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Editorial

Drug Repurposing: An Emerging Tool to Accelerate the Drug Development Process

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Abstract

Science and technology has greatly advanced in the past few years, and is progressing at an unmatched rate. With the several advancements, it has brought a lot of ease to the overall drug discovery and development method. It is known that the *de novo* development of drug is an extremely time-consuming and expensive process. Therefore, in order to find its potential alternative, 'Drug Repurposing' has come into practice for many years. Drug Repurposing has been considered as a revolutionary breakthrough in accelerating the process of drug development process. It involves seeking new indications of drugs that already been approved by Food and Drug Administration, thereby substantial reduction of cost and time. Ever-increasing molecular, genomic and pharmacological data has further contributed in the success of drug repurposing approaches. This editorial outlines the different tools used in Drug Repurposing.

Keywords: Drug Repurposing; In-silico Methods; Genomics; High-Throughput Sequencing Technologies; Literature Mining

Introduction

Drug Repurposing also termed as Drug Repositioning, is a method which involves identification of novel therapeutic drugs from the existing list of FDA approved drugs. It is a promising field and can offer significant benefits to pharmaceutical industry. This approach can overcome various roadblocks during the drug development process. The methods involved in repurposing will certainly improve the translation of drug discovery from bench to bedside. Drug repositioning has taken up a driver seat as a well-grounded strategy during emergency situation like COVID-19 pandemic for developing anti-viral strategies within a shorter time span. This editorial explains different strategies or methods used for drug repurposing studies, categorised as, *In-silico* methods, Genomics, High-Throughput Sequencing Technologies and Literature Mining. The *In-silico* methods explains different methods involved to explore the interactions between a biomolecules and drug moiety. Genomics section includes all the studies or maps being developed that integrates all the genomic information. High-Throughput Sequencing Technologies (HTST) briefs the relevance of screening methods for selecting potent drug candidates. Literature mining sheds light on different databases or repositories through which the literature or published data can be extracted. These strategies have greatly contributed to the better understanding of drug-disease relationships, clinical use or probable adverse effects for developing initial hypothesis and treatment of the disease.

In-silico Methods

In-silico methods or computational approaches has gained a lot of attention and scientific coverage over past few years owing to its promising outcomes in drug repurposing and discovery. These approaches are advantageous as it restricts the extensive use of various animal models, accelerates the repositioning of potent drug candidates and thereby adding to the overall efficiency of drug repurposing [1]. Another advantage of using the *in-silico* techniques is that, it enables the researcher(s) to highlight the possible adverse effects of the compound(s) [2].

There are numerous computational methods that are widely used for drug repurposing process: AI and Network-based Drug Repurposing especially using deep neural network (DNN), Cluster analysis, Ligand-based Approaches in Drug Repurposing, Structure-based Approaches in Drug Repurposing, Molecular Docking and Molecular Dynamics.

Network-based drug repurposing involves finding relationships or knowledge between biomolecules, drug compound, and biological targets primarily in the form of a connecting graphs. Such networking enables one to collect large amount of relevant data and arranging in concise format. Due to its networking strategy, it has been gaining great attention in the recent years [3,4].

Ligand-based approaches involves studying ligands possessing similar biological properties. It is extremely important method for predicting the probable activity of ligand(s) when bound to new targets. A number of databases and repositories have been created for storing ligand information, PubChem, ChEMBL, DrugBank, RepoDB being few of them. Similarly, for Structure-based method, proteins possessing similar structures and functions are used to search for similar ligands. Molecular docking is one of the commonly used methods in both drug discovery and repurposing. It is applied to predict the binding pose and energy of the potent drug candidate (ligand) with the protein. It is of great efficiency, less-time consuming and does not require much of materials [3].

All the ligand-protein interactions obtained from molecular docking are further analysed to Molecular Dynamics simulations to predict the free energies of binding. These are reliable approaches and can be performed based on various timescales [5,6].

Genomics

There has been a tremendous increase in the involvement of genomics and related studies after the successful completion of Human Genome Project in 2003 in drug discovery and repurposing. Recent developments and advances in genomics and system biology have enabled researchers to search for druggable targets along with therapeutic agents that are playing a role in the disease. A large scale genetic study namely 'Genome-Wide Association Studies' (GWAS) have greatly contributed to the understanding of the genetic basis of the commonly known diseases like cardiovascular disease, inflammatory disease, autoimmune disorders, diabetes etc. There are more than 800 human diseases for which approximately 53,000 unique variant-trait associations have been reported and deposited in GWAS database in past few years [7-9]. An interesting network based method is also used for drug repurposing study called as 'Genome-wide Positioning Systems network (GPSnet) algorithm, which involves collecting large-scale DNA and RNA sequenced data of around 5000 tumor genomes and merging with the protein–protein interactome of humans. Through this gene expression profiles, it is possible to predict the drug responses in cancer cell lines more precisely [10]. A novel strategy applied for drug repurposing studies is the Connectivity Map (CMap). The CMap database contains information regarding differential changes in gene expression due to drug treatment and gene perturbations in order to search for relation between genes and drug molecule [9].

High-throughput screening technologies

An ideal drug repurposing work includes identification of off-label uses of drug(s) which are already been by approved by Food and Drug Administration (FDA) and selecting it from drug libraries. Many pharmaceutical firms and research groups have employed a well-known method known as High-Throughput Screening (HTS). It is known to hold an integral part in drug development and repurposing. It involves screening of thousands of compounds against a receptor (target), stating the various interactions and binding energies, and filtering out potent drug candidates. Post screening, their action is even tested and validated by complex assays. There are several databases developed that aids the process of HTS, namely, PubChem Bioassay, ChemBank [11-14]. Its computational counterpart known as 'Virtual Screening' (VS) is also largely applied in both drug discovery and repurposing. It involves the use of

the employed *in-silico* methods for the selection of potent drug candidates from databases. There are majorly two types of VS, named as Ligand Based Virtual Screening (LBVS) and Structure Based Virtual Screening (SBVS). The former is used for screening of large molecular descriptors from all active compounds, while the latter is used for screening of the compounds by docking it in the pre-set binding site of the target [15].

Literature mining

Drug discovery and development is a long, expensive, laborious and high risk process. In order to bring ease and reduce the problem drug repurposing has been greatly researched, scientifically covered and highly appreciated worldwide. One of the preliminary steps for drug repurposing is literature or text mining. It is a powerful method to gather or extract key information from large amount of literature in order to be updated with the available or suitable data. For drug repurposing, the information regarding the disease-gene, gene-drug and drug-disease is collected from the literature which makes it simpler for designing methodology.

PubMed is one of the most widely used libraries for biomedical, biological, biotechnological and related life science fields, and contains approximately 26 million citations with over 8 lakh articles been submitted annually. The Therapeutic Target Database (TTD) stores information about targets (receptor, enzyme or hormone) and their corresponding drugs and diseases. It provides relevant data of around 2,723 types of diseases, 3,188 kinds of targets and 20,043 drugs, which makes it an appropriate repository [16,17]. Li., *et al.* in 2009, had proposed a novel strategy that includes literature text-mining data and protein interactions for developing a drug-protein connectivity map of a particular disease or disorder. For this, the researchers used Alzheimer's disease (AD) as a case study and showed that this approach was not only more appreciated than the usual drug-target databases and conventional information retrieval systems, but also suggested two important drugs i.e., Diltiazem, an antihypertensive agent and Quinidine, an antiarrhythmic agent, as potent candidate for curing AD [18-20].

Undoubtedly, the COVID 19 data portal was set up by European Commission in April, 2020 for dissemination of COVID related data such as drug descriptions, side effects, publications, therapeutic agents and drug-like synthetic or natural compounds [21].

Concluding Remarks

Drug discovery and development is an extremely long, exorbitantly expensive and tiresome process. With unprecedented outbreak of certain life threatening diseases like COVID-19, new drug discovery is not a viable process. As a potent alternative, 'Drug Repurposing' has been receiving great attention by researchers. It is one of the most appreciated, researched and promising strategies in Pharmacology, which involves the identification of new therapeutic uses of a drug beyond its prescribed indication by FDA. It has several impressive advantages, such as, reusing drugs, saving colossal development-time, cost and efforts; its already determined pharmacokinetic, pharmacodynamics, bioavailability and toxicity profiles in pre-clinical and Phase I studies makes it easier to enter further stages of clinical trials. Based on various success stories, drug repositioning has helped to mitigate false positive results in drug discovery which need to be used for further therapeutic breakthroughs. Drug repurposing is usually conducted by both computational and experimental methods, however, the former is used and preferred much over latter. The few network-based approaches give new ways to study all the links between drugs and diseases, adding more knowledge to computational biology and drug repurposing. The above discussed methods prove to accelerate the overall drug discovery process and develop initial novel hypotheses from diverse data (genomics, proteomics and transcriptional), to expand new areas of research regarding drug action and their possible uses, thus breaking the bottleneck of current drug shortage.

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