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EXPLORING THE ROLE OF DRUGBANK IN INVESTIGATING PHARMACOGENOMIC-DRIVEN NOVEL DRUG

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ABSTRACT
Bioinformatics plays a vital role in drug discovery and repurposing, yet challenges persist in data availability, biological complexity, and method standardization. The continued exploration and utilization of resources such as DrugBank will play a crucial role in advancing drug development and uncovering novel therapeutic opportunities. Our study presents a comprehensive analysis of the methodology utilized by bioinformaticians to integrate DrugBank with multiple databases, with the aim of facilitating the discovery of novel drugs. A literature review was conducted using Scopus and PubMed, focusing on articles from the last 10 years. Relevant articles meeting the inclusion criteria were collected between October and November 2022. The review identified 35 unique papers after removing duplicates. Screening led to 9 papers meeting inclusion criteria. The study reveals that DrugBank is an indispensable resource, aiding drug-gene interaction analysis and connecting gene data sources with potential drug candidates. It streamlines the multinetworking process and enables the identification and validation of new medications through clinical tools. These findings shed light on drug-gene interactions and drug repurposing, emphasizing the significance of leveraging multiple databases and network data. DrugBank's pivotal role in advancing drug discovery and personalized medicine underscores its importance in bioinformatics research.

Keywords: Bioinformatics; Drug Discovery; Drug Repurposing; Genomic Data Integration

1. INTRODUCTION

Bioinformatics has emerged as an essential tool in drug discovery, providing crucial biological, chemical, and toxicological information to expedite early-stage drug development (Balamurugan et al., 2021; Xia, 2017). Through the utilization of high-throughput molecular data, bioinformaticians effectively identify therapeutic targets, leading to a transformative shift in rational drug design and addressing the need for safe and effective medications (Ramharack & Soliman, 2018; Romano & Tatonetti, 2019; Santoso et al., 2021; Xia, 2017). Bioinformatics methodologies encompass various aspects of potential drug candidates, including the analysis of biological function and sequence, while in silico tools are extensively employed to predict the biological affinities of input structures (Lauria et al., 2020; Romano & Tatonetti, 2019).

In the field of drug repurposing, researchers have been exploring innovative bioinformatics-based approaches, such as two-stage prediction with machine learning and gene expression data clustering (Cong et al., 2022; Jarada et al., 2020; Nam et al., 2019; Saberian et al., 2019; Zahrah et al., 2024). They also develop computational techniques to classify research

examples based on evidence levels and leverage existing knowledge on disease-drug pairs for improved efficiency (Saberian et al., 2019; Vogrinc & Kunej, 2017). However, bioinformatics-based drug repurposing encounters challenges related to data availability, biological complexity, limited understanding of disease mechanisms, lack of standardization, and resource-intensive processes (Setiyaningsih et al., 2024). Despite these challenges, it holds the potential to accelerate drug development and provide novel treatments (Hernández-Lemus & Martínez-García, 2021; Jarada et al., 2020; Romano & Tatonetti, 2019).

DrugBank, an accessible online database, provides comprehensive drug-related information encompassing drug-target interactions, mechanisms of action, structure, pharmacology, pharmacokinetics, metabolism, and pharmaceutical properties of molecular drugs (Wishart et al., 2018). By utilizing DrugBank, researchers can identify established medications with potential efficacy for new indications, potentially reducing the time and cost associated with drug development (Feng et al., 2023). Despite the lack of guaranteed data accuracy, DrugBank is regarded as a reliable resource for drug research and development due to its meticulous curation, use of primary sources, and involvement of expert biocurators, ensuring the provision of high-quality data (Abiyana et al., 2024; Wishart & Wu, 2016). Noteworthy successful examples of drug repurposing using DrugBank include minoxidil for male pattern baldness (Zheng, 2016), thalidomide for leprosy and multiple myeloma (Krishnamurthy et al., 2022), metformin for various cancers (Zong et al., 2022), and sildenafil for erectile dysfunction (Jourdan et al., 2020).

Bioinformatics has significantly contributed to drug discovery and repurposing. However, there remain areas that require further investigation. Additional research is needed to address challenges related to data availability, biological complexity, and the standardization of methodologies. Efforts should also be directed towards improving our understanding of disease mechanisms and refining computational techniques to enhance the efficiency and reliability of bioinformatics-driven approaches. The continued exploration and utilization of resources such as DrugBank will play a crucial role in advancing drug development and uncovering novel therapeutic opportunities. Our study presents a comprehensive analysis of the methodology utilized by bioinformaticians to integrate DrugBank with multiple databases, with the aim of facilitating the discovery of novel drugs.

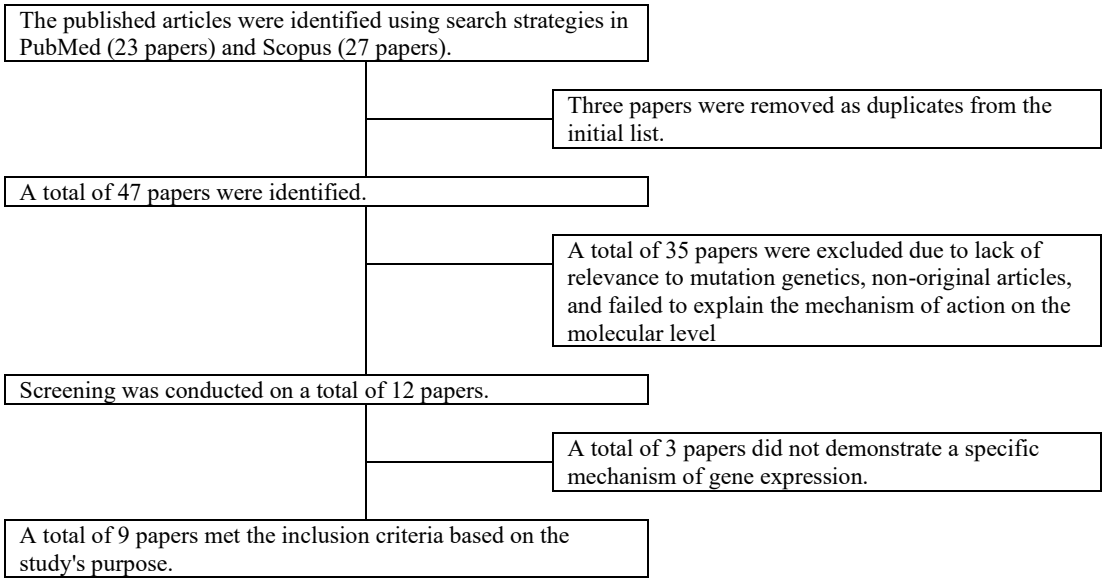
2. METHODS

The literature review for this study involved searching through the Scopus and PubMed databases. The search strategy employed a combination of the following keyword variants: keyword 1 - "Drugbank AND Genomic AND Repurposing Drug," and keyword 2 - "Drugbank AND Pharmacogenomic." The inclusion criteria for articles were limited to original English articles with no restrictions on the last 10 years of publication. The collection of relevant articles was conducted between October 2022 and November 2022.

Our literature review focused on identifying studies that met specific criteria. The inclusion criteria were as follows: (a) studies involving the identification of new drug candidate discoveries, and (b) validation studies of new drug candidate discoveries in a disease. For each relevant literature, the following information was extracted: journal publication name, author's name, publication year, title, disease studied, drug candidates, molecular targes, and the underlying mechanisms explored. By systematically extracting this information, the review aimed to provide a comprehensive overview of the identified studies in relation to their contributions to new drug candidate discoveries and their validation in specific diseases.

The initial search was conducted in PubMed, resulting in the identification of 23 relevant papers. Additionally, a search in Scopus yielded 27 papers. The duplicate papers were removed using reference management software (Zotero), resulting in a total of 47 unique papers. After the removal of duplicates, the remaining articles were screened for relevance. A total of 35

papers were excluded due to lack of relevance to mutation genetics, non-original articles, and failed to explain the mechanism of action on the molecular level. Following the screening process, 12 papers remained for further evaluation. Among these, three papers were excluded as they did not demonstrate a specific mechanism of gene expression. Finally, based on the predefined inclusion criteria and research objectives, 9 papers met the criteria for inclusion in the study (**Error! Reference source not found.**).



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3. RESULTS AND DISCUSSION

3.1. Main Result

In addition to DrugBank, we employed a comprehensive set of 15 integrated tools to conduct gene analysis and facilitate medication repurposing, following a well-established multinetworking bioinformatics approach (Error! Reference source not found.). These tools encompassed various resources, including; ClinicalTrials, PubMed (Adikusuma et al., 2021, 2022; Afief et al., 2022; Irham et al., 2022; Lesmana et al., 2022), HaploReg, STRING (Adikusuma et al., 2021, 2022; Afief et al., 2022; Lesmana et al., 2022), Gwas Catalog (Adikusuma et al., 2021, 2022; Afief et al., 2022; Irham et al., 2022), Phewas Resources (Adikusuma et al., 2022; Irham et al., 2022), Drug Gene Interaction Database (DGIdb) (Fabbri et al., 2021; Zhang et al., 2021), Gene Expression Omnibus (GEO), Cytoscape, GeneMania, PubChem (Zhang et al., 2021), Drug Repurposing Hub (DRH) (Fabbri et al., 2021), National Center for Biotechnology Information (NCBI) (You et al., 2019), UniProt, Protein Data Bank (Phatak & Zhang, 2013).

Integrated tools in gene analysis and medication repurposing offer hope for discovering new treatments across various diseases (Hikmah et al., 2024; Sam & Athri, 2019). The bioinformaticians used clinical data, human gene expression (Li et al., 2021; Santoso et al., 2023), and drug data to identify potential drug candidates (Wu et al., 2022) through a two-stage prediction and machine learning approach (Cong et al., 2022). They also developed a computational tool for rational drug repositioning, highlighting the synergy among these methods (Napolitano et al., 2018).

In alignment with this approach, a framework for identifying drug repurposing candidates from observational healthcare data was introduced, emphasizing the utilization of clinical practice data in drug repurposing (Park, 2021). This innovative strategy not only enables systematic searches for drug repurposing candidates but also emulates randomized controlled

trials (RCTs) using observational data, offering a cost-effective and time-efficient alternative to traditional drug discovery methods (Ozery-Flato et al., 2021). By efficiently emulating hundreds of RCTs from observational medical data, this computational framework provides estimates of drug effects, potentially revolutionizing the drug discovery process (Sam & Athri, 2019). Additionally, the discussion touched upon web-based drug repurposing tools, emphasizing their role in identifying novel indications or molecular targets beyond a drug's initial intended use (Cha et al., 2018). A multi-network mapping exploring the use of DrugBank in various applications for bioinformatics studies is listed in Figure 2.

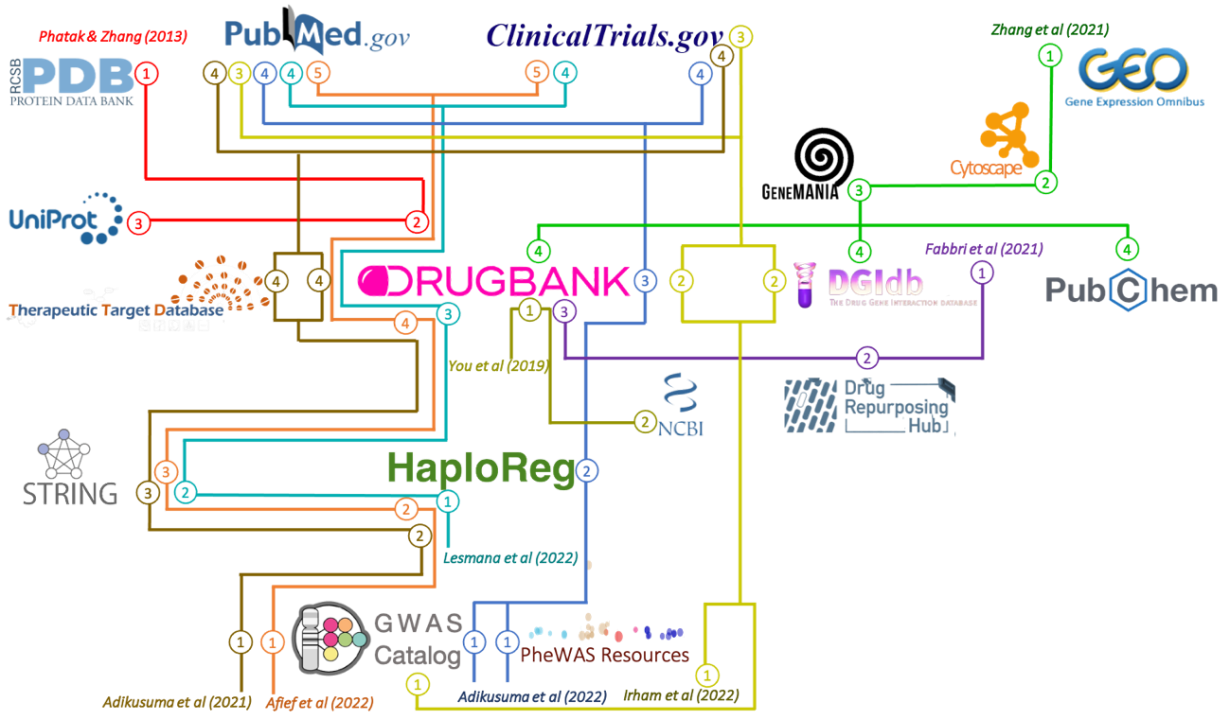

Figure 2. Mapping Multinetworking: Exploring the Use of DrugBank in Various Applications for Bioinformatics Studies.

3.2. Utilizing DrugBank in Multinetworking for Bioinformatics Study

3.2.1. DrugBank Leads the Multinetworking Process

During the initiation phase of multinetworking in bioinformatics research, DrugBank serves as a valuable resource for downloading drugs that interact with target genes. Researchers gather essential data on drug structure, chemical properties, topological properties, and geometric properties of these drugs (You et al., 2019) (Error! Reference source not found.). However, DrugBank may have limitations as a descriptor for certain drug structures. To overcome this limitation, researchers can employ an online chemical modeling environment application (OCHEM) to enhance DrugBank's role (Sushko et al., 2011).

Moreover, there are several alternative sources of information on drugs and drug targets. DrugPatentWatch, a subscription-based service, offers insights into drug patents, generic drugs, and drug litigation, enabling monitoring of the pharmaceutical industry and identification of drug development opportunities (Friedman, 2023). Additionally, RxNav, a web service, provides information on drug-drug interactions by utilizing ONCHigh and DrugBank as sources. ONCHigh is a curated list of high-priority drug-drug interactions determined by experts, while DrugBank offers non-commercial drug-drug interaction information from its database (Peters et al., 2018).

PubChem, a publicly accessible database, contains comprehensive information on chemical substances, including drugs and their biological activities. It provides details on chemical

structure, properties, and compound bioactivity (Kim et al., 2016, 2021). ChEMBL, another database, focuses on bioactive molecules with drug-like properties and offers insights into biological activity, pharmacology, and medicinal chemistry of compounds (Davies et al., 2015; Gaulton et al., 2017; Mendez et al., 2019). Lastly, ClinicalTrials.gov, a global registry of clinical trials, is a valuable resource for searching information on drugs currently undergoing clinical trials, including indications, dosages, and adverse effects (Tse et al., 2018; Zarin et al., 2019).

3.2.2. DrugBank Connects the Multinetworking Process

Here in, we present a team of scientists utilized DrugBank to explore a collection of single nucleotide polymorphism (SNP) genes obtained from various sources, including GWAS (Adikusuma et al., 2021, 2022; Afief et al., 2022; Irham et al., 2022), PheWas (Adikusuma et al., 2022; Irham et al., 2022), HaploReg (Adikusuma et al., 2021, 2022; Afief et al., 2022; Lesmana et al., 2022), and STRING (Adikusuma et al., 2021; Afief et al., 2022; Lesmana et al., 2022) as target genes for drug action. DrugBank provided drugs capable of binding to these genes. The drugs that successfully bound to the target genes, as identified by DrugBank, were considered potential candidates for new medications. The efficacy of the drugs obtained from DrugBank was validated through the simultaneous use of ClinicalTrials and Pubmed tools (Adikusuma et al., 2021, 2022; Afief et al., 2022; Irham et al., 2022; Lesmana et al., 2022) (Error! Reference source not found.).

In addition, DrugBank, as the provider of candidate drugs to be tested with SNP genes, was combined with the Therapeutic Target Database (TTD) to optimize the drug-gene interaction map (Adikusuma et al., 2021). In a parallel study, the combination of DrugBank with DGIdb was explored to expand the selection of drugs interacting with a gene (Adikusuma et al., 2021) (Error! Reference source not found.). Protein structures identified as specific drug targets from the Protein Drug Bank (PDB) were directly tested with a wide range of drugs available in DrugBank. The curated results from DrugBank were visualized in a graph illustrating the interactions between drugs and targets. To address the limitations of information within DrugBank, the researchers further processed the data using UniProt, with the assistance of Biophyton's annotations (Phatak & Zhang, 2013) (Error! Reference source not found.).

Utilizing structural information and curated drug-gene interaction data provides researchers with a better understanding of how drugs interact with target proteins and influence gene expression (Lahti et al., 2012). This knowledge contributes to the development of more targeted and effective drugs. Additionally, testing a wide range of drugs with specific protein structures enables researchers to explore the potential of repurposing existing drugs for new indications (Parisi et al., 2020). These findings have significant implications for drug repurposing and personalized medicine, as identifying drugs capable of binding to specific genes opens up new possibilities for repurposing existing drugs (Challa et al., 2019).

It should be noted that gene expression data alone can predict only a small fraction of known drug targets (Isik et al., 2015). However, incorporating network data enhances target prediction, suggesting that the combination of different data sources, as employed in this study, offers a more comprehensive understanding of drug-gene interactions (Pabon et al., 2018). The utilization of DrugBank, TTD, DGIdb, and other databases in this study aligns with previous research that has also utilized these resources to predict drug-target interactions and prioritize drug candidates (Isik et al., 2015; Quan et al., 2019).

Previous studies have explored the connection between drugs and genes, with one study demonstrating how drugs interact with target proteins, affecting downstream effectors and influencing the transcriptome of cancer cells (Isik et al., 2015; Pabon et al., 2018). Another study highlighted the limited regulation of drug targets at the mRNA level, suggesting that gene expression data alone can only predict a small fraction of known targets (Mensa-Wilmot, 2021). However, the use of network data improves target prediction (Isik et al., 2015).

The results of this study suggest that drug molecules profoundly modify downstream genes and induce specific reactions by binding to targets with complementary structures. The observed patterns in gene expression changes may reflect the characteristics of target binding (Lee et al., 2023). To predict drug-target interactions, the researchers utilized CMap, a database containing information on human cell cultures treated with bioactive compounds. The study also suggests that drugs binding to common targets exhibit higher pairwise similarity (Wang et al., 2013).

The implications of the results are significant both in theory and in application. The study provides insights into the relationship between drugs and genes, specifically in terms of drug targets and drug signatures (Quan et al., 2019). The findings suggest that by leveraging genetic information and computational models, it is possible to predict drug-target interactions and identify potential drug candidates (Pulley et al., 2020).

3.2.3. DrugBank Finalizes the Multinetworking Process

In the final stage of the bioinformatics study, a comprehensive analysis was conducted by integrating DrugBank with PubChem and DGIdb to evaluate the potency of interactions between repurposed candidate drugs and pre-identified target, which included gene expression data collection from the Gene Expression Omnibus (NCBI-GEO), gene network reconstruction via GeneMANIA, and network clustering with Cytoscape (Zhang et al., 2021).

DrugBank, a unique bioinformatics and cheminformatics resource, played a crucial role in our study. It provides detailed drug information, including chemical, pharmacological, and protein data, along with comprehensive drug target information, all of which are meticulously curated (Kim, 2021). PubChem, on the other hand, serves as a public repository of chemical data maintained by the National Institutes of Health (NIH). The chemical-protein and chemical-gene interaction data in PubChem are derived from various sources, including DrugBank, DGIdb, and ChEMBL (Kim, 2021; Zhu et al., 2019).

The Drug-Gene Interaction database (DGIdb) plays a pivotal role in the study (Kunz et al., 2016). As a central aggregator, DGIdb compiles valuable information on drug-gene interactions and druggability from a diverse array of sources (Freshour et al., 2021; Muresan et al., 2012). The most recent release, DGIdb 4.0, has integrated crowdsourced contributions and added seven new sources, expanding the total number of sources included to 41 (Freshour et al., 2021). These resources collectively formed the backbone of bioinformatic study, enabling us to assess the strength of drug-candidate interactions with previously identified seed genes within our networking framework, which encompassed gene expression data collection, gene network reconstruction, and network clustering (Freshour et al., 2021).

The integration of DrugBank, PubChem, and DGIdb is essential for bioinformatics in drug discovery and development. DGIdb is a critical component of The Genome Institute's Genome Modeling System, facilitating automated analysis of cancer genomes in clinical settings. It allows querying genes with potential cancer-driving events through the API and collaborates with databases like DoCM, DrugBank, and Jax-Clinical Knowledgebase to import drug-gene interaction data and metadata (Cotto et al., 2018). PubChem contributes data that can be integrated with in-house RDF data and provides chemical-protein and chemical-gene interaction data sourced from various databases, including DrugBank, DGIdb, and ChEMBL (Cotto et al., 2018). DrugBank plays a vital role in supplying comprehensive drug information and drug-gene interaction data, particularly for drug classes like nonsteroidal anti-inflammatory drugs, and supports drug-protein interactions mined by DGIdb for drug repurposing efforts (Cotto et al., 2018; Zhu et al., 2019).

4. CONCLUSION

The utilization of DrugBank as a central resource in this bioinformatics research has proven invaluable, facilitating the gathering of crucial drug information and enhancing drug-gene interaction analysis. DrugBank not only leads and finalizes the multinetworking process,

but also connects various gene data sources with potential drug candidates, thus enabling the identification of new medications and their validation through clinical tools. The study's findings offer significant insights into drug-gene interactions and the potential repurposing of existing drugs for new indications. This underscores the importance of leveraging multiple databases and network data in bioinformatics research, with DrugBank playing a pivotal role in advancing drug discovery and personalized medicine.

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6. CONFLICT OF INTEREST

All authors declared that there was no conflict of interest.

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