of drugs which can affect a particular biological target. These techniques are usually divided into three categories, including (i) the text mining [14], through which raw data of different sources are mined and organized for extracting information using efficient algorithms, (ii) the machine-learning [15], in which machines generate a model (e.g., artificial neural network, support vector machine, decision tree, random forests, and other machines) to be used for predicting drug-target interactions [16], and (iii) the network-based approaches [17], by which biological data (e.g., metabolic pathways, drug-target interactions, protein-protein interactions) are modeled as a network to be applied for obtaining novel information and finding new therapeutic properties of drugs. After predicting drug-target interactions, several databases such as MalaCards [18] and DisGeNET [19], which contain information related to diseases and genes, can be used for discovering new treatment benefits of the existing drugs.

In the drug discovery scope, databases are in the greatest level of importance given that they are the basis for drug repositioning methods. Hence, it is necessary that they are designed in a proper manner and included capabilities which help researchers to achieve

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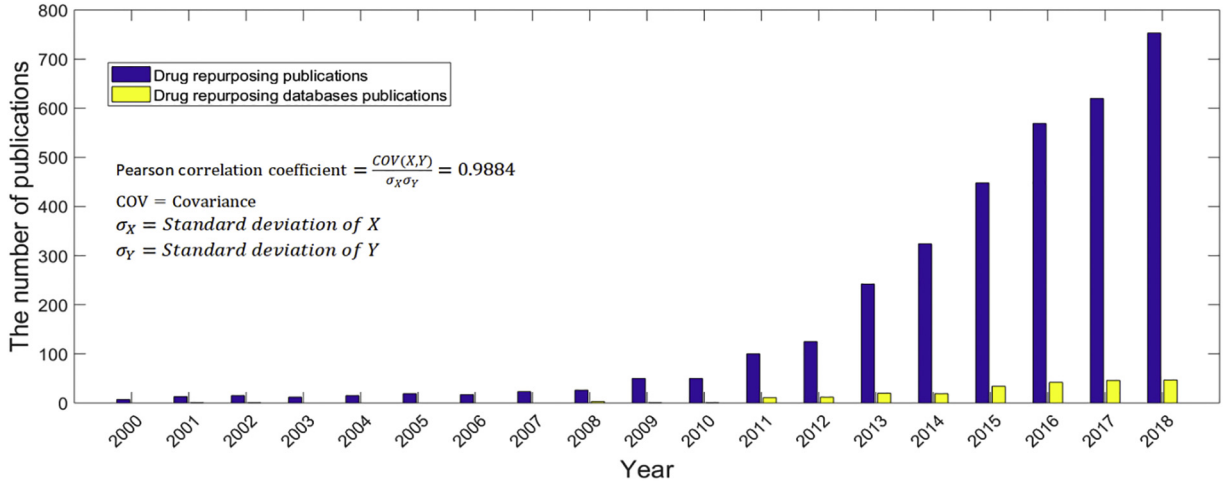

Fig. 1. The number of publications between 2000 and 2018. Blue and yellow bars show the number of publications for drug repurposing and specific databases for drug repurposing respectively. The number of drug repurposing researches has been enhanced with increasing the databases, providing possibilities for the repurposing applications with high Pearson correlation coefficient. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

better results. Fig. 1 represents a statistic of published researches related to drug repurposing. To obtain the statistics of *drug repurposing publications*, the search space was limited to papers consisting of "drug repurposing or repositioning" keywords in the PubMed section of NCBI [20]. Further, to acquire the statistics of *drug repurposing databases publications*, the outcomes of PubMed section of NCBI were confined to those consisting of "drug repurposing or repositioning" and "database" keywords. For the generated lists, a handheld curation was done. And then, the results were reported.

In Fig. 1, the number of publications, related to the drug repurposing and databases designed for it, is presented between 2000 and 2018 years. In range 2000 and 2010, the researches rate of drug repurposing is almost constant. After 2010, the number of researches is also enhanced with increasing the number of specialized databases for the drug repurposing. This can be due to providing suitable data and tools such as web services which mine and analyze them. The Pearson correlation value between the numbers of publications for drug repurposing and specific databases designed for it is acquired 0.9884. Given the value of the correlation coefficient, one can find a meaningful relationship between them. In this study, we investigated the role of databases in drug repurposing scope and discussed their limitations and advantages. Furthermore, we articulated some capabilities which might be useful in developing new ideas and improving the existing databases in this field.

2. A classification of databases and their contributions

Since emerging the drug repurposing in the drug discovery field, several databases (DB), which consist of various data, have been designed. Fig. 2 categorizes them based on their data content and applications in drug repositioning and describes how each of the categories may be used in drug design and drug repositioning.

i) Raw data DB: The databases of this category contain different data contents which are organized into some tables. Although these data are precious, and plenty of times have been spent on developing them; most of them do not involve data that are suitable for a specific view of drug repurposing. However, they may have hidden information which can be extracted by the data mining approaches and useful in developing new databases. In creating this type of DB, five data sources are used. In the first one, literature and their results of drug repurposing are gathered and arranged as a database [21]. In the second one, some expert persons are employed and educated for inserting data into a database manually [22]. Similar to the manual method, a large number of biologists have been involved in the curating process of the existing data [23]. Next, the curated data are systemized and published as a new database [24]. In the integrated class, disparate data are obtained from individual databases and are introduced as a new database which can accelerate and improve drug repurposing applications [25]. In addition to the mentioned sources, clinical data, which are in the highest level of importance and may lead to new scientific concepts for the repositioning of drugs, are placed in the fifth DB source of the raw data [26].

ii) Target-based DB: This category contains databases which hold drugs' targets, including genes [27,28] along with complement MAP database (CMAP) [29,30], RNAs such as long noncoding RNA (lncRNA), mutation information [31,32], proteins along with drug-protein connectivity MAP (DMAP) information [33], pathways [34], enzymes [35], side effects [36], or a collection of several targets [37,38]. Using the DB of this group, drug repositioning can be considered in a specific level. Some examples may be as follows: (a) GWAS (Genome-Wide Association) [39] and PheWAS (Phenome-Wide Association) [40] drug repurposing methods examine gene targets and evaluate their effects on a disease or vice versa. If a gene relates to a disease, drugs, which can inhibit it, are introduced for treating the anomaly. (b) Side effects are an interesting choice for the repositioning of drugs [41], in part because all of the side effects are not unfavorable while some of them (e.g., the sildenafil) may provide useful indications. (c) Both signaling and metabolic pathways are a proper option for curing orphan or rare diseases [42]. By investigating pathways, the main cause of a rare or orphan disease can be discovered. As a result, the drugs, which can prevent or induce the pathways, are analyzed and proposed for treating the disease. (d) LncRNAs are a class of transcribed RNAs which consist of more than 200 nucleotides. Although they do not code proteins, lncRNAs can inhibit or active genes. Hence, they can be considered as an attractive option for treating diseases.

iii) Specific DB: Some databases comprise data which are provided for a special application. These databases fit into the third category (Fig. 2) and encompass three diverse data, as follows: (a) Traditional medicine data [43], which is usually referred to use herbal drugs for curing diseases [44,45]. Like drug repurposing, these data can be used for discovering new usages of the existing herbs. Besides, it can be investigated that a herb can be replaced with a drug or not. If it can be done, there will be many advantages in exploiting

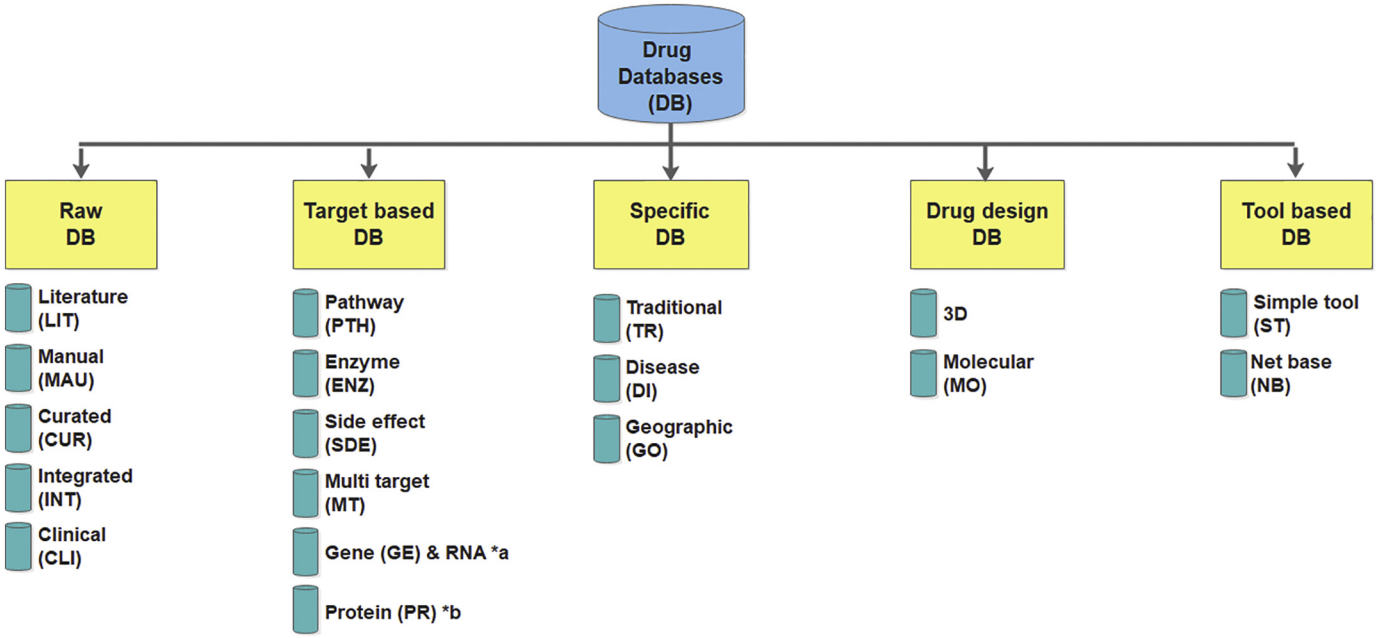

Fig. 2. A classification of the databases. The databases have been categorized based on data content. In the classification, the databases are divided into five classes, including raw data, target-based, specific data, drug design, and tool-based DB. Besides every sub-category, there is an abbreviation of it. *a: This class includes simple genes targets along with CMAP (Complement MAP Database), RNA, and mutation information. *b: This category consists of simple protein targets along with DMAP (Drug-protein connectivity MAP) information.

them because most of the herbs have not drug complications. (b) Disease-specific data [46,47], in which some databases have been designed for a determined disease such as HIV [48]. With preparing suitable data, researches can be precipitated, and novel treatment methods can be discovered. (c) Geographical DB [49] can be favorable in terms of diseases distribution as some diseases appear in a special area of the world. Therefore, geographical DB may lead to finding the reason for the diseases by comparing others and introducing the existing drugs for treating them.

iv) Drug design DB: These databases typically embrace data such as small molecules which have a low weight. Based on a biological target, a drug which can interact or connect to the target is designed. As we know, the process of drug design is time-consuming and expensive. Furthermore, many drug design projects fail, and only a few numbers of them can obtain FDA certificate. In fact, the existing drugs, which consist of similar molecules and can correctly bind to the target, can be investigated and proposed for the desired application. For this purpose, several databases, containing the 3D structure of molecules [50,51] and molecular replacement information [52], which are based on the resolved protein structures [53], have been developed. With proposing docking packages, web servers, and tools, drug repurposing researches based on 3D structures have also been extended. In this scope, software applications and databases which calculate the similarity score of two structures and hold the scores, experimental data, and reported results can be useful. Further, the obtained data may reveal novel side effects of the medications.

v) Tool-based DB: Databases, which consist of tools and web servers [54] for the repurposing usages, are placed in the fifth category [55]. These types of databases are usually based on the data gathered by other DB [56]. Conventionally, they are used to mine the data utilizing various methods such as network theory [57,58] and data mining approaches and then propose a list of predicted drugs for an entered drug. For validating drug repositioning researches, these tools can play an important role. For instance, a list of repurposed drugs for a specific drug, which is acquired by machine learning or other methods, can be compared with a list which is obtained by the tools. By doing this, the intersection of the lists can present significant relationships between the selected drugs and the predicted targets. Also, the results of the tools and web servers can lead to some relevant empirical studies.

3. The databases

So far, several databases, which have been developed, can be used for the repurposing of drugs or play a useful role in such a process. In addition to databases, the tools (TO), which have been developed based on the databases and may be used for the repurposing of drugs. After explaining them, their capabilities and content are investigated and discussed. The databases (DB), their abbreviations (ABR) used in this paper, web links, a short description of them, and their references (REF) are listed in Table 1. Fig. 3 presents the databases and their data contents that have already been categorized in Fig. 2. For example, the DrugB database includes enzymes, 3D structures, clinical drugs and targets, pathways, and side effects information. Also, for all the databases, their main category has been shown.

The existing databases face some limitations. With modifying them, their applications and popularities can be increased. Furthermore, they may speed up researches in the drug repositioning scope. The mentioned limitations are described below:

i) Availability: It is favorable that the published databases be accessible [59]. However, it is observed that some of them are not available after their publications. For instance, the PDTD (Potential Drug Target Database) is not available now and is out of service. In checking the availability of the related websites, an anti-filter is also used for enhancing reliability that the websites are not filtered to our location.

ii) Update: Although most of the databases are available and continue to their services, some of them (e.g., TCM (Traditional Chicness Medicine)) is not updated. In spite of that, most of them are upgraded from both data and web interfaces aspects. By updating the databases, new opportunities for the repositioning of drugs will appear [60].

Table 1
The investigated databases.

Group	DB/TO	Abr.	Weblink	Description	Ref
Raw data category	CMAP	CMAP	http://www.complement.us/cmap	CMAP includes experimental data curated by experts	[30]
	Drug repurposing hub	DHUB	https://clue.io/repurposing	It has created a huge library including repurposed drugs, news, tools, etc.	[21]
	THIN	THIN	https://www.ucl.ac.uk/	THIN has collected results related to drugs and diseases which are reported in different studies.	[26]
Target-based category	Drug signatures DB	DSDB	http://tanlab.ucdenver.edu/DSigDB	DSDB has been developed for hold drugs or compounds and their gene targets.	[27]
	Drug2Gene	D2G	http://www.drug2gene.com	D2G integrates drug-target information from 19 popular databases.	[31]
	DrugBank	DrugB	https://www.drugbank.ca/	DrugBank provides a comprehensive database of drugs, their different targets, 3D structure of them, and other useful information.	[34]
	Drug-path	DPTH	http://www.cuilab.cn/drugpath	DPTH contains pathways which are induced by drugs.	[22]
	GeneSetDB	GSDB	http://genesetdb.auckland.ac.nz/haeremai.html	GSDB is an integrated meta-database which interprets a list of genes.	[28]
	PDTD	PDTD	http://www.dddc.ac.cn/pdtd/	PDTD is an integrated database for identification protein targets.	[50]
	SIDER	SIDER	http://sideeffects.embl.de	SIDER contains the main targets of drugs and their side effects.	[36]
	Therapeutic target database	TTD	http://bidd.nus.edu.sg/group/ttd/ttd.asp	TTD has been developed for drug discovery based on target information.	[38]
	Tuberculosis drug resistance	TBDB	http://www.tbdb.org	For the repurposing applications, TBDB including gene expression data and their annotations has been extended.	[32]
Special category	DRUGSURV	DSRV	http://www.bioprofiling.de/drugsurv	DSRV holds information of experimentally repurposed drugs for oncology.	[47]
	HIV drug-resistance database	HIVRT	https://hivdb.stanford.edu/DR/	HIVRT covers information on drug resistance of HIV.	[48]
	Ontario	ODB	www.healthinfo.moh.gov.on.ca	ODB involves described drugs and their claimed indications in Ontario.	[49]
	SuperCYP	SCYP	http://bioinformatics.charite.de/supercyp	SCYP is a comprehensive database for cytochrome P450 (CYP) along with a tool to predict drugs which can interact with CYP.	[35]
	TCM	TCM	http://tcm.cmu.edu.tw/	TCM has been developed in Taiwan and consists of insilico drug screening of traditional medicine.	[43]
	TCMSP	TCMP	http://sm.nwsuaf.edu.cn/lsp/tcmsp.php	TCMSP is a database for drug discovery from herbal medicine.	[44]
	TDR	TDR	http://tdrtargets.org	TDR comprises tropical diseases information and can offer a list of genes for the repositioning applications.	[46]
Drug design category	CancerHSP	CHP	http://lsp.nwsuaf.edu.cn/CancerHSP.php	Anti-cancer herbs along with their molecular information are available in CHP.	[45]
	CheMBL	CHM	https://www.ebi.ac.uk/chembldb/	CheMBL consists of a large number of drug-like compounds for drug discovery applications.	[23]
	DMAP	DMAP	http://bio.informatics.iupui.edu/cmaps	To obviate the data limitation of CMAP, DMAP has been designed.	[33]
	PROMISCUOUS	PROM	http://bioinformatics.charite.de/promiscuous/	PROM has gathered various drug repositioning drugs using text mining methods.	[24]
	Swiss BIOisostere	SBIOS	http://www.swissbioisostere.ch	SBIOS incorporates information on molecular replacement and their biological effects.	[53]
Tool-based category	DRAR-CPI	DRAR	http://cpi.bio-x.cn/drar/	Using the adverse reaction of drugs on proteins, DRAR predicts their interaction based on the collection of drug molecules.	[52]
	DrugMap central	DMC	http://r2d2drug.org/DMC.aspx	DMC includes a tool which integrates multi data from various sources and proposes a list for drug repositioning studies.	[37]
	DrugNet	DNET	from http://genome2.ugr.es/drugnet/	DNET integrates heterogeneous data and prioritizes effects of drugs on diseases.	[58]
	DTome	DTOM	http://bioinfo.mc.vanderbilt.edu/DTome	It is a tool which helps to understand the molecular mechanism of drug bioactivities.	[57]
	DT-Web	DTW	http://alpha.dmi.unict.it/dtweb	Based on DrugBank data, it provides a network-based drug-target prediction tool.	[54]
	e-Drug3D	D3D	http://chemoinfo.ipmc.cnrs.fr/e-drug3d	D3D contains the 3D chemical structure of drugs and fragment-based information.	[51]
	KsRepo	KSRPO	http://github.com/adam-sam-brown/ksRepo	KSRPO encompasses a tool for predicting drug-target interactions in the gene level.	[25]
	NFFinder	NNFIN	http://nffinder.cnb.csic.es	NNFIN searches similar transcriptome data in different contexts.	[55]

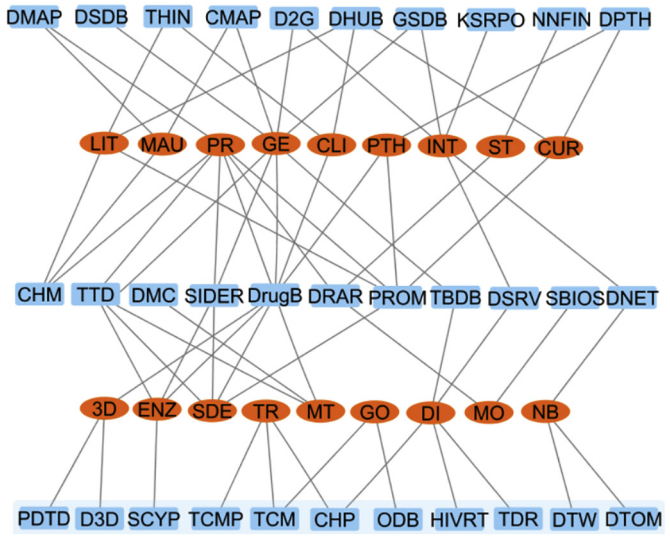

Fig. 3. The databases and their main contents. Blue and orange colors show the databases and their main contents, respectively. By searching the figure, a user can find the main content of a database and vice versa. For example, the D2G database consist of integrated and gene data. CHM: CheMBL; DrugB: DrugBank; ODB: Ontario database; THIN: The Health Improvement Network; TCM: Traditional Chicness Medicine; TBDB: Tuberculosis Database; TTD: Therapeutic Target database; PDTD: Potential Drug-Target Database; TDR: Tropical Diseases Research; HIVRT: HIV Drug Resistance Database; TCMSP: Traditional Chinese Medicine Platform; SCYP: Super Cytochrome P450; DHUB: Drug Repurposing Hub; DSDB: Drug Signatures Database; PROM: Promiscuous; DRAR: Drug Repurposing Adverse Reaction; DMAP: Drug-Protein connectivity MAP; CMAP: Complement MAP database; DMC: Drug Map Central; SIDER: Side Effect Resource; KSRPO: A platform for drug Repositioning; NNFIN: Network-based similarity finder; DSRV: Drug survival database; CHSP: anti-Cancer Herbs database for System Pharmacology; D2G: Drug to Gene; GSDB: Gene Set Database; SBIOS: Swiss BIOisostere; DTOM: Drug Target interactome database; DPTH: Drug Pathway database; DTW: Drug Target Web; DNET: Drug-disease Network database. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

iii) Tool: To elevate the capability and popularity of the databases, some of them (e.g., SCYP (Super Cytochrome P450)) have provided a suitable tool for the repurposing of drugs. Nevertheless, having a tool is not considered in the definition of a database. Instead, providing information retrieval and storage capabilities are discussed [61].

iv) Advanced search: It is referred to as supply ability for quickly retrieving data. For example, DrugB (DrugBank) incorporates the capability, whereas some others like THIN (The Health Improvement Network) do not involve it. In this paper, SQL query [62] power is not noted as an advanced search and explained in the next case.

v) Query: Several databases such as DHUB have their query language. Of note, a standard query language (SQL) is a declarative database language which can join, summarize, select, classify, project, encrypt, decrypt, and restrict data in such a straightforward manner [63]. In addition, a database management system (DBMS), which supports the SQL, optimizes the expressed queries using efficient methods [64]. Therefore, queries are executed with high performance and reliability. Except for DrugR+, none of the databases provide the SQL features.

vi) Export: The existing databases include useful information which can be searched using various methods. After showing the results, it will be great for researchers if they can obtain them as an individual file for further processing. To this end, several databases (e.g., TDR (Tropical Disease Research)) have created the export capability.

vii) An application programming interface (API): It is a web programming concept, which enables client-side to exploit a database using a systematic programming method [65]. By using an API, expert users can acquire their desired results and then utilize them for the repositioning of drugs [66]. Thus, databases like CheMBL provide great capability in terms of data mining.

viii) Responsive: With developing and prevailing mobile technologies, many commercial companies and financial institutes have made a huge investment in offering their services on mobile platforms [67]. Meanwhile, different studies have investigated the effect of mobile technology in accepting and extending services [68]. Hence, it seems that a database provided for the repurposing applications will be more accessible and practical if it can be used in mobile platforms.

ix) Full download: Although some databases have fascinating and helpful abilities, all part of them is not downloadable. In some cases, users need to download all data and put their methods on them. For that reason, all part of a database must be downloadable in a proper manner. From this point of view, databases (e.g., TBDB (Tuberculosis Database), TDR, TTD (Therapeutic Target Database), THIN, DSDB (Drug Signatures Database), and TCM) are fully downloadable, but not the graphical 3D structures of DrugB.

x) Classified structure: The drug databases have a large size and contain different information [69]. Thus, categorizing them into several parts can enable the users to obtain their required data in an appropriate approach. However, most of the databases have classified their data; some others such as ODB (Ontario Database) have not grouped their data.

xi) Free: A drug database development is a time-consuming and complicated project, which needs experts and enough investment [70]. Accordingly, some developers limit their users to pay a charge in order to get data or use the capability of their database. Even, some of them request to submit and validate the information. For instance, users must buy a license for applying its API. Free drug databases accelerate academic researches and can lead to discoveries in the drug repurposing area.

Based on the mentioned capabilities, the key databases and their abilities using tick marks are listed in Table 2.

As Table 2 shows, DrugR+, CheMBL, and TDR have more capabilities relative to others based on the mentioned criteria. Based on data type and the contribution of the databases discussed above in the repositioning of medications, the following categories can be created:

i) Raw databases: This class covers databases that hold primitive information of drugs and their targets. Usually, text mining and machine learning methods are suitable approaches for the repositioning of drugs. The databases, which fit into this class, are as follows: (a) THIN database consists of general practices information of drugs in which age, gender, socioeconomic, and other parameters are considered. Based on the reported results, the effectiveness of drugs in different conditions can be discovered. Moreover, these data show that drug repositioning can be considered in various states which are ignored in related works. Hence, new drug repurposing opportunities can be introduced. (b) ODB includes prescribed medications related to patients in Ontario. As we know, genomic information of live creatures is slightly different from each other in divergent parts of the world. Therefore, the efficacy of drugs on targets may be varied from one place to another one. Meanwhile, the reported data may manifest new indications or usages for the existing drugs. (c) HIVRT has been developed for holding information about HIV disease and medicines which can prevent or inhibit it. Its data covers surveillance and antiretroviral information of medications along with drug-resistant viruses which their mutations frustrate the efficacy of drugs. To this end, drug repositioning can be a promising remedy method because of saving

Table 2
A comparison of the database based on their capabilities.

DB/TO	Available	Update	Tool	Advanced search	Query (SQL)	Export	API	Responsive	Full download	Classified structure	Free
CHM	✓	✓		✓		✓	✓		✓	✓	✓
DrugB	✓	✓		✓			✓	✓		✓	✓
ODB	✓	✓									
THIN	✓	✓									
TCM	✓			✓					✓	✓	✓
TBDB	✓					✓			✓	✓	✓
TTD	✓	✓		✓					✓	✓	✓
PDTD			✓								
TDR	✓	✓	✓	✓		✓		✓	✓	✓	✓
HIVRT	✓	✓								✓	
TCMSP	✓	✓									✓
SCYP	✓	✓	✓							✓	✓
DHUB	✓	✓				✓	✓	✓			
DSDB	✓								✓	✓	✓
PROM	✓		✓	✓							✓
DRAR	✓		✓								✓
DMAP	✓	✓		✓						✓	✓
CMAP	✓	✓		✓						✓	
DMC			✓								
SIDER	✓	✓							✓	✓	✓
KSRPO	✓		✓						✓		✓
NNFIN	✓		✓				✓				✓
DSRV	✓										✓
CHSP										✓	
3D	✓	✓							✓		✓
D2G										✓	
GSDB	✓			✓					✓	✓	✓
SBIOS	✓	✓	✓								✓
DTOM			✓								
DPTH	✓								✓		✓
DTW	✓		✓								✓
DNET			✓								✓
DrugR +	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓
SUT	✓	✓		✓						✓	✓
DTC	✓	✓		✓			✓	✓	✓	✓	✓
KEGG	✓	✓		✓			✓		✓	✓	✓

CHM: CheMBL; DrugB: Drug-Bank; ODB: Ontario database; THIN: The Health Improvement Network; TCM: Traditional Chicness Medicine; TBDB: Tuberculosis Database; TTD: Therapeutic Target database; PDTD: Potential Drug-Target Database; TDR: Tropical Diseases Research; HIVRT: HIV Drug Resistance Database; TCMSP: Traditional Chinese Medicine Platform; SCYP: Super Cytochrome P450; DHUB: Drug Repurposing Hub; DSDB: Drug Signatures Database; PROM: Promiscuous; DRAR: Drug Repurposing Adverse Reaction; DMAP: Drug-Protein connectivity MAP; CMAP: Complement Map database; DMC: Drug Map Central; SIDER: Side Effect Resource; KSRPO: A platform for drug Repositioning; NNFIN: Network-based similarity finder; DSRV: Drug survival database; CHSP: anti-Cancer Herbs database for System Pharmacology; D2G: Drug to Gene; GSDB: Gene Set Database; SBIOS: Swiss BIOisostere; DTOM: Drug Target interactome database; DPTH: Drug Pathway database; DTW: Drug Target Web; DNET: Drug-disease Network database; SUT: SuperTarget database; DTC: Drug Target Commons; KEGG: Kyoto Encyclopedia of Genes and Genomes.

time and cost. (d) DHUB has provided a library for the repurposing applications and new achievements related to the mentioned area. For instance, it involves articles, news, previously repurposed drugs, and many other data published in this field. To search and acquired data, it supplies a query language with a specific syntax. (e) DRAR is a library for drugs and their side effects which are known adverse reactions of drugs. Besides the data, it comes up with a web service which accepts a drug or a molecule and suggests a potential list of indications for the entered drug. In getting the list, the interaction between drugs and targets are investigated, and the obtained results are compared with those acquired based on the gene-expression profile. (f) 3D fits into the class of databases which contain 3-dimensional chemical structures of drugs and data related to fragment-based drug design. To enhance the effectiveness of a drug on a target, it is essential that they lock suitably. Based on the 3D structure information, docking methods search a form in which medication and a target have a more stable connection. (g) CHSP contains information about the pharmacological effects of herbs on cancerous diseases. The mechanism of action of some natural products and their bioactivity properties are astonishing and can lead to new opportunities for the repositioning of drugs. Further, some databases such as RNAcentral [71], NONCODE database [72], lncRNAdb [73], and lncRNADisease [74] compromise RNA information and can be useful in researches which examine the interactions between drugs and RNAs.

ii) Experimentally curated databases: This class of databases comprehends raw data which have been curated by experts. Like the first category, text mining and machine learning methods are suitable approaches for the repositioning of drugs. The databases, which fit into this class, are as follows: (a) KEGG [75] and CheMBL are large databases which contain drug-like bioactive compounds and their useful information such as absorption, distribution, metabolism, excretion, and toxicity (ADMET). To guarantee the quality of data, experts have followed several rigorous data curation steps in them. Although KEGG and CheMBL have not been designed for the repurposing of drugs, they may be used for it by providing a tool which mines its data and proposes a list of potential medications. Also, preparing SQL query and response capabilities will make them more applicable. Considering the importance of KEGG and CheMBL, some databases have been established based on them. For instance, DPTH consists of signaling pathways data which are taken from KEGG and enriched. The data enables researchers to discover medications for the orphan and rare diseases using signaling pathways induced by the disorders. (b) DrugBank is one the most critical databases in drug discovery scope and contains comprehensive information of drugs and their various targets such as genes, proteins,

enzymes, and different type of pathways. Whereas some databases hold predicted drug-target information, its data incorporates experimentally validated and approved data. Thus, most of the researches have been done based on these data in order to obtain real-world results. (c) TTD consists of drugs and their targets information. In comparison to DrugBank, TTD provides information with details and determines how much a drug affects a target. In addition, it includes some synergic effects of medicines, knockout genes, clinical trials efforts, etc. (d) Tuberculosis comprises information of mutations related to viral targets. Using this database, drug discovery researches can be accelerated, and novel ideas can be made up for the repurposing of drugs. (e) SIDER includes information about side effects of drugs or their adverse reactions which have reported clinically. This database is a convenient choice for drug repurposing methods which are based on phenotype consequences. (f) TCM is a database embracing traditional chines medicine information. In this database, 3D structures of small molecules, which have a low molecular weight and can be used in virtual screening and molecular simulation studies, are accessible. For the mentioned applications, TCM has provided a web-based query capability which enables users to search ingredients, small molecules, and substructures.

iii) Integrated databases: The databases, gathering data from different sources, place in the combined group. Integrating the existing data enables computational methods to obtain more accurate and useful information. The databases, which can be considered in this class, are as follows: (a) TCMSP has been developed based on an interesting and traditional idea in which herbal drugs treat diseases. In addition to several herbal ingredients, this database takes in pharmaceutical properties of herbs. It seems that drug repositioning concepts can be extended to herbal repurposing, and their method can also be used in this area. (b) SCYP keeps information related to cytochrome P450, which is an enzyme responsible for repulsing toxic materials. This enzyme considers a drug as a poisonous compound which must be metabolized. Accordingly, some drugs lost their usefulness because they are discarded and cannot interact with the targets. In these conditions, combination therapy may be an appropriate option for enhancing the effectiveness of a drug. (c) DMAP embraces drugs and their protein targets and has been designed to conquer the data limitation of CMAP. For the repositioning utilization, it scores the efficacy of a drug on the protein targets. Using the earned outcomes by the systematic method, new applications for an entered drug can be explored and discovered. (d) DMC is an integrated database comprehending chemical information, drug-targets, and signaling pathways. Furthermore, its web-service supports a query language which looks for data in multiple levels and predicts new indications for the current drugs. (e) KSRPO gathers gene expression data (related to prostate cancer) from various sources and presents them as a comprehensive database. Like some databases, it provides repositioning capabilities and computationally predicts drugs which can affect prostate cancer. (f) DSRV, encompassing some datasets related to cancer diseases, introduces new usages of drugs with applications in oncology and ranks them based on patient survival information. Therefore, the role of this web-based database is critical in the health area. However, the repurposing methods only suggest a potential list of drugs for a specific disease, and the practical experiments will determine how much the generated list is useful. (g) D2G collects data from 19 public databases and displays them as an integrated database. The main idea of D2G is that the consolidated data manifest relationships between drugs and targets in an appropriate manner. Hence, the studies related to drug discovery can accelerate. (h) GSDB examines genes from the set perspective and enriches them. Its data is a collection of genes which have been gathered from 26 public datasets. In collecting data, the developers have focused on pharmacology and human diseases information. Also, SuperTarget [76] and DTC [77], consisting of useful information such as drugs and their various targets, have provided a proper platform to consensus drug-target interactions.

iv) Computational databases: In addition to data, This category of databases comes up with a tool which mines the existing data and proposes a list for the repurposing benefits. Some examples of the databases, fitting into the computational class, are as follows: (a) TDR, which consists of pathogens and genomic data, prioritizes genes and includes a tool which predicts drug-gene interactions. The main goal of TDR is to facilitate identifying potential drugs for tropical diseases. By creating SQL query or API capabilities, it will be more convenient for the repositioning of drugs. (b) DrugR+, existing at (http://drugr.ir), facilitates drug repurposing applications using data mining methods [78]. To this end, DrugR+ looks for drugs-targets, the mechanism of action of drugs on targets, and drug-drug adverse reactions. Next, the acquired results are ranked based on the number of side effects. Besides drug repurposing applications, the list may be used for combination therapy [79]. (c) DSDB is a gene-based database and covers gene information, drugs, and some of the compounds which affect gene targets. Because the expressing of a gene may lead to the expressing others, they are analyzed and considered as a set. For this purpose, DSDB has proffered a tool which can be used for gene set enrichment. (d) PDTD, placing insilico target identification methods, is a web-based database which contains the 3D structure of proteins and provides data which are proper for docking applications. By applying it, potential targets which can interact with the specified drug are introduced. (e) PROM organizes data based on network concepts and predicts new usages for the existing drugs with considering side effects. In the data collection phase of PROM, data mining methods such as text mining have been employed for acquiring drug-target and protein-protein interaction information. After that, a handheld data annotation has been done to enhance data legibility. In PROM, various reported information like approved, clinical trials, and withdrawn drugs can be found. (f) NNFIN searches transcriptomic data to find similar information. When the homologs data are discovered, the drugs may be repositioned from the previous application to the new one. This method is one of the most important methods for treating orphan or rare diseases. (g) SBIOS, which can be used for the repurposing of drugs and ligand design, has provided a way for the phase problem in which physical information of molecules are disappeared. For this purpose, it mines solved proteins information and fulfills this gap using the obtained results. (h) DNET supplies drug repurposing capability based on network concepts. To this end, it combines heterogeneous genomic data and then prioritizes drugs based on an entered disease or vice versa. In addition to the databases mentioned above, there are also several tools that rely on them. For instance, DTOM has been provided a repurposing tool based on DrugBank data, or DTW constructs a bipartite network based on DrugBank for the repositioning applications.

4. Conclusion

Drug repurposing is an emerging field in drug discovery scope, which aims to find new applications for the existing drugs. Once applied, the time and cost of drug development can be saved, and an appropriate remedy for the orphan and rare diseases may be realized. Given the value of the correlation coefficient between published databases and articles for the repositioning of drugs, it seems that there is a significant connection between the publication of databases and the publication of drug repurposing studies. Therefore, designing and developing suitable databases can lead to better results in this area. Surprisingly, to the best of our knowledge, the importance and potential of DBs in drug repurposing are yet to be emphasized. Based on data content, the available databases can be divided into several groups, and

different classes can be applied to find a new application of the existing drugs. For example, the raw data category includes hidden information that can be extracted by data mining methods. Next, the acquired knowledge can be examined for discovering new usages of drugs. From the database perspective, several criteria which can accelerate and improve drug repurposing researches have been investigated. Taken altogether, the requirements like to be available, updated, free, fully downloadable, and responsive should be considered for the drug repositioning process, in which expressing of SQL query, API, classified data structure, and results in export play key roles.

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