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A Comprehensive Review on Technological Advances in Alternate Drug Discovery Process:Drug Repurposing

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Abstract

The traditional de novo drug discovery is time consuming, costly and in some instances the drugs will fail to treat the disease which result in a huge loss to the organization. Drug repurposing is an alternative drug discovery process to overcome the limitations of the De novo drug discovery process. Ithelps for the identification of drugs to the rare diseases as well as in the pandemic situationwithin short span of time in a cost-effective way. The underlying principle of drug repurposing is that most of the drugs identified on a primary purpose have shown to treat other diseases also. One such example is Tocilizumab is primarily used for rheumatoid arthritis and it is repurposed to treat cancer and COVID-19. At present, nearly30 % of the FDA approved drugs to treat various diseases are repurposed drugs. The drug repurposing is either drug-centric or disease centric and can be studied by using both experimental and *in silico* studies. The *in silico* repurpose drug discovery process is more efficient as it screens thousands of compounds from the diverse libraries within few days by various computational methods like Virtual screening, Docking, MD simulations,Machine Learning, Artificial Intelligence, Genome Wide Association Studies (GWAS), etc. with certain limitations.These limitationscan be addressed by effective integration of advanced technologies to identify a novel multi-purpose drug.

Keywords: Drug repurposing, Screening, Drug-centric, Disease-centric, FDA, Pandemic, GWAS, Machine Learning, Artificial Intelligence

Introduction

De novo drug discovery method is the traditional drug discovery process which is tedious, time-consuming and expensive with high attrition values. In De novo drug discovery process of new drug identification, testing drug safety, efficacy and toxicity studies costs up to 2.6 billion dollars and it takes nearly 15 years for its approval from the screening to final approval of a drug candidate (1). Most traditional drugs were not approved or withdrawn because of the toxicity profile, adverse effects (especially hepatotoxicity) and limited financial support (2). The failure of a drug not only results in financial loss but also it costsboth the individual health and life in some cases.Besides, it is difficult to find drugs by traditional methods for the pandemics like COVID-19 as it is a phase beyond the containment (3).Hence, there is need to study in detailed about this complex process i.e. drug mechanism of action on humans at gene level by employing various novel strategies.

Most of the pharma companies will invest only in the specific diseases which have the scope

to generate more revenue and hence their treatments are expensive. There are various other rare diseases, where pharma companies would refrain themselves to focus because of low populations. Hence, to meet the unmet medical needsof rare diseases, the researchers have adopted many novel alternate optimization approaches for the discovery of new drugs or drug candidates and found promising results in the identification of multipurpose application of various drugs. Of the different methods adopted by the pharmaceutical companies, the most revolutionized alternate technology is drug repurposing which works on the multiple usage of the drugs that are approved or still under clinical trials(4). The repurposing drug discovery is more efficient because of the existing data (toxicology and pharmacology) of the drugs which are already approved or still in the clinical trials phase. It was reported in the literature that, 30% of the existing FDA approved drugs are the repurposed drugs accounting for 25% of the global pharmaceutical market revenue (5). Hence, to overcome the tedious traditional process many applications based on bioinformaticswere developed to screen thousands of the drugs within less time. The time instance for both the De novo drug discovery and drug repurposing is as shown in the below Figure 1.

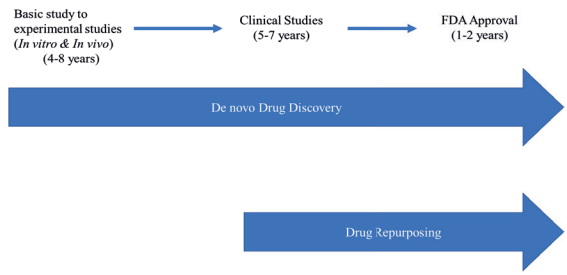

Figure 1. Overview of De novo drug discovery and Drug Repurposing

The *in vitro* and *in vivo* repurposing studies takes longer times and it is difficult to screenthousands of compounds at an instance. This can be met by the application of computational repurposing methods which can screen thousands of compounds, either based on the disease pathways or gene expression profiles within the less time as it accounts the available research data for screening drug candidates(6).

In addition to drug discovery the computational methods will be helpful in predicting the market value with in less time,if in case the drug fails or gets success by using the existing data.This lays the basis for the computational drug repurposing to study multiple applicationsin pharmaceutical industry. Hence, it is a potential breakthrough in the drug discovery process of identifying multiple applications for the same drug. Besides, there is need for the identification of drugs having multi disease potential by various computational studies as they require only 2D/3D structures of the targets before it is studied in experiments. The computational tools will help to build 3D structures of the target by using modelling techniques. The interactive effect between the target and the drug can be studied by docking and Molecular Dynamics (MD) and Simulations studies (7). Hence, it is important and will be advantageous to screen the drugs with multiple targets to achievesuccess.

Many reports were published about the application of the drug repurposing for the FDA approved drugs and other clinical drugs. This willminimizeboth time and cost of production. In addition to FDA approved and other clinical trials, many researchers are working on the application of the enzymes as alternative medication to minimise the side effects of the chemically synthesised drugs (8-10). So many enzymes as drugs such as L-Asparaginase, L-Glutaminase are currently in use to treat cancer (11-12). Hence many recent technologies based on the Bioinformatics, Cheminformatics, Artificial Intelligence andSystems Biology are being implemented by the researchers across the world to find the multipurpose application of the drugs to treat various diseases (13).

Many examples of the successful application of the repurposed drug as an anticancer, anti-malarial, antibiotic etc. are currently in use (14). The present review will discuss about the principles of drug repurposing, associated methodological strategies,available databases, applications, challenges and recommended solutions to improve effective integration of drug repurposing in pharmaceutical industry.

Principle of Drug Repurposing

Drug repurposing has gained momentum and leveraged by the pharmaceutical companies to improve the drug efficiency and its development (15).The principles on which the drug repurposing is based are: 1. Many drugs have cryptic biological activities with observed side effects-Multiple targets for the same drug. 2. Many diseases share same molecular pathways or genetic factors -Disease similarity. 3. Pleiotropic effects of the target based on their molecular function.

The alternate drug repurposing strategies were successful in identification of various repurposing drugs in the treatment of diseases like cancer, Cardio Vascular Diseases (CVD), arthritis, COVID-19, etc. by the application of advanced computational studies to find the multiple use of the same drug for various diseases. Table 1 demonstrates the reported applications of drugs for what disease treatment they are synthesized and their repurpose application to treat other diseases. The overview of drug repurposing was shown in the below Figure 2.

The most demonstrated example of the repurposed drug discovery process is Sildenafil (Viagra) which is developed for the treatment of hypertension but its repurposed application is for erectile dysfunction and pulmonary arterial hypertension (16).

The advantages of using drug as a repurposing which in clinical trials not only cut down the time, cost but also associated risks which makes drug repurposing as an attractive alternate drug discovery process.

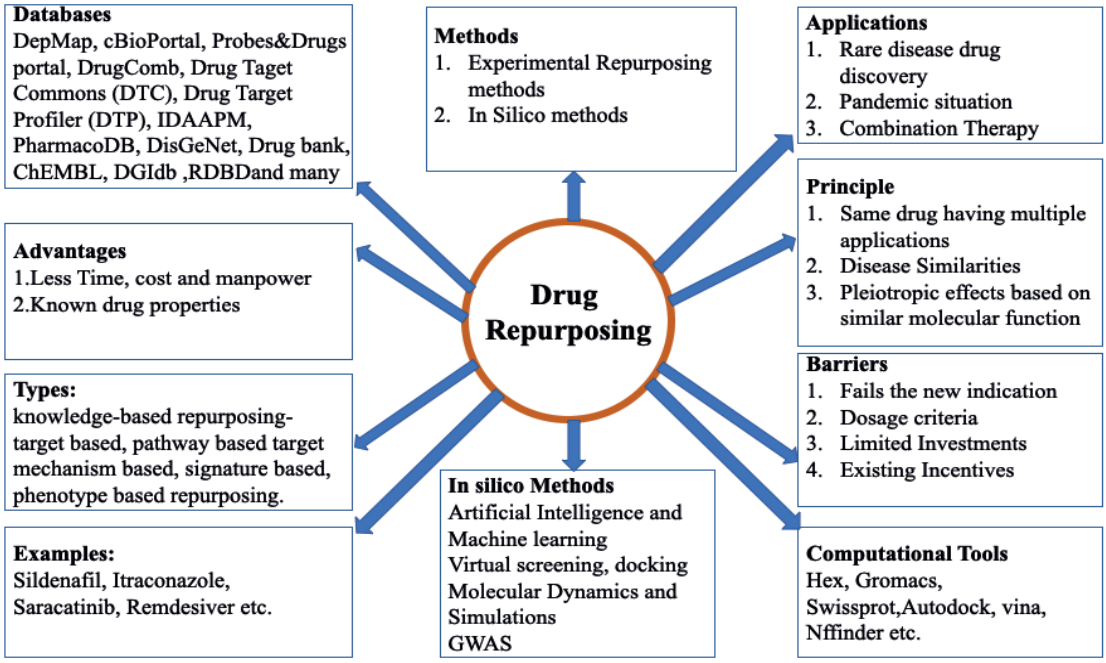

Figure 2. Overview of Drug Repurposing

Table 1: Drugs their primary purpose and Repurpose treatment

S. No	Drug	Purpose	Repurpose
1	Sildenafil	Hypertension & Angina	Erectile Dysfunction
2	Itraconazole	Anti-Fungal	Lung and Prostate Cancer
3	Saracatinib	Failed Anti-Cancer	Alzheimer's Disease
4	Remdesivir	Ebola	COVID-19
5	Toremifene	Breast Cancer	COVID-19
6	Hydroxychloroquine	Antimalarial Drug	COVID-19
7	Bupropion	Depression	Smoking Cessation
8	Thalidomide	Morning Sickness	Multiple Myeloma
9	Chlorpromazine	Antimalarial Drug	Cancer
10	Aspirin	Analgesic	CVD and Cancer
11	Statins	Lipid Disorders	Cancer and COVID-19
12	Metformin	Type-2 Diabetes	Cancer
13	Raloxifene	Osteoporosis	Breast Cancer
14	Cardiac glycosides	Cardiac Conditions	Cancers
15	Chlorpromazine	Schizophrenia	Prostate Cancer
16	Penfluridol	Schizophrenia	Cancer
17	Fluspirilene	Schizophrenia	Cancer
18	Artemisinins	Antimalarial Drug	Cancer
19	DHA	Antimalarial Drug	Leukemia
20	Mebendazole	Parasitic Infections	Cancer
21	Itraconazole	Anti-Fungal	Angiogenesis & Lung Cancer
22	Ritonavir	HIV	Breast Cancer
23	Nelfinavir	HIV	Multiple Myeloma Cells
24	Doxycycline	Angiogenesis Inhibition	Cancer And COVID-19
25	Leflunomide	Rheumatoid Arthritis	Cancer
26	Auranofin	Arthritis	Cancers
27	Thalidomide	Sedative	Cancers
29	Favipiravir	Flu	COVID-19
40	Darunavir	HIV	COVID-19
41	Arbidol	Influenza	COVID-19
42	Tocilizumab	Rheumatoid Arthritis	Cancer and COVID-19
43	Nafamostat	Anti-Coagulant	COVID-19

Drug Repurposing Strategies and Methods

Drug repurposing can be done in two ways-experimental or computational (*In silico* drug repurposing - disease centric or drug centric). There are different types of drug repurposing strategies i.e. knowledge-based repurposing- target based, diseased-based, pathway-based target mechanism based, signature based andphenotype-based repurposing (17).The technological advancements will help to employ classification and segmentation algorithms for early disease diagnosis (18).

Technological applications for drug repurposing include Artificial Intelligence, Machine learning and Computational methods.

Artificial intelligence

Zhou et.al. (2020) has employed Artificial Intelligence (AI) combined with the network intelligence for the precision medicine discovery and development which is based on the hidden patterns based on the existing biomedical data (19). Denovo drug discovery helps to find the efficacy of the existing drugs by minimizing their side effects and it was stated by Sir James Black that they start with the basis of the old drug for the discovery of new drugs (20). The technique of drug repurposing is the most promising solution for the emergency pandemic like COVID-19. In the case of COVID-19, for the identification of it repurpose drugs the AI and network approaches are less effective due to the limited data available about the organism and which makes us understand how the basic knowledge is useful for the biomedicine research in the identification of the drugs (17).

Machine learning

It is of prime importance in the pharmaceutical industry to study the drugs mechanism of action, pharmacokinetic and pharmacodynamic properties.The other application of the Machine Learning algorithmsis on the radiographic images analysis for accurate disease diagnosis based on the features selection (21). Machine learning algorithms can be employed to get better insights to mine the drugproperties and activity in both time and cost-effective manner.Each characteristic of the drugs can be assumed as molecular fingerprints and the application of neural networks will help to understand the features in an effective manner. Yang et.al. (2022) has employed machine leaning methods to employ Chinese traditional medical therapy as one of the drug repurposing approach in the treatment of COVID-19 (21). Many other machine learning algorithms such as UG-RNN (Update gGteRecurrent Neural Network) and GCN (Graph Convolution Network). Some are using deep-learning algorithms for the identification of both chemical and physical structures of the compounds while some are using reinforcement algorithms for the identification of small molecule inhibitors against COVID-19 (22, 23). The studies of Yang et.al., (2022) are in agreement with the various studies,concluding that the application of machine learning algorithms has provided insight of traditional Chinese medicine application for COVID- 19 treatment. Various network-based models can be integrated to employ text-based mining as wells structure-based mining studies in the small molecule identification. The application of the machine learning algorithms for drug repurposing studies was shown in the below Figure 3.

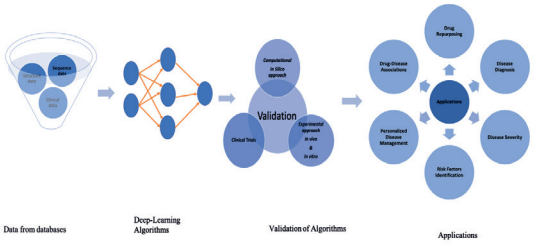

Figure 3. Application of Machine learning for Drug repurposing

Computational methods

The repurposing of the drugs has started long back and the applications of the computational approaches has gained importance. The computational methods were classified into target-based, knowledge-based, signature-based, network-based, phenotype-based repurposing and targeted mechanisms (6). Computational repurposing is also known as *in silico* drug repurposing. It was reported by Sanseau& Koehler (2011)that the computation repurposing can be either based on the disease (studying the associated drugs based on their properties) or targets (based on the compound's protein interactions based on the structural similarity of chemical entities and their binding sites- High -throughput screening of drugs for prediction of new indications (24).

The MER-SuMo approach was developed by the Moriaud et.al. for the identification of the new proteins based on the known compound off-target interactions. Cote

et.al. developed The Rare Disease Repurposing Database (RDBD) which constitutes the list of 200 repurposed drugs that can be used for treating the rare diseases complex and chronic diseases where the treatment is limited (24).

Farha & Brown (2020) worked on the repurposing of antimicrobial drugs, because the resistance towards the existing drugs is one of the potential threats across the worldaccounting for nearly 700000 deaths annually because of associated infectious diseases (malaria, pneumonia, Ebola etc.) and their number increases in the proceeding's years (15).

Virtual screening,docking and molecular dynamic and simulation studies are the other computational studies which were studied for screening of the compounds. It was understood that some of the drugs act on the causative agents like virus and bacteria whereas, some drugs act on the host by providing the immunity (25).

Genome wide association studies (GWAS)

The usage of GWAS for the new drug identification for complex diseases is based on the gene loci targets and the associated pathways. GWAS studies is the most common variants of the population. The data is collected by integrating omics data sets with the genes which are interconnected by various biological networks (26). Different ways of employing GWAS was summarised below:

By either mapping the genome for loci identification

IL-23 was identified as the repurposing candidate in treating Crohn's disease and the identified repurposed drug candidates are Ustekinumab and Risankizumab by Single Nucleotide Polymorphism (SNP) (27). The initiation of the SNP approach is its limited by size of the study.

Transcriptomic imputation

The transcriptomic repurposing of the GWAS study is based on mRNA expression, protein abundance and epigenetic modifications and can be analysed based on TWAS Z score (28).The limitation associated with transcriptomic imputation is trait-associated expression changes.

Gene-set association

Gene set association repurposing is based on the genes associated with various biological networks and it was reported that bipolar disorder and the insulin secretion pathways are associated with each other. The other GWAS methods are mandolin randomization. Poly-genie scoring- helps for the heterogeneity of the individual disorders and their targets.

The software which is integrating the GWAS is the Open Targets Genetics resource which predicts variant genes. GREP framework-gent set association based on the GWAS functional loci and pathways. The DrugTargetor platform, for the identification of gene variants and matching drugs uses various drug repository databases like Drug Bank, DGIdb- drug gene interaction database (29). The Overview of GWAS association in repurpose drug discovery was shown in Figure4.

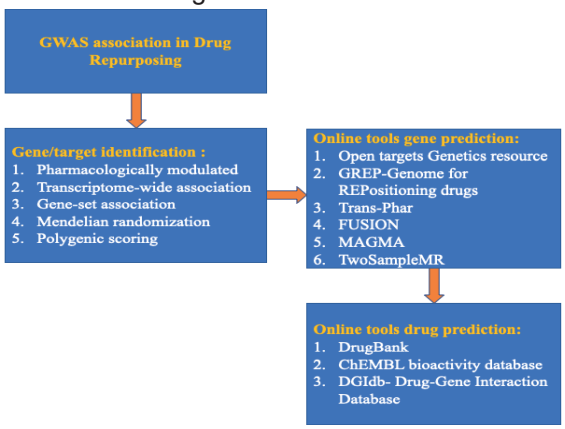

Figure 4. GWAS association in Drug repurposing

Databases Associated with Repurpose Drug Discovery

Many databases are available on the internet which constitutes the information associated with the pathways, diseases, some contain the drugs and other properties, some contain the information only about the repurposed

drugs, some contain the information of the gene targets (30). Most of the pharmaceutical companies have their own databases where they keep the drug data information secularly and in most cases this data will not be shared to the public because of various market associated risks. Some of the databases available are shown in the below Table 2.

Table 2. Databases and associated storage information

Database	Information
DepMap	Cancer data
cBioPortal	Cancers genomics data
Probes&Drugs portal	Bioactive compounds
DrugComb	Cancer data portal
Drug Target Commons (DTC)	Compound-target interaction profiles
IDAAPM	FDA approved drugs
PharmacoDB	Pharmacogenomic studies
DisGeNet	Gene database
Drug Bank	Molecular information about drugs
ChEMBL	Chemical database of bioactive molecules
DGIdb	Drug-gene interactions

Validation of the repurposing willbe done by using Computational methods-AUROC values, target based using PubMed, Clinical Trials/ EHRs and experimental-(*in vivo* and *in vitro* validation).

For a better efficient repurposing drug development there is need for the better integration of data sources, genomic, biomedical and pharmacological data and this has gained importance because of personalized and precision medicine which accounts for heterogeneity and complexity to minimize drug toxicity (31).

Applications of the Drug repurposing

The Applications of the repurpose drug discovery is advantageous. It helps for

Rare disease drug identification

For the identification of the drug candidates to a specific disease which is rare and is less commonly observed among the individuals.Most of the pharma companies will not worry about the rare diseases because of the limited market.

Uncommon pandemic situations

Sudden pandemic situations like COVID-19, as there is no previous knowledge about the disease and there is an utmost concern as most of the people are dying and there is no time to conduct the clinical trial. Hence, the only available option is the drug repurposing by the *insilico* methods due to the limited time constraint and finding the repurpose of the existing drugs either individually or in combinations.

To overcome the adverse effects of the monotherapy by working on the combination therapytreatments(31).

Challenges of Drug Repurposing

Each and every drug discovery process will encounter challenges at any one stage or sometimes at all the stages of the drug discovery (32). Some of the reported challenges of the drug repurposing are:

Dosage limitations of the repurposed drug

The drug dosage can be similar to the original dosage or in some non-antibiotics

where the dosage is more than the antibiotic drug is causing adverse toxicity effects (ex: Anti-microbial compounds). Sometimes the repurposed drug may fail in demonstrating the new indication and the differences in the new benefit of the drug will affect the market.

Effect of pharmacokinetic properties

The pharmacokinetic profiles of the original drugs may affect the repurposed activity leading to impaired antimicrobial properties.

Need for clinical trial

Sometimes clinical trials need to be conducted to prove the efficacy of the approved drug.In some cases, the previous data cannot be considered for the regulatory approval of the repurposed drug and repetitive experiments may increase the cost of the drug and lack of efficient funding for the repurposed drug studies. Sometimes the results are not reliable because of data sensitivity to datasets from the previous studies.

Limited investments and Existing incentives

Breckenridge & Jacob (2019), have studied the legal and the regulatory barriers in the drug repurposing. Patents (protection of new drugs into the market) and the regulatory data exclusivity (prevents the usage of data for the purpose of generic applications) are the two intellectual property rights which are involved in the protection of the drug from the competition. The intellectual properties of the repurposed generic drugs will differ which limits the data of the drug for further studies (33).

Possible solutions to overcome the legal and regulatory barriers

The possible solution for the drug repurposing is:

The possible solution is to produce all the data information in the prescription and ensure the reimbursement which will allow the stakeholder to ensure the knowledge about the differentiation between the patented and unpatented drugs. Second medical use of the drug- if the company is ready to provide the original data of the drug. Bypass exclusivity related incentives and provide incentives for the new drug developments for rare diseases.

Conclusion

Drug repurposing is one of the best alternative drug discovery processes and this has been proved from the literature studies in the pandemic situation for the identification of drugs to COVID-19. It was not only COVID-19, but drug repurposing studies have been performed on other diseases like cancer, Alzheimer's disease, Cardiovascular diseases and many others. Still, there is need to study in detail about various drugs to treat multiple diseases with in less time in an economical manner with high efficacy by integration of various genomic, proteomic, pathway data by using various computational tools.

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