



REVIEW ARTICLE

Network-based Drug Repurposing: A Critical Review



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Abstract: New drug development for a disease is a tedious, time-consuming, complex, and expensive process. Even if it is done, the chances for success of newly developed drugs are still very low. Modern reports state that repurposing the pre-existing drugs will have more efficient functioning than newly developed drugs. This repurposing process will save time, reduce expenses and provide more success rate. The only limitation for this repurposing is getting a desired pharmacological and characteristic parameter of various drugs from vast data about medications, their effects, and target mechanisms. This drawback can be avoided by introducing computational methods of analysis. This includes various network analysis types that use various biological processes and relationships with various drugs to simplify data interpretation. Some of the data sets now available in standard, and simplified forms include gene expression, drug-target interactions, protein networks, electronic health records, clinical trial results, and drug adverse event reports. Integrating various data sets and interpretation methods allows a more efficient and easy way to repurpose an exact drug for the desired target and effect. In this review, we are going to discuss briefly various computational biological network analysis methods like gene regulatory networks, metabolic networks, protein-protein interaction networks, drug-target interaction networks, drug-disease association networks, drug-drug interaction networks, drug-side effects networks, integrated network-based methods, semantic link networks, and isoform-isoform networks. Along with this, we briefly discussed the drug's limitations, prediction methodologies, and data sets utilised in various biological networks for drug repurposing.

ARTICLE HISTORY

Received: September 28, 2021

Revised: November 17, 2021

Accepted: November 30, 2021

DOI:
10.2174/2589977514666220214120403



CrossMark

Keywords: Drug repurposing, biological network analysis methods, network analysis, data sets, predicting methods, drug development.

1. INTRODUCTION

Drug development is an expensive and time-consuming process from the beginning. A new medication is anticipated to cost between \$2 and \$3 billion to create, with a development time of at least 13-15 years. Only 10% of medications that make it through phase I clinical trials are authorized, with the rest failing owing to significant toxicity or inefficacy. The inexact identification of the target or reaction is the primary cause of these attritions. The primary reason for this failure is erroneous medication target or response identification. Furthermore, only 5% of oncology-related medicinal compounds that enter Phase I clinical trials are approved.

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There are around 8000 orphan diseases, making *de novo* drug development impossible for such a large number of diseases at current R&D costs [1]. Drug repositioning (DR) aims to find new uses for existing medications that have been proven to be safe in humans. The process of discovering new indications for existing drugs is referred to as DR in technical terms [2]. Pharmaceutical repositioning or repurposing (creating a new purpose for an approved drug) can help pharmaceutical companies solve their difficulties. In comparison to the conventional 10-17 years taken to bring a new chemical entity to market, the drug development cycle for a repurposed medicine can be as fast as 3-12 years. This is because, during repurposing attempts, numerous stages of the drug development pipeline might be removed [3]. Over the last few decades, technological breakthroughs have permitted the collecting of massive volumes of data, resulting in the so-called "Big Data" era. The Big Data revolution is ex-

pected to significantly impact many parts of the health sector, including the ability to assess an individual's risk of developing sickness and improving personalized disease treatments. While the results of individual tests can be somewhat varied, many data sets are driven by a graph structure. The presentation of persons in a social network, each individual is shown as a node in the network, and an edge links two nodes if the respective individuals know each other, is a well-known example of graph-structured data. From a biological perspective, we can say proteins, for example, can be shown as networks, with nodes representing amino acids and edges representing physical interactions. The origins of biological networks can be from systematic experimental screening, literature curation, or computational inference. The number of available molecular networks, as well as the complexity of those networks in terms of the number of nodes and edges, has increased dramatically over the previous decade. For instance, the Bio GRID database, which covers protein-protein interactions, included protein interactions for 17 organisms in January 2010, comprises 270695 genetic connections involving 80754 distinct proteins in *Homo sapiens*. Ten years later, in February 2020, BioGRID has 4170446 unique interactions between 240730 human proteins reflecting a 16-fold increase in the number of interactions and a 3-fold increase in the number of known proteins. Due to the vast increase in data availability, the complexity has increased in predicting, utilizing, and interpreting those data. Hence, various advanced computational and statistical methods are required to easily utilise data, as shown in Fig. (1) [4].

Different computational tools for drug repositioning (or repurposing) detect new uses for current, existing, and

shelved medicines. Many drugs have protein targets, and many complicated diseases have similar characteristics (mutations, pathways, clinical manifestations). As a result, a medicine that targets these common factors may theoretically be effective for various disorders. Computational approaches aid in systematically evaluating all potential repurposing candidates in this context, giving high-quality predictions for the further experimental phases. This computational network method aims to find more productive and cost-effective drugs than current ones [5]. Several drug repositioning computational techniques have been reported. These strategies can be classified as either "drug-based," in which the discovery of repositioning possibilities begins with a chemical or pharmacological approach, or "disease-based," in which the discovery begins with disease prevention, symptomatology, or pathology. Disease-based techniques may be adopted to overcome a lack of information on a drug's pharmacology [3]. Gonen divided traditional computational DR methods into three groups: (i) docking simulations, (ii) ligand-based approaches, and (iii) literature text mining [2]. One of the best computational methods is network analysis. Networks are primary and flexible data structures that may be used to identify correlations using various statistical and computational methods. Biology widely uses the concept of an interaction network. Nodes indicate constituents (genes, proteins, complexes), and edges indicate their connections in biological networks. Furthermore, quantitative information (weights) produced from high-throughput studies can be annotated on edges and nodes [5]. Various network-based drug repurposing methods include (1) gene regulatory networks, (2) metabolic networks, (3) drug interaction networks, (4) drug-disease interaction net-

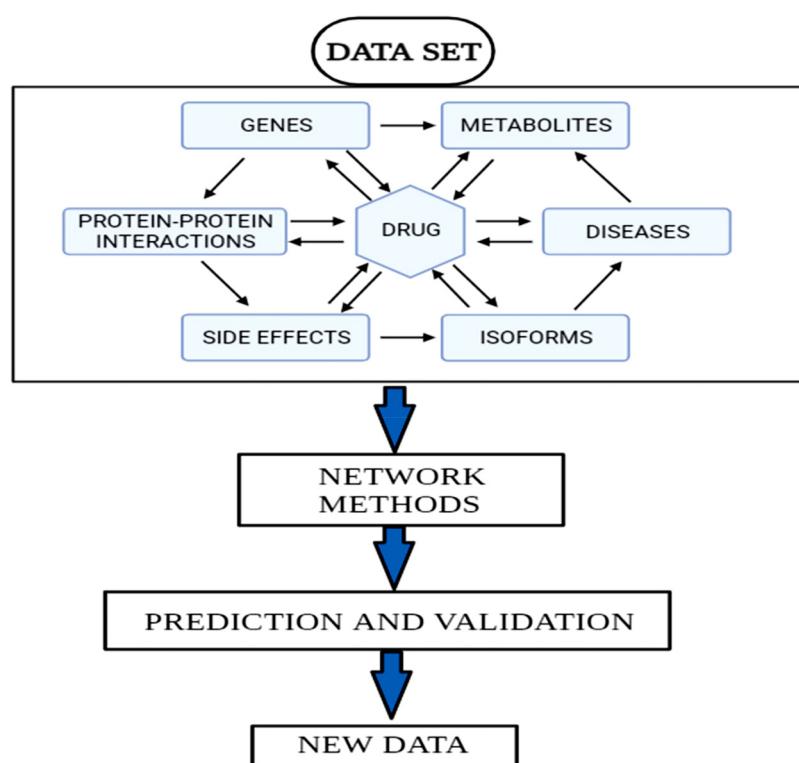


Fig. (1). Data collection process from database through network methods. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

works, (5) protein-protein interaction networks, and (6) isoform-isoform networks were used based on biological concepts. Semantic and integrated approaches can also be added as an additional category with multiple data sources simultaneously. The subsequent part describes various network-based drug repurposing techniques with their methods and limitations.

2. BIOLOGICAL NETWORKS

Health and disease are based on systems biology to integrate different components and interactions that underlie the functions of cells, organs, and organisms. Outside of the box techniques that concentrated on specific substances or pathways with the help of high-throughput data bioinformatic network analysis. Sets are used to integrate biological complexity and multi-level interconnection [6]. Biological connections can be represented as a network at many levels of complexity, from nuclear interactions in a folded structure of the protein to relationships between animals in a community or ecosystem [7]. The edges of a network can also be used to show different biological concepts that establish a relationship between nodes, such as interactions among proteins, gene regulation, and the functional similarity between genes [8]. Some biological networks at molecular levels are gene regulation networks, metabolic networks, protein interaction networks [9]. Biomolecular and cellular networks can now be reconstructed by collecting varied high-throughput data [10]. High-throughput experiments have recently developed vast networks of interacting molecules, represented as nodes in complicated graphs connected by edges [11]. A network is a collection of nodes and edges that may be mathematically represented using graph theory. A node is a biological molecule extracted from a cell, such as a gene, RNA, or DNA. It could be a protein, a metabolite, or a chemical. An edge can be used to represent the complicated interaction between two nodes coordinating their biology-related activities [10]. Determining protein-protein interactions is arguably the most straightforward using interaction trapping, FRET, and MS techniques. A complete (but still partial) picture is provided for a small number of living organisms in the transcriptional regulatory networks. Rather than using high-throughput methods, it was built over several years of genetics and biochemistry. Due to the methods of deciphering such networks, results can sometimes be placed on the edges if they are concentrated, indicating whether or not a connection represses. It is often used in biochemistry. However, they are omitted from these networks, such as how the posttranslational modification, complexation, and degradation regulate transcription factor activity. Metabolic networks are the most comprehensive of the three, but their intricacy comes from the numerous hours spent studying individual enzymes. The presence of ubiquitous networks dramatically enhances networks. Enzymes and metabolites have feedback loops, complicating direct stoichiometric analysis [7]. Some DTI approaches depend solely on pharmacological and therapeutically relevant correlations, while others incorporate additional network information such as drug-drug similarity or protein-protein similarity [12]. Transcriptome, proteome, and metabolome information have been combined into a single network structure using extensive integration of several system levels to successfully model metabolism [6].

2.1. Limitations

Even though network pharmacology is gaining traction and shedding light on the multiple off-target effects of medications, it still has some inherent limitations. Some of them are:

1. Some network techniques tend to set parameters and thresholds that determine whether edges are in operation, causing inconsistencies in the extraction of the subnetwork.
2. These techniques can discover genes that are altered as a result of medication therapy, but they are unable to explain the relationships between gene expression changes. As a result, they cannot estimate the drug's off-target effects on these genes.
3. In addition, these techniques often ignore modified genes not contained in the signatures of the genes. In fact, because of the limitations of gene expression comparison methodologies, results in unbalanced derived reaction prediction from a network are not reliable due to noise in some gene expression data.
4. On the other hand, many of the accessible chemical structures and chemical attributes contain errors, and some information is even rejected.
5. Drugs are subject to substantially uncharacterized metabolic or pharmacokinetic modifications in the human body; therefore, testing for chemical similarities alone is insufficient for the repositioning of drugs.
6. Because there are no significant changes in terms of expression between the genes which are used as pharmacological and target-regulated targets such as transcription factors, the mathematical optimum of reactive networks with the highest biological value is not always exact.
7. Similarly, several techniques have been implemented by evaluating phenotypic data to elucidate a correlation in drug modes of action (indications and side effects). However, because drug side effect data is noisy and limited, these strategies are ineffective and not enough to investigate medication repositioning [12].

2.2. Gene Regulatory Networks

Thousands of genes are expressed in each cell and work together to maintain the cell's function, fitness, and survival. Each gene should be expressed at a particular moment and at the appropriate levels to achieve the optimal functional outcome [13]. Gene Regulation is a biological mechanism that allows a cell, in response to intracellular and extracellular conditions, to regulate the synthesis and activity of gene products [14]. The regulatory networks of genes support any life process, including cell differentiation, metabolism, cellular cycling, and signal transmission. A gene regulatory network consists of the collection and interaction of molecular entities that regulate the number of gene products. Understanding the dynamics of these networks can give us a better

understanding of the processes that arise behind the disease in biological processes [15]. Gene regulation networks (GRNs) are complex networks of genes and chemical signals that are linked with specific DNA sites through the transcription factor protein (TF) connection. In the study of regulatory networks in recent years, mathematical and computational models have grown more and more critical [14]. Network-like architectures are formed by developmental control genes' regulatory inputs and functional outputs [16]. Transcriptomic data can record a cell's dynamic features and provide insight into a drug's function processes. Some (dysregulated) genes have significantly different amounts of messenger RNA transcripts in disease and control samples, which can be discovered through differential gene expression analysis [2]. Networks of gene regulations govern these gene products. A gene regulatory network consists of a group and interactions of molecular entities that control the number of gene products. There are three primary stages to building a model they are [14]:

1. The use of assumptions and approximations based on prior information to translate biological occurrences into acceptable mathematical and computational models.
2. Theoretical research into the phenomena aims to the patterns, correlations, and numerical values discovered to correspond to those observed in the real GRN.
3. The biological context is used to evaluate and validate the theoretical results [14].

A GRN is bipartite, which has two node types: genes and regulators, and is guided by the control genes of regulators. While GRNs and reconstructions of the metabolic networks are modelled in various respects, modelling metabolic results of regulatory disruptive activities will help understand the

pathogen's physiology and discover new therapeutic goals. Using this method, the MTB PROM2.0 model was constructed by combining Mtb's genome-scale metabolic model iSM810 with its transcription regulatory network. The integrated model uses probabilistic regulation of the metabolism framework to simulate the growth effects of 104 TFs knock out or overexpressing under multiple media conditions to prioritize possible therapeutic targets and uncover viable combination therapy choices. The model effectively predicted the synergistic interaction between whiB4 TF overexpression and two TB anti-INZ and ethionamide medications using this technique (ETH). GRNs live in highly heterogeneous conditions in which a diverse set of biomolecular constituents engage at multiple spatiotemporal scales to produce biological function and structure [17]. The ability of the RNA polymerase (RNAP) enzyme machinery can affect TFs in the development and initiation of transcriptional active transcriptional complexes in Gene sequential (referred to as promoters). TFs are classified as activators when they help the transcriptional complex assemble or function. Repressors are molecules that have an inhibitory action. The primary regulators for Mtb bedaquiline-tolerant Mtb through the Mtb EGRNI and PROM networks are expected to be Rv0324 and Rv0880. Simulating the deletion of these two regulons resulted in Mtb becoming hypersensitive to bedaquiline, proving the model's predictions [17]. Despite its biological intricacy, a GRN can be imagined using a connection graph that includes real-time information about the network's status [14].

2.2.1. Limitations of Gene Regulatory Network

However, all of the approaches in Table 1. have been proven successful, those based on relative gene expression have some disadvantages.

Table 1. Considering gene expression data, a summary of network-based drug repurposing approaches [2]

Methods	Data Sets	Case Studies
Functional linkage network	A drug response expression data set (The Library of Network-Based Cellular Signatures (LINCS) profiles), CMap, DrugBank, OMIM, GEO, and The Cancer Genome Atlas (TCGA) portal	Breast, prostate, and leukemia cancers
Virtual gene technique, Bayesian networks	Gene disruptant microarray data and time-course drug response microarray data	<i>Saccharomyces cerevisiae</i>
Statistical analysis	GEO, CMap, and DrugMatrix	Neurofibromin
Neighborhood scoring, interconnectivity, network propagation, random walks	Gene Expression Omnibus (GEO) repository and integrity	Scleroderma, different types of cancer, and diabetes type 1
Kolmogorov–Smirnov enrichment	Comparative Toxicogenomics Database (CTD) and GEO	Prostate cancer
Bayesian networks	Genetic interactions	Mammary epithelial carcinoma cell proliferation and breast cancer
Maximum flow	DrugBank, Online Mendelian Inheritance in Man (OMIM), KEGG and PGDB	Prostate cancer

1. Because some gene expression data contains noise, it may be challenging to define a robust gene signature, leading to biased retrieved response networks.
2. Genes used as pharmacologically determined targets and target-regulated genes may not always show significant changes in expression (in the case of transcription factor as a medication target). As a result, the notion that the mathematical optimum of responsive networks is comparable to the maximum potential biological relevance is not necessarily true.
3. There is no significant relationship between suspected target proteins and critical network sites, according to previous network topology research.
4. The approaches in this group usually depend on the gene networks predicted because of the problem of connecting a responsive network with the reaction of a living organism [2].
5. Given these limits, we believe that integrating data from additional sources, such as molecular interaction networks and gene expression profiles will be required for effective medication repurposing.

2.3. Metabolic Networks

Drugs are designed to penetrate an organism's metabolism and generate an intended effect. From a chemical standpoint, cellular metabolism is a complicated web of processes that change metabolites into one another. The design of a metabolic network could aid in the development of novel drug design strategies and the understanding of the causes of known unexpected side effects [18]. The catabolic, energetic, and biosynthetic metabolic networks of small entities provide a foundation for the vast genetic and metabolic networks that functional genomics research is beginning to unravel. It is impossible to analyse the structure of previously undiscovered networks with hundreds or thousands of components using only visual inspection; hence quantitative methodologies like metabolic networks are required [19].

The nodes are chemical compounds and metabolites in a metabolic network. Directed edges indicate the reactions of one or more enzymes. Each edge in a different model of metabolic networks represents a reaction between two physical elements (nodes) [2]. Implying the relationships between genes, proteins (enzymes), and reactions in a metabolic system are the first step in recreating a metabolic network. This is typically accomplished through the use of comparative genomics and using metabolomic information [20]. Several metabolic reconstruction techniques with varying degrees of automation and human interaction are currently available. The following are the main steps in the bottom-up reconstruction methodology used by these technologies.

1. Genes exhibiting metabolic roles should be identified.
2. Using a reaction database, get the relevant biological reactions.
3. To create a rough metabolic network.
4. The draft mode should be manually curated.

The activities in the final steps include the inclusion of missing reactions necessary to create precursors of biomass, restoration of elementary balance and reaction direction, the deletion of inhibited reactions and dead-end metabolites [21].

There are two types of issues to consider when studying metabolic networks: analysis and synthesis.

1. The analytical problem entails investigating a set of biological reactions and determining every potential pathway for producing a biochemical substance from a particular set of beginning compounds *via* a set of known biological reactions and chemicals. Artificial intelligence algorithms, stoichiometric analysis, and graph network analysis are computational methods to solve this issue.
2. Exploring the novel biochemical compounds and their reactions from the given set of enzymatic reactions and initially given compounds are included in synthetic problems [22].

Ex 1: FAB Method of Analysis

Flux balance analysis (FBA) is a popular tool for determining pharmacological targets. Essential enzymes, which are necessary for pathogen survival and proliferation, are frequently predicted using such approaches. FBA is a factor-based technique for linear programming optimization of an objective function. Different steps in the FAB method are:

1. Finding the system that is incorporated with modelling and identification of all reactions and metabolites of the system.
2. Reactions are converted into matrix format.
3. Determining the main target activity and its related problems.
4. Determining the best solution to an objective function [2].

Ex 2: CarveMe is a revolutionary reconstruction tool that uses a top-down reconstruction strategy to change the paradigm. Using a technique known as 'carving,' the universal model is turned to an organism-specific model for each subsequent reconstruction. CarveMe combines selected individual model sets into community-scale networks to automate the building of microbial community models.

2.4. Protein-Protein Interaction Networks (PPINs)

Proteins are the principal catalysts, building blocks, signalling messengers, and molecular machinery types of the biological tissues. PPINs are a type of network of molecular interaction that shows links between the known targets and other proteins and proteins that connect indirectly to targets [2]. As one of the most well-known types of biological networks, the structure and nature of protein interaction networks is a significant topic in system biology, thanks to a large number of protein interaction datasets available for research [23]. Protein-protein interactions underpin many biological processes, including signal transduction and transcriptional regulation. The examination of interactions with-

in cellular macromolecules is generally recognized as critical to understanding biological systems [24]. Functional, genetic, and physical connections are just a few possible forms of protein-protein interactions. Nodes in networks represent biomolecules like genes and proteins, and edges between nodes show interactions between the associated biomolecules, as shown in Fig. (2) [25]. Because proteins work in the context of interaction networks, structural analysis of PPINs is thought to aid drug-target prediction was shown in Table 2 [2].

2.4.1. Identification of Protein-protein Interactions by Computational Methods

2.4.1.1. Genomic Context-based Methods

a) Domain Fusion

A domain fusion or Rosetta Stone approach proposed by Eisenberg was suggested. The method is based on the idea that X and Y are functionally related if the domains X and Y are combined into one polypeptide XY in another organism. The idea is to have a specific interaction of pairs developed

from proteins that contain interacting areas X and Y on polypeptide because the affinity between protein X and Y is substantially increased when X is fused to Y. The underlying idea is that because eukaryotes have a higher volume, they can not afford to have distinct proteins X and Y, as they tend to interact to attain equilibrium.

Limitation: - One drawback of this method is its poor coverage based on genetic context.

b) Conserved Neighbourhood

The matching proteins are likely to be functionally connected if the genes encoding two proteins are located next to each other on the chromosome in different genomes. This approach is very effective in prokaryotes, which have a lot of operons, or in organisms with a lot of operon clusters.

Bork and colleagues have introduced a new method that uses the preservation of divergent gene pairs (bi-directional). The method works in conjunction with the existing neighbourhood gene method, where operons are concentrated, all genes are transcribed in the same way.

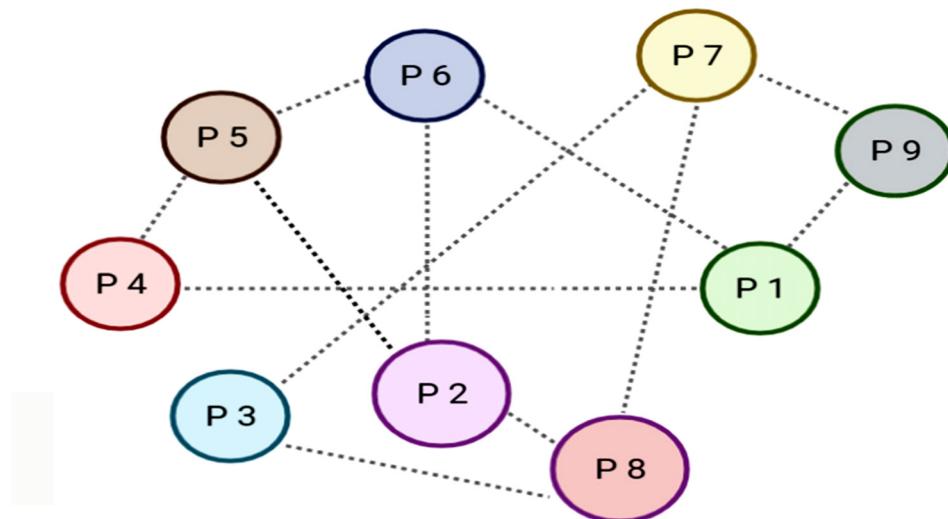


Fig. (2). Diagrammatic illustration of protein-protein interactions. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

Table 2. Some of the methods and data sets used for drug repurposing in PPINs.

Methods	Data Sets
Similarity comparison	Genotator, Drug Bank, and STRING
Support vector machines	Human PPIN data set UniHI, DrugBank, and GeneCards database
Cross talk by analysis of betweenness centrality	KEGG, OMIM, and iRef Index database
Set-cover based formulation of coordinate dysregulation in complex phenotypes	GEO

2.4.1.2. Methods Based on Co-evolution

Computational approaches to determine the extrapolation of ideas for molecular level co-evolutional studies are used to identify PPI's by co-evolution characteristics. The idea is that a specific number of compensatory mutations in homologous proteins from various species can be used to discover the coadaptation of interacting proteins. The distribution of correlation values is used to calculate an interaction index. An advanced method evaluates a comparative similarity between almost any two protein's phylogenetic trees, using the entire phylogenetic tree network, to better account for the coevolutionary context of the proteins-all protein pairings in the genome [24].

2.4.2. Drug Target Prediction in PPI Network

Engin *et al.* have launched a new PPI network form, known as the P2IN (protein interface network), where nodes with interface structures are tagged for network-scale examination of protein interfaces. The interactions are represented in this illustration by the edges in between interfaces. This illustration shows several interfaces that a protein pair uses to interact and different protein pairings with comparable drug-target interface architectures. Proteins that compete for a particular surface region can also be detected. Engin *et al.* used this method to simulate pharmacological actions on a system level and detect adverse drug effects. For this purpose, they created a novel network assault model termed "interface attack". In PPI networks, the interface attack imitates the effects of medication. An interface attack breaks edges between proteins with identical interface structures at the same time because a drug can bind to all proteins with identical interface motifs and inhibit their interactions with their physiological partners. They created a structural network using PRISM, including protein complexes and their connections. PRISM is a computer protein docking approach that predicts the binding of protein pairs using existing interface structures taken from the PDB (protein data bank) as templates [26].

2.4.3. Limitations

Despite their considerable success, PPINs for repositioning medicines have certain limits. PPINs may have functional links that are not fully defined because they are derived from various experimental backgrounds. The derived network is biased because the required data is noisy and limited. Furthermore, there is no easy way to link a responsive network to an entire organism's reaction [2].

2.5. Drug-target Interaction Networks (DTNs)

An interaction between the drug and the target is critical in the drug development process. Predicting drug-target interaction networks in significant human diseases might provide helpful information for determining disease mechanisms of action [27]. If the drug targets are precisely predicted, the DR (drug repurposing) task is more straightforward. The experimental determination of DTI takes both time and resources. As a result, computational methods for predicting potential DTIs are required [2]. At the system level, identifying both on- and off-target chemical probes increases our understanding of their therapeutic potential and potential

adverse effects, speeding up and de-risking the drug discovery process [28]. Enzymes, ion channels, G protein-coupled receptors (GPCRs), and nuclear receptors are among the protein targets affected by ligand interactions. Several high-throughput experimental programmes examining the genome, transcriptome, and proteome are helping us understand the genomic areas occupied by these protein classes. Using high-throughput screening of large-scale chemical compound libraries and a variety of biological tests, we may simultaneously explore the chemical space of candidate compounds [29]. There are a variety of strategies for forecasting potential DTIs, with many of them relying on a network representation. A bipartite interaction network is formed in network-based models, with nodes representing medications and targets and edges denoting interactions [2]. A range of computational techniques has been developed to investigate and predict drug-target interactions. Docking models and literature text mining are two of the most often utilized methods. Both approaches, however, have obvious limitations. Docking, for example, cannot be used on proteins with uncertain 3D structures, making it impossible to utilize on a broad scale. Because text mining methods are typically based on keyword searches, they cannot uncover new biological results and suffer from repetition in compound/gene names in the literature [29]. Different kinds of data are needed to develop drug and target interaction networks. Some of the data are genomic, drug-protein interaction, and chemical data. Chemical structures of drug compounds and genomic data can be derived from the KEGG LIGAND database's DRUG and COMPOUND sections [30].

Traditional biological experiments are used to identify DTIs by comparing the inhibition constant (K_i), dissociation constant (K_d), half-maximal inhibitory concentration (IC_{50}), or half-maximal effective concentration (EC_{50}) values of drugs (e.g., approved drugs, drug candidates in clinical trials, drugs withdrawn from the market, and drug-like new chemical entities) to tar. However, systematically and empirically determining all possible DTIs is time-consuming and costly [31].

2.5.1. Prediction of Compound-target Interaction Networks Using a Computational Method

As illustrated in the cases later in this section, computational prediction methodologies enable massive, systematic pre-screening of chemical agents, exposing the potency of investigational compounds and potential new contexts for previously licensed treatments. The network approach allows data from large-scale experiments to be abstracted, integrated, and organized, making it easier to extract relevant information from complicated biological systems [28].

2.5.1.1. In the DTI Prediction, the Topology of the DTI Network is used

The topology of the experimentally mapped interaction network can provide essential data about the system under investigation, allowing for predicting new compound-target linkages. Van Laarhoven *et al.* presented the Gaussian Interaction Profile (GIP) kernel, a similarity metric based on binary vectors, each representing the presence or absence of a drug's (or target's) interaction with each target in the DTI network under consideration. This study shows that previous

interactions are a valuable source of information for prediction algorithms. Cheng *et al.* introduced the node- and edge-weighted variants of the NBI (Network-based inference) technique. The EWNBI/NWNBI (node and edge weighed network-based inference) allows you to rank drug-target relationships based on their quantitative binding affinity values. NWNBI/EWNBI provides a more accurate technique for resource distribution than the original NBI method, which dispersed information evenly among all nearby nodes. The methods presented above can only forecast binary DTIs and provide no extra information about their nature. To overcome this issue, Wang and Zeng introduced a constrained Boltzmann machine technique based on a two-layer graphical model that can distinguish direct from indirect DTIs and predict binding, activation, and inhibition kinds of connections [28].

2.5.1.2. Inference Using Chemical and Genomic Profiles in a Network-based DTI

Approaches that rely purely on topological data from compound-target networks have the drawback of being unable to predict interactions for therapeutic candidate compounds with no known targets in the training data. Supervised approaches that use additional sources of information, such as chemical and genomic profiles of the molecules, can effectively overcome this challenge by integrating drug-drug and target-target interrelationships in the prediction process. The method entitled Network-based Random Walk with Restart on the Heterogeneous Network also used chemical and genetic information sources (NRWRH). To determine drug-drug (or target-target) links, NRWRH uses a weighted sum of chemical structure (protein sequence) similarity matrix based on the number of known targets shared by each pair of pharmaceuticals [28].

2.5.1.3. Limitations / Challenge

Because they are relying on training data, they are unable to anticipate novel drug/target candidates reliably. Some of the issues in developing computer algorithms for predicting such potential interactions are as follows: First, because known DTIs are rare, prediction accuracy should be tested with novel drugs with no known target interactions. Another one is the scarcity of empirically validated negative DTI exemplars; selecting negative examples is challenging, if not impossible [2].

2.6. Drug-drug Interaction Networks (DDIs)

Polypharmacy has been more common in recent years, particularly among the elderly who have various ailments. One of the critical concerns in pharmaceutical research is drug-drug interactions (DDIs). Many machine learning-based approaches for DDI prediction have been presented, but the majority of them predict whether two medications will interact or not [32]. Two drugs are considered to interact if they have been shown to have the same molecular profiles, such as gene expression patterns in cultured cells, or if they have been reported to have similar adverse effects [2]. Several publicly accessible databases can assist healthcare providers in locating DDIs. Drug Bank, for example, is an online drug database that has 8311 medication listings. Almost 200 fields in each drug entry, including a DDI field

[33]. There are two types of DDI extraction methods available: one-stage and two-stage approaches. By training a multiclass SVM (support vector machines), the one-stage technique achieves DDI detection and classification concurrently. It quickly assigns each candidate instance to one of the five DDI classes. The learning methods are divided into three steps by the two-stage method: first, all DDIs are recognised, and then the identified DDIs are classified into one of four unique DDI classes [34]. The DDI extraction CNN (convolutional neural network) model is a layered model, which is a version of the sentence classification model. In addition to word embeddings, the CNN model incorporates position embeddings to represent relative distances between words and the two medications of interest [34]. MANTRA is a community detection-based DR technique. Its main goal is to predict medication interactions and mechanisms of action (MOA). Its primary data sources are the Connectivity Map (cMap), DrugBank, and ChemBank. It was used to demonstrate the effectiveness of anticancer drugs. SITAR is a classifier for logistic regression. Five drugs were used, as well as three target similarities. Drug similarities are determined using chemical structure, pharmacological side effects, gene expression profiles, and the Anatomical, Therapeutic, and Chemical classification system. Target similarity measures were calculated using sequence similarity, PPIN closeness, and semantic gene ontology similarities. It aimed to find which similarity combinations would result in the most accurate forecasts. KEGG Drug, DrugBank, DCDB, and Matador are data sources. A frequent alternative for drug-drug interaction (DDI) prediction is a similarity-based technique. Most similarity-based DDI prediction algorithms, on the other hand, focus solely on immediate similarities, ignoring the transitivity of similarity [2].

2.6.1. Limitations

The inaccuracy of numerous structural and chemical properties of known pharmacological compounds is one of the fundamental limitations of DR based on drug-drug similarity. Furthermore, structural traits alone cannot predict many physiological outcomes. To address these constraints, a variety of similarity measures, such as the one employed, can be used [2].

2.7. Drug-disease Interaction Networks

Drug-disease connections provide crucial data for drug development and repositioning. Drug-disease relationships can have various impacts, with the therapeutic effect attracting the most attention shown in Fig. (3). As a result, creating drug-disease connection prediction methodologies is critical, distinguishing therapeutic correlations from other types of associations shown in Fig. (3) [35]. An essential challenge is the development of an integrated methodology for detecting drug-disease connections using informational data [36]. There are different methods for predicting drug-disease interactions. Some of them are Proph Net, which can integrate data from complicated networks with a variety of elements and interactions [37]. Traditional methods for *in silico* drug repositioning can be divided into two categories: those that rely on the medication's composition (chemical or molecular properties) and those that rely on knowledge of diseases,

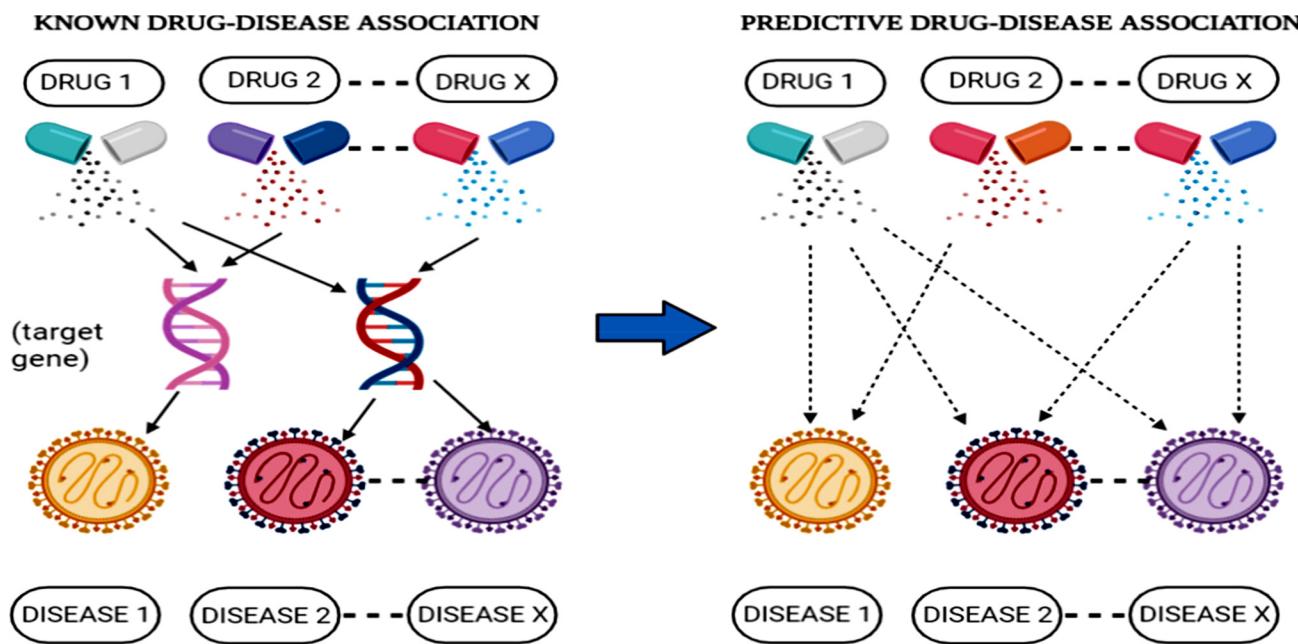


Fig. (3). Diagrammatic representation of drug-disease association prediction. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

their underlying mechanisms, or symptomatology [37]. Drugs can be connected to disease states and repositioned using computational analysis of similarities in molecular profiles. When a biological system is exposed to a pharmacologically active chemical, the molecule's MOA affects the system. Online resources such as Drug vs. Illness, Database for Annotation, Visualization, Integrated Discovery, and Gene Set Enrichment Analysis allow you to compare drug and disease markers in gene expression profiles. As a result, a 'signature' of a pharmaceutical chemical's molecular activity in a biological system can be established. Even when the MOA or primary medicine target is unclear, a study of these molecular activity markers shows therapeutic correlations between medications and disorders [2].

2.7.1. Methods for Evaluating Drug-disease Links

2.7.1.1. Adjacency-based inference

This is a grading technique for drug-disease interactions based on documented drug-disease connections and adjacencies. The three methodologies employed in this method are drug-adjacency-based inference, disease-adjacency-based inference, and combination adjacency inference. The basic principle of drug-adjacency-based inference is that if one medication has been linked to an ailment, another drug similar to it will also have been linked to the sickness.

2.7.1.2. Module-distance-based inference

A topological module is a group of genes that are topologically connected. The topological module shared by two medications is retrieved for a specific ailment. One of the drugs has a known drug-disease link, while the other is a disease candidate drug. The d-module distance-based inference, p-module distance-based inference, and a combined module-distance inference method are used in this method [38].

2.8. Drug-side Effect Networks

Side effects are unintended consequences of medication therapy and valuable sources of human phenotypic data. The side effect resource (SIDER), a side effect database, was recently released as a first step toward documenting the relationship between drugs and their adverse effects. Pharmacological effects on phenotype will be more efficient and systematic to examine which pathways respond to medicines that modify phenotype [39]. Network-based models can be utilised to uncover molecular roots of safety issues, like side effects, in addition to therapeutic benefits. In a recent study, the bSDTNBI (balanced substructure-drug-target network-based inference) technique was utilized to forecast possible targets for GPCR (G-protein coupled reaction) medicines in terms of adverse effects. Then, drug-gene-disease networks were constructed (1) [40]. In their underlying systems, medications with comparable side-effect profiles may have similar therapeutic properties, making it possible to link pharmaceuticals to disorders. Drug impact techniques, such as gene expression profiles, assume that medications with similar therapeutic effects are targeting the same protein(s). The similarities in side effects can be used to build a pharmacological network. In this method, the functional distribution of a drug's surrounding medications can be used to anticipate its indications [2]. SIDER was designed to look into the links between side effects and pharmaceuticals, and it already has 888 medications linked to 1,450 distinct types of side effects. It gives information on the frequency of occurrence of medications and side effects for one-third of all drug-side effect pairs. The network can automatically discover the relationship between biological processes and side effects by creating a hierarchical network of drug-biological processes impacted by the association of targets with side effects using the connection map and SIDER [39]. Some of the methods and data sets used in the drug side effect network are shown in Table 3.

Table 3. A summary of network-based DR methods based on drug indications and drug side effects.

Methods	Data Sets
Two clustering algorithms	DrugBank, KEGG Medicus
Computational inference	CTD
Logistic regression classifier	DailyMed, SIDER, OMIM, DCDB, Matador, KEGG DRUG, DrugBank
Statistical analysis	FDA drug approval package, Side Effects of Drugs Annuals

2.8.1. Limitations

Since adverse effects are not always visible in gene expression data, the drug-side effect relationships available in SIDER are incomplete. As a result, drug-side effect interactions found in SIDER have to be filtered to uncover persistent gene expression data connections [39]. However, in the similarity determining method, the approaches discussed above are limited to well-studied medications due to a lack of adverse reaction data. Indeed, side-effect similarity techniques require each treatment to have its side-effect profile; regrettably, current illness and drug phenotypic data are noisy and incomplete. After years of clinical use and post-market surveillance, the side-effect profile of a newly licenced medicine can be fully determined. It is frequently necessary to predict a drug's side effects in the absence of such information. Furthermore, some medications with similar side effects do not have a target protein. This might lead to prediction algorithms that determine the adverse effects of medicine based on the molecular structures of its targets. Furthermore, there is no apparent relationship between phenotype and MOA. The incomplete side-effect information received through spontaneous reporting systems during post-marketing surveillance is further muddled by individual patients' drug histories or traits, as well as other hidden factors, according to another apparent flaw of the side-effect similarity technique [2].

2.9. Drug-toxicity Association Networks

Type A toxicity, or intrinsic toxicity, is dose-dependent and linked to the drug's primary pharmacological target. In contrast, Type B toxicity, or idiosyncratic toxicity (IT), is unpredictable, occurs in less than 1 in 5000 instances, is not dose-dependent, and is linked to off-target effects [41]. One of the most common reasons for dropout is safety during clinical trials. All clinical candidates are assessed in animals before clinical testing to determine the range of toxicities that may occur in human subjects and the safe dosage for clinical testing. Nonclinical safety assays are still utilised to forecast clinical liabilities for novel drug candidates, despite investments in toxicogenomics. Whole-genome transcriptional profiling with limited numbers of treatments for phenotypes of interest can be problematic with network-based genomic analysis techniques [42]. Drug-induced cardiotoxicity was assessed using innovative methodologies such as network-based drug-target interactions and drug-side effect interactions. A network-based system pharmacology technique can be utilized to find well-known chemotherapeutic

medications as well as novel oncological-drug-induced cardiotoxicity [43]. Gene signatures, pathway-based enrichment analysis, co-expression networks, and adverse outcome pathways have all been used to assess the risk of utilising transcript profiling in risk assessment. Toxicogenomic safety testing approaches, on the other hand, are difficult to utilise and have little utility in resolving ambiguity in safety forecasts, serving primarily as an investigative tool [42]. Adverse drug events (ADE) based model is one of the computational methods to determine drug toxic effects. The steps for predicting include data collection, network generation, and prediction. The previously published and proven methodology used the protein-protein association network (P-PAN) to create the ADE model [44]. The Drug Matrix (DM) and open TG-GATEs (TG) databases, as well as GEO microarray data processing, are two massive publicly available databases that document drug and other chemical effects [42]. The sparse nature of the dataset is one challenge with adding drug-binding protein data, as each medication will only bind a small subset of all available proteins, and this number will vary between medications. Due to the small number of confirmed harmful medications that meet our criterion, many bound proteins and most interactions will only occur once in the whole dataset [41].

2.10. Integrated-network Based Methods for Drug Repurposing

Drug repurposing has grown in importance in the field of drug development. Several computational methodologies have been proposed or modified from past applications to assist reveal new repurposing prospects and ease the discovery process [45]. Drug repositioning and computational prediction of drug-target interactions (DTIs) are two approaches to drug discovery and development that are both low-cost and high-efficiency. Traditional social network-based techniques based on naive DTI topological data cannot predict potential targets for new chemical entities or failed clinical trials drugs [46]. It is vital to keep in mind that none of these approaches will be able to show (or even simulate) the complex interactions between drugs, targets, and diseases on their own. As a result, we are left with the option of using one or more computational methods to "navigate" through the massive amounts of data accessible and maybe uncover "clues" strong enough to form a repurposing hypothesis worth testing experimentally [45]. The network architecture integration of large-scale genomic, transcriptomic, and proteomic data with signalling and metabolic data has offered

new insights into the molecular basis of complex illnesses and enabled a network-based approach to drug discovery and development. The introduction of network medicine not only raises the chances of a better and deeper understanding of the molecular complexities of illnesses, but it also serves as an effective tool for evaluating new drug targets and generating new disease linkages, allowing for medication repositioning. Drug target prediction and repositioning were handled as two different processes in many of these classic inquiry methodologies [47]. Because some components of noise in each data modality are independent, combining these modalities reduces the obfuscating impact of such noise. By combining gene expression, chemical structure, and target interaction profiles into a personalised drug matrix and feeding it into a multiclass SVM (support vector machine) classifier, Napolitano *et al.* demonstrated the benefits of data integration for predicting medication therapeutic class. For example, Zitnic *et al.* used a simultaneous matrix factorization approach to integrate a variety of drug, gene, and disease information sources to develop a data-driven disease classification system that found literature support for all 14 predicted disease–disease associations that were not already in the Disease Ontology [48]. The integrated strategy allows for the repositioning of known therapeutic targets for other diseases to the specific disease, as well as the prediction of hitherto unexploited pharmacological targets that are not currently used for any disease therapy. The technique inputs a disease gene expression profile and a high-quality interaction network and outputs a prioritised list of therapeutic targets [49]. It is undeniably challenging to integrate the vast and diverse amount of available data (chemical, biological, structural, and clinical) into a cohesive workflow. In this sense, combining and utilising a variety of computational methodologies, as shown in Table 4. Will provide significant opportunities to expand the breadth of each method's application and more completely exploit data from multiple sources shown in Fig. (4) [45].

2.10.1. Different Methods of Integrated Based Network

2.10.1.1. DReSMin (Drug Repositioning Semantic Mining)

DReSMin is a semantic distance threshold-based technique for searching integrated networks for instances of a particular semantic subgraph. DReSMin decreases the search time for more significant subgraphs by incorporating a semantic graph pruning step and employing a mechanism for partitioning enormous subgraphs before searching. For example, this method searches an integrated drug dataset for semantic subgraphs that indicate drug repositioning prospects, emphasising inferring D-T (DRUG-TARGET) interactions. Thus, this integrated method is used to determine D-T interactions effectively [50].

2.10.1.2. A Two-layer Heterogeneous Network Model for Drug Repositioning

This is an integrated system. The two-layered heterogeneous network model has two types of nodes (drug nodes and sickness nodes) and three types of edges (drug-drug edges, drug-disease edges, disease-drug edges). The goal is to find hidden linkages between pharmaceuticals and diseases based on drug-drug similarities, disease-disease similarities, and known drug-target interactions [47].

2.10.1.3. A Three-layer Heterogeneous Network Model for Drug Repositioning

A three-layer heterogeneous network is a multi-layer system having a large number of edges and three different types of nodes (disease nodes, medication nodes, and target nodes). The goal is to capture disease-drug, drug-target, and target-target similarities, as well as known disease-drug and drug-target interactions.

2.10.1.4. An Iterative Updating Algorithm

This system is founded on the guilt-by-association notion, which argues that unique disease–drug correlations can be extrapolated from similar disease–drug relationships. Similarly, known associations between similar medications and targets can be used to infer a novel drug-target interaction. Similarly, known associations between similar medications and targets can be used to infer novel drug–target connections [47].

2.10.1.5. Substructure-drug-target Network-based Inference (SDTNBI)

To bridge the gap between unknown chemical compounds and the known DTI network, SDTNBI integrates network and cheminformatics. Using four benchmark data sets, including G protein-coupled receptors, kinases, ion channels, and nuclear receptors, SDTNBI achieved high performance in 10-fold and leave-one-out cross-validations. Using a resource diffusion technique, SDTNBI uses established DTI networks, drug–substructure links, and novel chemical entity–substructure links to infer novel targets for old pharmaceuticals, failed pharmaceuticals, and novel chemical entities. The ChEMBL database revealed two DTI networks containing known chemical–protein interactions for G protein-coupled receptors (GPCRs) and kinase superfamily members (Kinases). In the DrugBank database, two external validation sets corresponding to the two DTI networks were discovered [46].

2.10.1.6. Drug Target Interactions Network (DTINet)

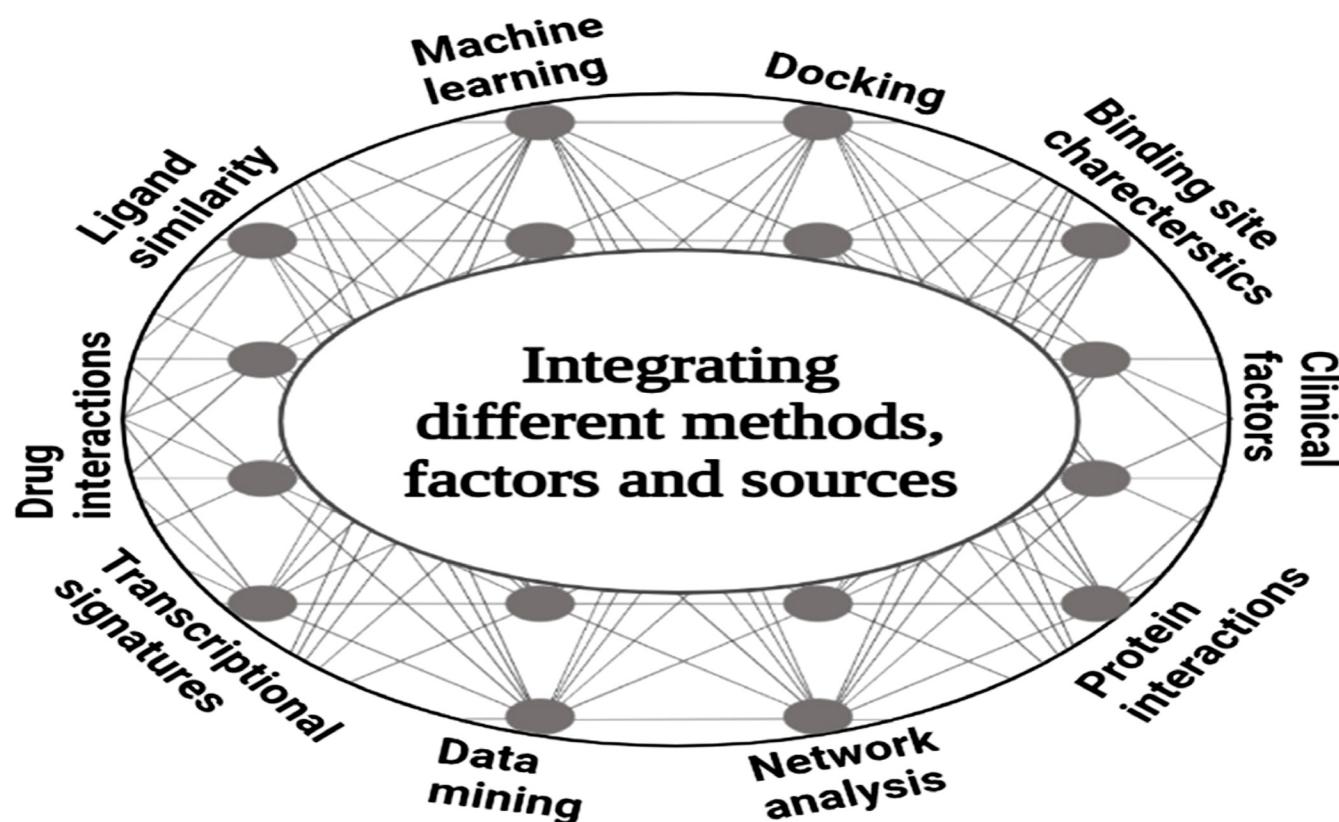
DTINet is a DTI prediction pipeline that uses a unique network integration approach. DTINet not only integrates data from a variety of sources (such as drugs, proteins, diseases, and side effects), but it also deals with the noisy, incomplete, and high-dimensional nature of large-scale biological data by learning low-dimensional but informative vector representations of features for both drugs and proteins. In a wide number of networks, DTINet keeps track of the environment as well as the topological aspects of nodes (such as drugs or proteins). The DTINet algorithm then identifies the best projection from drug space to target space, allowing additional DTIs to be predicted based on the geometric proximity of the mapped vectors in a unified space [51].

2.10.1.7. Predictor for Drug Repurposing (PreDR)

PreDR classifies drugs based on their chemical structure, similarity to target proteins, and similarity to adverse effects. These parameters are used to create a kernel function that connects medications and disorders. Then, to anticipate novel drug–disease interactions, a support vector machine (SVM) is trained [5].

Table 4. A summary of integrated network-based DR (drug repurposing) methods.

Methods	Data Sets
Canonical correlation analysis and large margin method	DrugBank, PubChem, UMLS, UniProt Knowledgebase, SIDER
Supervised bipartite graph inference	KEGG DRUG, KEGG LIGAND, Japan Pharmaceutical Information Center
Semantic subgraph detection	DrugBank, ChEMBL, UniChem and DisGeNET
Classification based on a logistic regression	Chemical genomics data set (LINCS), PubChem, DrugBank, KEGG, TCGA data portal
Ontology-based reasoning	FDA-approved drugs, KEGG, PharmGKB
Monte Carlo Multiple Minimum conformational analysis	ChEMBL and SIDER
Bipartite network projection and prioritization	KEGG, OrthoMCL database, ChEMBL, and PubChem
Random walk with restart	Data sets
SVM classifier based on kernel fusion	PubChem, KEGG BRITE, BRENDA, SuperTarget and DrugBank
Information flow-based method	DrugBank, OMIM, and Sophie Integrated Druggable Genome Database

**Fig. (4).** Diagrammatic illustration of integrated network method. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

2.10.1.8. Network-based Random Walk with Restart on the Heterogenous Network (NRWRH)

The DTI network used by NRWRH is rich in drug-drug and target-target interactions, which are estimated using structure and sequence similarity. As a result, to forecast novel interactions, a random walk method is used [5].

2.11. Semantic Link Network for Drug Repurposing

Many network-based medication repositioning strategies have been developed based on similarity networks that incorporate multiple sources of drug and disease information. In a heterogeneous network, these approaches, on the other hand, may simply treat nodes as having the same type and ignore the semantic meanings of different meta-paths [52]. Tim Berners-Lee designed the Semantic Web to provide the foundational technology for a "Web of Data" that allows machines to interpret data better and provides a set of interoperable data formats that can be used across platforms. To achieve this purpose, many basic formats were created to provide a more in-depth means of modelling, describing, and querying data [53]. The semantic web-linked data format RDF (Resource Description Framework) is a semantic web-linked data format. The data is stored as triples (subject, predicate, and object) using a graph model, defining the subject-object relationship. This makes it possible to break down almost any dataset into these triples. This linked data format allows data important to drug discovery to be structured and integrated with a standard interoperable format within a knowledge base, resulting in a more detailed description [53]. To examine the association of drug target pairings and anticipate missing connections, a novel statistical model called Semantic Link Association Prediction (SLAP) was developed based on semantic networks. SLAP can distinguish between known drug-target pairs and random drug-target pairs, as well as build indirect drug-target associations. The SLAP network, which has 295,897 nodes and 727,997 edges, is heterogeneously made up of 17 public data sources about drug-target interactions. A previously created systems chemical biology / chemo-genomics ontology was used to semantically label each node and edge. Each path is an instance of a path pattern, which are collections of nodes and edges with the same meaning (but different data) [54]. For the prediction of drug repositioning, HeteSim DrugDisease (HSDD), an innovation, is developed based on a semantic network. HeteSim is a path-based assessment that accurately assesses the relatedness of nodes in a heterogeneous network of diverse sorts. This technique can capture the semantics of meta-paths, which is necessary for evaluating the significance of nodes in heterogeneous networks [52].

2.12. Isoform-isoform Networks

Isoform-isoform networks are similar to PPI networks; however, they represent interactions between isoforms rather than individual proteins. Protein-isoforms are various protein variants of a single gene that result through alternative splicing, transcription, translation, or post-transcriptional changes. Isoforms derived from the same gene might have diverse functions or even opposite effects in certain processes. Normal PPI networks, which link isoforms of the same protein into the same node, do not reflect this diversity in

function. As a result, isoform-isoform networks account for the wide range of descendants of the same gene, with each node representing an isoform and edges representing connections between them. It is estimated that each of the approximately 200000 human proteins produces about 1000000 different isoform transcripts. Isoform -isoform networks record connections between isoform transcripts in genes and provide more depth than PPI networks [4]. For Isoform-Isoform Interaction (III) reconstruction, RNA-sequence data provides unique, informative sources. IIIDB (isoform-isoform interaction database) is a database that is used to retrieve and manage projected human IIIIs. Users of IIIDB can distinguish between high-confidence and low-confidence human III predictions, as well as review the total evidence values for each projected III. Thus, IIIDB act as an efficient data source for isoform-isoform networks [55]. Another database used for the III network is APPRIS (Annotating principle protein splice isoforms) database. The APPRIS database efficiently estimates main isoforms based on protein sequence, structure, and function conservation. Although the construction of sophisticated functional networks requires identifying important isoforms from MIGs (multi-isoform genes) in normal tissues, inference of co-expression networks only requires gene/isoform expression data. Every node in a gene co-expression network represents a gene, and if there is significant co-expression between two connected nodes, the network is called a gene co-expression network. The degree of a node is determined by the number of edges emanating from it in a biological network. Hubs in co-expression networks are nodes with significantly greater degrees than the others [56].

CONCLUSION

It is more time-consuming, complex, and high-cost-oriented to discover a new chemical entity. Getting regulatory approval is also a tedious process for novel drugs. Thus, the technique of repurposing already existing drugs for novel uses is one of the best ways to overcome this problem. One of the most effective methods to generate new indications for pre-existing medications is to use computational approaches for repositioning. Network-based computational methods are the best tools for discovering the drug targets by linking molecular and phenotype levels. Various studies have proved that drug repurposing based on network models will give satisfactory results. The main advantage with these biological networks in drug repurposing is this method gives interpretation and prediction results not only by mathematical basis but also by considering different types of biological concepts. These biological networks cover different biological and pharmacological aspects like gene regulatory interactions, isoform-isoform interactions, protein-protein interactions, drug-target, drug-disease, and drug-side effects interactions, metabolic effects considering ADE properties and can be chosen depending upon desirable requirements. Utilizing information from various databases and various experimental gave additional benefits for network-based drug repurposing methods. Along with these, due to modern developments, integration of different network methods together with different data sets gave these network methods a noble path in utilizing pre-existing drugs for new indications (drug-repurposing/ drug repositioning). Every network method comes with its methodologies, ad-

vantages, and challenges. The absence of adequately structured standard data for DR is the most serious issue, making comparison and performance evaluation of different computing approaches difficult. Comparing multiple methods will be challenging because they depend on various data sets. The absence of standard reference data also restricts network methods as a standard operating tool for drug repurposing regardless of whether these network-based methods become standard tools for drug repurposing. However, it is certain that network-based approaches offer more advantages than other traditional ways for drug repurposing and make this repositioning a simple process despite all limitations and challenges.

RECOMMENDATIONS

This motivates the integration of different biological information, molecular data, and online health community information, leading to the construction of multiple interaction networks. They mainly have to be constructed using heterogeneous information sources to improve the reach and reliability of new drug repurposing methods. As any single type of data presents a one-dimensional view of a biological system, evaluating the performance of an integrative method based on a single data type may not be reliable; thus, the use of the integrated networking to correlate all the parameters may overcome the majority of limitations. Therefore, we need to create a reference body of data for the standardized evaluation of integrative network approaches to better predict models.

LIST OF ABBREVIATIONS

DR	= Drug Repurposing/Drug Repositioning	PDB	= Protein Data Bank
R&D	= Research and Development	DTIN/DTINet	= Drug-target Interaction Networks
FRET	= Forster Resonant Energy Transfer	DTI	= Drug-target Interactions
MS	= Mass Spectrometry	GPCRs	= G Protein-coupled Receptors
DNA	= Deoxyribonucleic Acid	Ki	= Inhibition Constant
RNA	= Ribonucleic Acid	Kd	= Dissociation Constant
DTI	= Drug-target Interactions	IC50	= Half-maximal Inhibitory Concentration
GRN	= Gene Regulatory Networks	EC50	= Half-maximal Effective Concentration
TF	= Transcription Factors	GIP	= Gaussian Interaction Profile
Mtb	= Mycobacterium Tuberculosis	NBI	= Network Based Inference
MTB PROM	= Mycobacterium Tuberculosis Probabilistic Regulatory Mechanism	EWNBI	= Edge Weighed Network-based Inference
INZ	= Isoniazid	NWNBI	= Node Weighed Network-based Inference
ETH	= Ethionamide	NRWRH	= Network-based Random Walk with Restart on the Heterogeneous Network
EGRNI	= Gene Regulatory Network Interface	DDINs	= Drug-drug Interaction Networks
FBA	= Flux Balance Analysis	DDIs	= Drug-drug Interactions
PPIN	= Protein-Protein Interaction Networks	SVMs	= Support Vector Machines
PPI	= Protein-Protein Interactions	CNN	= Convolutional Neural Network
P2IN	= Protein Interface and Interaction Network	MOA	= Mechanisms of Action
PRISM web server	= Protein Interaction by Structural Matching	CMap	= Connectivity Map
		SIDER	= Database-side Effect Resource Database
		bSDTNBI	= Balanced Substructure-drug-target Network-based Inference
		IT	= Idiosyncratic Toxicity
		ADEs	= Adverse Drug Effects/Adverse Drug Events
		P-PAN	= Protein-Protein Association Network
		GEO	= Gene Expression Omnibus
		TG database	= Therapeutic Good Administration Database
		DReSMin	= Drug Repositioning Semantic Mining
		RDF	= Resource Description Framework
		SLAP	= Semantic Link Association Prediction
		HSDD	= Hete Sim Drug Disease
		IIDB	= Isoform-Isoform Interaction Data Base
		APPRIS database	= Annotating Principle Protein Splice Isoform Database
		MIGs	= Multi-isoform Genes

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

The work was supported by JSSAHER Research grant (Ref: REG/DIR (R)/URG/54/2011-12/5663, dated 1/10/2021).

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

"We acknowledge the generous research infrastructure and supports from JSS College of Pharmacy, Ooty, The Nilgiris, Tamilnadu, India."

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