ejpmr, 2016, 03(1), 454-464

SJIF Impact Factor 7.065

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

DRUG REPURPOSING: A STRATEGIC APPROACH TO ACCELERATE DRUG DEVELOPMENT - REVIEW ARTICLE

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Article Received on 05/12/2015 **Article Revised on 25/12/2015** **Article Published on 15/01/2016**

ABSTRACT

Background: The pharmaceutical industry faces significant challenges, including declining productivity in drug development and a growing gap between therapeutic needs and available treatments. The lengthy and costly process of developing new drugs, combined with high attrition rates, necessitates innovative strategies for drug discovery. **Aim:** This review explores drug repurposing as a strategic approach to expedite drug development by leveraging existing therapies for new therapeutic applications. **Methods:** The article analyzes advancements in computational pharmacology, focusing on three key areas: predicting drug-target interactions (DTIs), identifying potential adverse effects, and drug repurposing methodologies. Key databases and resources facilitating computational pharmacology are also discussed. **Results:** The integration of diverse data sources enables the identification of novel therapeutic applications for existing drugs, addressing the urgent need for treatments for rare diseases. Additionally, computational methods enhance the understanding of drug mechanisms and adverse effects, potentially reducing therapeutic failures. **Conclusion:** Drug repurposing offers a promising pathway to accelerate drug development, optimizing resource utilization while improving patient outcomes. Future research should continue to refine computational approaches and leverage rich datasets to enhance drug discovery efficiency.

KEYWORDS: drug repurposing, computational pharmacology, drug-target interactions, adverse effects, rare diseases

INTRODUCTION

Contemporary pharmaceutical research encounters significant obstacles with diminishing productivity in drug development and a persistent discrepancy between therapeutic requirements and existing treatments.[1-4] The approval rate of new drugs per dollar invested in research and development has been on a downward trajectory, with recent investigations indicating that the process to bring a new drug to market now spans over 15 years and costs upwards of $1 billion.[2, 4] This trend can be attributed, in part, to substantial attrition rates; only about 10% of compounds advancing to Phase II clinical trials ultimately receive approval[6], with most failures stemming from safety issues or inadequate efficacy.[7, 8] Amidst this declining productivity, there exists an urgent demand for treatments addressing rare diseases. The National Organization for Rare Disorders reports approximately 7,000 rare diseases that collectively impact around 10% of the population in developed countries; however, only a small fraction of these conditions have accessible pharmacological therapies.[9] Given the current expenses associated with research and development, creating novel therapies for each rare disease is impractical. These challenges highlight the necessity for innovative strategies to identify new therapeutic avenues and to enhance understanding of drug mechanisms and adverse effects related to investigational compounds.

In this context, advancements in genomics and computational methodologies offer new avenues for research and drug development. A wealth of data—including gene expression profiles, drug-target interactions (DTI), protein interaction networks, electronic health records, clinical trial documentation, and adverse drug event reports—is rapidly accumulating and becoming increasingly standardized and accessible.[11, 12] However, this data often presents complexities due to its high dimensionality and inherent noise, posing both challenges and opportunities for the development of computational methods that can integrate these datasets to expedite drug discovery and uncover new insights into drug mechanisms, side effects, and interactions.

Computational pharmacology represents an expanding set of methodologies designed to specifically tackle these challenges. This review will focus on three primary objectives within the field of computational pharmacology. First, we will explore the prediction of

DTIs, which are essential for understanding drug functionality and often serve as a crucial foundation for subsequent research in computational pharmacology. Secondly, we will examine methodologies aimed at predicting or elucidating potential adverse effects or drug reactions, as a deeper understanding of off-target effects could significantly reduce therapeutic failures resulting from unintended physiological responses. Lastly, we will address techniques for drug repurposing, which involves identifying new therapeutic applications for existing medications. This review will also highlight computational pharmacology methods that synthesize data from multiple sources or across numerous compounds. Such integration can minimize noise and enhance the predictive capability of high-dimensional datasets.[14-19] Data integration across various compounds can facilitate novel inquiries, such as determining how information about one drug may inform our understanding of another. For instance, similarity-based approaches (often referred to as guilt-by-association) evaluate whether "similar" drugs may share common targets or exhibit analogous side effects or therapeutic indications.[20-24][25][26-29] We will begin by examining the quantification and measurement of various dimensions of pharmacological space, including a discussion of key databases and resources. Following this, we will provide an overview of three applications of computational pharmacology: predicting DTIs, forecasting and interpreting side effects, and drug repurposing. Finally, we will discuss the importance of data integration in computational pharmacology and outline potential future directions within the discipline.

The resources that facilitate computational pharmacology and drug repurposing include several databases, each serving specific purposes. For general compound information, PubChem contains over 60 million compound structures and related data, while ChEMBL features over 1 million such entries. DrugBank provides binary DTI information for more than 7,000 drugs, and BindingDB offers detailed binding affinity data. The SEA and DR. PRODIS databases are valuable for predicted DTIs, employing different methodologies to yield insights. Cmap v2 compiles data on drug-induced transcriptional alterations across 1,309 compounds, while LINCS provides extensive profiles from chemical and genetic perturbations. The Cancer Genome Atlas (TCGA) encompasses RNAseq and microarray data across more than 30 cancer types. The Gene Expression Omnibus (GEO) archives diverse high-throughput genomic data. Phenotypic drug screens, including those from NPC (NCGC) and PD2, document results from extensive testing of approved compounds against various assays. Pharos connects drugs, targets, and diseases, while ClinicalTrials.gov offers a registry of clinical studies worldwide. SIDER provides information about adverse drug events and side effects from marketed compounds, whereas Offsides and FAERS report additional side effects and adverse events not typically listed. Lastly, the DvD pipeline enables dynamic comparisons between drug and disease gene expression data, enhancing the capability for signature-matching repositioning.

Quantifying And Representing Drug Space

The characteristics of a drug or drug-like compound and its interactions with the human body can be quantified and described in various ways, enabling downstream analyses and predictions. The physicochemical properties of a drug, such as chemical structure, melting point, and hydrophobicity, can be quantified. Interactions between compounds and biological targets can be assessed using measures of binding and kinetic activities. Furthermore, downstream biological perturbations can be quantified by measuring changes in cellular states or gene expression. Drugs can also be represented through categorical metadata, including diseases and conditions for which a drug is indicated, side effects, or known physiological interactions with other drugs. Such quantitative measures and metadata can be transformed into numerical representations, allowing for analysis to discover patterns and relationships between compounds and to generate new hypotheses.

Chemical Structure

Different methods exist for representing the chemical structure of small molecule compounds. For example, the three-dimensional geometry of atoms and their electronic structures can be utilized in simulation-based analyses, such as molecular docking. Alternatively, the chemical structure can be codified into a character string or line notation like SMILES, which is derived from printing the atomic symbols during a depth-first tree traversal of the chemical graph.[30] The InChI string (International Chemical Identifier), which encodes various layers of information such as atoms, bonds, electronic charge, and tautomers, is a more recently introduced option.[32] While SMILES is generally considered more human-readable, InChI can capture more detailed information and, unlike SMILES, is unique, making database mapping easier.[33] Although these character string representations can be analyzed algorithmically, they are variable-length and non-numeric, which can complicate analyses. To address this issue, fixed-length binary fingerprints have been developed[34, 35], where each bit may correspond to the presence or absence of a specific atom, moiety, aromatic ring, etc. The distance between two chemical structures can then be easily quantified, for example, using the Tanimoto coefficient (Tc), which represents the Jaccard similarity ($|A \wedge B|/|A \vee B|$) of the two fingerprints. Both PubChem[36] and ChEMBL[37] are widely used databases of chemical compounds containing chemical structure and many other properties, with information on over 60 million and 1 million compounds, respectively.

Drug–Target Interactions

A drug–target interaction (DTI) can be assessed through various experimental techniques, such as direct binding or competition binding assays[23], and can be summarized using a dose–response curve that plots a readout

corresponding to the amount of protein–ligand complexes formed relative to the logarithm of ligand (drug) concentration. A significant interaction typically yields a sigmoidal curve, with the inflection point and height of the curve characterizing the compound's potency and efficacy against the target, respectively. This inflection point is referred to as either the EC50 or IC50 value, indicating the half-maximal effective or inhibitory concentration, depending on whether the curve is increasing or decreasing with concentration. Although EC50/IC50 values can vary based on experimental conditions (e.g., target concentration), they can sometimes be related to the binding affinity, denoted by Ki, which represents the intrinsic strength of the interaction.[38]

Public databases provide various levels of DTI information. Binary-level information, indicating the presence or absence of an interaction, is available in DrugBank[39] for several thousand drugs, representing over 4,000 unique targets. This information can be organized into a binary target interaction profile vector for each drug, with a length equal to the number of targets. Alternatively, more detailed, experimentally determined binding data for hundreds of thousands of drugs and drug-like compounds are captured in databases such as ChEMBL[37], PubChem Bioassay[36], and BindingDB.[40]

Drug Perturbations of Gene Expression

Genome-wide mRNA expression levels can be employed as a proxy for measuring chemical perturbations of cellular states by comparing expression levels in cellular samples with and without exposure to a chemical compound. Each perturbation can be represented as an expression profile, where each gene is assigned a value corresponding to the degree of up- or down-regulation relative to a control (e.g., the difference in mean expression values); alternatively, this can be further processed into a signature, defined here as the sets of significantly up- and down-regulated genes. Although less commonly used, one could also consider differential variance[41] or drug-induced changes in gene–gene covariance, known as differential coexpression.[42] Several publicly available resources are noteworthy in this context. The Connectivity Map[43] and its recent update utilizing the L1000 technology as part of the LINCS[44] project have generated publicly accessible expression measurements from thousands of in vitro drug perturbations across multiple human cell lines. GEO[45] serves as a public gene expression repository with over one million samples, covering a wide range of experiments, including both drug and disease perturbations. Additionally, as part of a crowdsourcing initiative[46] organized by the LINCS data integration and coordination center, over 900 drug-perturbation experiments have been extracted from GEO and processed into signatures that are freely available for download. Different metrics can be utilized to evaluate the similarity between two expression profiles and/or signatures[47, 48], including correlation, cosine distance, and Gene Set Enrichment Analysis.[43]

Cell and Animal Phenotypes

Beyond molecular analysis, a compound's phenotypic impacts can be evaluated in cellular samples or animal models, such as assessing cytotoxicity in cancer cells[49-51] or monitoring sleep patterns in zebrafish.[52] Until approximately 30 years ago, this was the primary method for drug discovery. Although rational (i.e., target-centric) drug discovery has largely supplanted this approach, phenotypic methods continue to be a vital source of new therapies, notably accounting for the majority of first-in-class FDA approvals between 1998 and 2008.[53] Phenotypic screening is beneficial because it assesses a drug's effects within the intricate dynamics of biological systems, enabling the identification of compounds whose mechanisms may involve novel or multiple targets, thereby facilitating clinical translation.[54] Within this paradigm, Zheng et al.[54] discuss the trade-offs between cellular and animal models; while cell-based screens often allow for higher throughput, animal models enable exploration of more complex phenotypes.

Typically, phenotypic screens are conducted on a one-assay-at-a-time basis with a specific disease or outcome in focus. However, data from multiple screens can be aggregated to create a phenotypic profile for each compound. For instance, the Bioassay feature of PubChem[55, 56] contains over 740 million data points from both biochemical and phenotypic screens, encompassing more than 1 million small molecules, with many compounds evaluated in hundreds or even thousands of assays. ChEMBL also includes bioassay data with over 12 million data points.[37] Additionally, several publicly available resources contain comprehensive drug-by-phenotype matrices. One example is NPC-PD, which includes results from nearly 2,500 clinically approved compounds screened across 35 phenotypic assays targeting cardiovascular disease, diabetes, and cancer.[57] The NIH Chemical Genomics Center has compiled a dataset of roughly 2,500 approved compounds screened in approximately 200 phenotypic and target-based assays, focusing on various cancers, malaria, nuclear receptors, and signaling pathways.[58]

A notable category of cell-based phenotypic screens involves cancer cell line sensitivity studies[49-51], where growth rates (or cell viability) are measured before and after drug exposure across a panel of cancer cell lines. For instance, the Cancer Therapeutic Response Portal[49] has assessed the sensitivity of 242 genetically characterized cancer cell lines to 354 small molecule probes and drugs. Similarly, the Genomics of Drug Sensitivity in Cancer database[51] has evaluated 138 anticancer drugs across 700 cell lines. The Cancer Cell Line Encyclopedia[59] provides additional context, offering detailed genetic characterization of 1,000 cancer cell lines, which can be utilized to assess cell line

similarity and predict drug-perturbed growth rates in additional cell lines.[60]

Side Effects and Adverse Drug Events

A final example of potentially useful drug-related information is given by side effects and adverse drug events (ADEs). Similar to disease indications, side effects terms and adverse events are represented in structured ontologies such as MedDRA®. Several important resources organize complementary aspects of side effect information. First, SIDER[76] (Side Effect Resource) is a public side-effect database with compiled information from FDA package inserts connecting 888 drugs to 1,450 side-effect terms. Another resource is the OFFSIDES[77] database, generated by analyzing over 400,000 adverse effects not listed on the FDA's official drug label, and identifying an average of 329 off-label ADEs per drug. Finally, the FDA Adverse Event Reporting System (FAERS) is a database of information on adverse event and medication error reports submitted to the FDA by manufacturers, healthcare professionals, and the general public. Now that we have considered various ways to quantify and represent drug-related information, we will see how such information can be used in several different applications of computational pharmacology, starting with target prediction.

Predicting Drug-Target Interactions

At the most basic level, drugs exert their effects on biological systems by binding with protein targets and affecting their downstream activity. Knowledge of these interactions provides a key toward understanding and predicting higher-level information such as side effects, therapeutic mechanisms, and novel indications. However, there are still many gaps in our knowledge of which drugs bind to which targets. At the time of writing, DrugBank[39] lists, on average, less than two targets per drug, whereas a recent article[78] predicted that the true average number of targets per drug is a staggering 329. Even if this is a gross overestimation, it provides some indication that there are many more interactions than are currently known. Filling these gaps by experimentally testing all drugs against all possible protein targets is currently infeasible, and hence a variety of computational methods have been developed to predict likely interactions. De novo prediction, that is, based only on structure, is useful for virtual screening of large compound libraries, while other methods make use of related interactions to generate new predictions for compounds that have already been shown to have pharmacological activity.

De Novo Structure-Based Prediction

Molecular docking is a popular approach that uses three-dimensional modeling and computer simulation to dock a candidate drug into a protein-binding pocket and then score the energetic favorability or likelihood of the pair's interaction.[79, 80] This approach is advantageous in that it can provide structural insights into the nature of the interaction, which might enable further optimization of the compound's structure to increase binding affinity for its target. However, molecular docking depends on the existence of a reliable three-dimensional model of the protein, and for certain target classes such as membrane-bound proteins, this often does not exist due to experimental limitations. Further, the approach is very computationally demanding, limiting its feasibility for large-scale, many-to-many DTI prediction tasks. While molecular docking is considered a target-based approach, as each compound is evaluated against the selected target's structure, one can alternatively take a ligand-based approach, constructing a sort of abstract 'pseudo-drug' representation called a pharmacophore model, containing the chemical features deemed to be important for interaction with the chosen target.[81] Compounds can then be aligned and scored against the model through a process that is much less computationally demanding than molecular docking. Pharmacophore models can be constructed from analysis of the target's binding pocket or, moving beyond the de novo prediction setting, could alternatively be derived using a set of positive and negative examples of compounds interacting with the target. Compared with molecular docking, this approach is more computationally efficient, and some studies indicate that it generally has better accuracy.[82, 83] Pharmacophore models are often used to screen large compound libraries (e.g., millions of compounds) in order to prioritize potential lead compounds for experimental follow-up, sometimes improving hit rates by an order of magnitude.[84] However, the hit rate will naturally depend on the quality of the pharmacophore model, which can be sensitive to the specific compounds or algorithm used and hence prone to high false-positive and false-negative rates.[81]

Learning from Related Interactions

When existing compounds are known to interact with similar or identical targets, this information can serve as an additional resource for predicting novel interactions. This is achieved through the application of a guilt-by-association (GBA) principle, which posits that analogous drugs may share target proteins, or that similar proteins might be influenced by the same drug. Recent studies substantiate this perspective by revealing that out of approximately 20,000 human proteins, there are only about 1,000 unique conformations of binding pockets.[85] This finding suggests that proteins possess numerous shared binding sites and consequently, common binding partners. Supporting the GBA methodology, Paolini et al.[86] combined drug–target interaction (DTI) data from various sources to develop a bipartite DTI network, demonstrating that proteins within the same classification tend to have overlapping drug interaction partners.

Several methodologies leverage knowledge of related interactions. One previously discussed approach is DTI-based pharmacophore modeling. Another prevalent strategy[87, 88] involves framing the issue as a binary classification task, utilizing supervised machine learning

models where the inputs consist of physicochemical characteristics of the drug and/or protein, and the output (whether known or predicted) indicates the presence or absence of an interaction. For instance, Nidhi et al.[87] employed a Naïve Bayes framework to predict targets solely based on chemical structure, achieving a 77% recall rate of known interactions among the top three predicted targets for each drug. Alternatively, DTI prediction can be approached as a regression challenge aimed at estimating binding affinities. Notable examples include the research conducted by Bock and Gough[89], which utilized support vector regression to identify high-affinity ligands for orphan G protein-coupled receptors (GPCRs), and the more recent study by Cao et al.[90], where random forest regression applied to both drug and target features achieved area under the curve (AUC) values of up to 0.96.

Recent investigations have also explored deep neural networks to forecast drug–target interactions based on chemical structures and known interactions.[92, 93] For example, Ramsundar et al.[92] integrated millions of data points representing both positive and negative DTI examples across over 200 distinct targets. They implemented a 'multi-task' framework, treating the prediction for each target as an independent task requiring its own linear classifier, while all classifiers utilized the same feature representation optimized via the neural network. This deep-learning approach attained a maximum cross-validated AUC of 0.87 and illustrated that the multitask component of their method consistently yielded marginal enhancements (approximately a 0.01 increase in AUC) over a corresponding single-task analysis using the same dataset. It is noteworthy that the task-specific linear classifiers, along with the aforementioned machine learning models, exhibit similarities to pharmacophore models, as they all identify the structural features deemed most critical for interaction.

The methodologies detailed above invoke the similarity principle in an implicit manner, for instance, by adjusting coefficients for drug and/or protein features, leading to similar predictions for drugs with comparable characteristics. However, several machine learning techniques have been developed that explicitly utilize a similarity-based framework, operating directly with similarity matrices between drugs and/or targets. A straightforward example is the nearest-neighbor approach[21], where one might predict the likelihood of interaction between drug D and target T by assessing whether the drug 'closest' to D interacts with T, or conversely, whether the target nearest to T interacts with D. In a similar context, Bleakley et al.[20] proposed a more sophisticated method called bipartite local models, training distinct support vector machine (SVM) classifiers for each drug and target. In this model, user-defined drug- and target-similarity matrices are input into the SVM algorithm, while known interactions serve as labels. Ding et al.[21] provide a coherent and insightful review of similarity-based machine learning techniques, including experiments that benchmarked the performance of eight different algorithms in recovering known DTIs. Although their results did not identify a definitive winner, AUCs reached as high as 0.98 for ion channels, with significant variations across target classes, likely attributable to the differing amounts of available data for each class, complicating direct comparisons with the AUCs derived from the previously mentioned deep-learning approach.

While structural similarity of compounds is perhaps the most intuitive and well-supported metric employed for DTI prediction, other similarity concepts have also proven effective. For instance, Campillos et al.[22] developed a metric for assessing side effect similarity across a dataset of 746 marketed compounds, uncovering around 1,000 side-effect-driven drug–drug relationships and confirming 9 out of 20 subsequent DTI predictions through cell-based assays. Intriguingly, roughly one-quarter of the identified drug pairs were both chemically dissimilar and had distinct therapeutic indications, suggesting that side effect information offers a somewhat orthogonal perspective on compound relationships that is still informative regarding target activity. Keiser et al.[94] introduced an alternative framework based on their similarity ensemble approach (SEA)[23], wherein each target is represented by its known binding ligands (including endogenous ligands), and the similarity between the candidate drug and the ligand set is evaluated through a statistical framework developed by the authors.[23] Out of 30 tested predictions, 23 were experimentally validated, including the activity of the drug DMT on serotonergic receptors, indicating a previously unrecognized mechanism of action for DMT. Another example employing a different notion of similarity is the network-based inference (NBI) method[24], which utilizes known DTIs to predict new interactions; in this case, the drug similarity metric (though not explicit in the NBI framework) is based on target interaction profiles.

A crucial consideration when applying any technique rooted in related interactions is the scarcity of high-confidence negative examples. This limitation arises because it is challenging to ascertain whether a specific drug–target interaction is genuinely not feasible or if the interaction might occur under different biological conditions. Recent research[91] sought to tackle this issue by developing an in silico approach to identify high-confidence negative examples, demonstrating that the inclusion of such examples enhances predictive performance. DTI prediction remains a well-explored problem, encompassing numerous techniques that collectively utilize a range of data, including chemical structure, protein structure, side effect associations, ligand sets, and other drug–target interactions. While computational chemistry can facilitate the generation of de novo predictions and thereby investigate novel areas of pharmacological space, similarity-based

methodologies offer the benefit of improving accuracy as additional data become available. Many of these methods have exhibited a high degree of precision and have proven useful in virtual screening scenarios to prioritize compounds for high-throughput screening, as well as in identifying new targets for established drugs. The subsequent sections will illustrate how these techniques can also lay the groundwork for predicting side effects and discovering new therapeutic applications.

Predicting and Explaining Side Effects and Adverse Events

Ensuring drug safety is paramount for the success of pharmaceutical development. Enhancing the ability to model and anticipate drug side effects and adverse events is vital for optimizing drug discovery processes. Early detection of unwanted toxicity can avert unnecessary resource allocation towards non-viable drug candidates. Traditionally, safety screening relies on pre-clinical assessments using animal disease models. However, such methodologies are prohibitively expensive[95] and introduce significant uncertainty regarding their translatability to humans[96, 97], owing to genetic and environmental disparities. Computational methodologies can mitigate some of these challenges. In silico strategies possess the potential to forecast undesirable side effects at earlier stages in the drug development process, utilizing predicted drug–target interactions[78, 98] or in vitro drug-induced alterations in gene expression.[99] Furthermore, Lum et al.[100] propose that employing a computational systems biology approach could reduce translational uncertainties between animal models and human subjects by modeling the conserved responses of molecular networks across different species.

Identifying novel side effect associations with approved drugs is another crucial objective, fitting within the domain of pharmacovigilance. Such associations may not be evident during clinical trials, often due to their infrequent occurrence or delays between medication initiation and symptom manifestation.[101] Computational techniques are particularly advantageous in this context, as they can mine data related to a compound's post-market usage and effects.[25, 101, 102]

Target-Mediated Connections

Certain protein targets have been identified as causally linked to adverse effects[103, 104], and this knowledge can be utilized to associate drugs with these effects. For instance, Lounkine et al.[98] employed the SEA method[23], previously discussed, to assess the activity of 656 marketed drugs on 73 proteins associated with side effects. They devised a method to identify predicted off-targets that elucidated side effects more effectively than any established targets of a drug. This led to the prediction that abdominal pain resulting from the synthetic estrogen chlorotrianisene is mediated by its newly identified and validated interaction with the enzyme cyclooxygenase-1. Zhou et al.[78] adopted a similar strategy, utilizing their FINDSITEcomb method[105] to predict drug–target interactions (DTIs) for all drugs listed in DrugBank against the majority of proteins in the human proteome. By combining these predicted DTIs with known drug-side effect associations, they were able to link targets to side effects, even in cases where the targets lacked experimentally validated drug interactions. The authors introduced a "killing index," estimating the probability that a compound may lead to severe adverse effects such as death, stroke, or heart failure. They discovered that 44% of small molecules from DrugBank were predicted to possess a killing index greater than zero, whereas only 16% of FDA-approved drugs exhibited this characteristic, thereby validating their analysis and suggesting the killing index could serve as a useful filter for identifying investigational compounds during early drug development stages.

Molecular Network Modeling:

While the previously described approaches are founded on established links between targets and side effects, molecular network modeling can be employed to hypothesize novel connections and elucidate physiological mechanisms. This is illustrated by research from two groups aiming to clarify the fatal hypertensive response observed in some individuals taking the CETP inhibitor torcetrapib, which led to the drug's failure in Phase III clinical trials.[106] Understanding the molecular mechanisms underlying this adverse response would help prevent similar occurrences in the future and determine whether other CETP inhibitors should continue to be explored. Chang et al.[107] developed a framework utilizing structure-based target prediction alongside a technique called metabolic modeling[108] to implicate targets in the hypertensive response, hypothesizing that the adverse effect stemmed from renal regulation of blood pressure through metabolite reabsorption and secretion. They identified a list of 41 metabolic proteins predicted to be off-targets of the drug using structure-based target prediction. Subsequently, they constructed a renal metabolic network model encompassing 338 genes to simulate the phenotypic outcomes resulting from the inhibition of each target, yielding six out of 41 predicted to influence renal function. Two of these targets had existing literature supporting their connection to hypertension in humans, mice, or rats, while the remaining four represented novel hypotheses. Fan et al.[109] also employed network analysis to investigate potential explanations for torcetrapib-induced hypertension. They constructed a context-specific human signaling network filtered by genes that were differentially expressed in adrenal carcinoma cells treated with torcetrapib, identifying several enriched signaling pathways previously linked to hypertension.

Other Approaches

A variety of alternative methodologies have been utilized to analyze or predict associations between drugs and adverse effects. Scheiber et al.[110] connected specific chemical characteristics of drugs to 4210 adverse drug

event (ADE) terms by utilizing known drug–ADE associations in an extension of Naïve Bayes modeling, Similarly, Liu et al.[111] employed causality analysis based on Bayesian network structure learning to establish connections between both chemical and biological attributes of drugs and ADEs, presenting a causally interpretable framework. As a final illustration, Vilar et al.[25] utilized a guilt-by-association (GBA) approach on a substantial insurance claims database to estimate drug associations with four distinct ADEs: acute renal failure, acute liver failure, acute myocardial infarction, and upper gastrointestinal ulcers. The authors assessed various compound similarity metrics, including chemical structure, targets, Anatomical Therapeutic Chemical (ATC) codes, and other ADEs, concluding that the latter two metrics, informed by phenotypic associations, achieved the highest area under the precision-recall curve (AUPR) scores in three of the four ADEs evaluated.

CONCLUSION

The ongoing challenges within pharmaceutical research and development underscore the necessity for innovative strategies that can enhance drug discovery and delivery processes. The significant investment of time and resources required to bring a new drug to market—often exceeding $1 billion and taking over 15 years—highlights the need for more efficient approaches. This review emphasizes drug repurposing as a pivotal strategy that can facilitate quicker access to therapeutic options while optimizing existing resources. Computational pharmacology serves as a cornerstone for drug repurposing efforts, enabling the integration and analysis of vast datasets to uncover novel therapeutic applications for existing drugs. The prediction of drug-target interactions (DTIs) is crucial, as it lays the groundwork for understanding drug functionality and efficacy. Furthermore, methodologies aimed at identifying potential adverse effects are essential for improving drug safety, thereby addressing the primary reasons for the high attrition rates observed in clinical trials. The potential for leveraging advancements in genomics, high-throughput screening, and computational methods offers a promising landscape for drug discovery. By utilizing data from various sources—ranging from electronic health records to gene expression profiles—researchers can not only enhance the understanding of drug mechanisms and interactions but also expedite the identification of new therapeutic avenues for rare diseases. Given the multitude of rare conditions affecting a significant portion of the population, drug repurposing becomes a strategic priority to meet these unmet medical needs. In conclusion, continued investment in computational pharmacology, data integration, and collaborative research efforts will be essential to advancing drug repurposing initiatives. As we move forward, fostering a culture of innovation and collaboration in the pharmaceutical industry will be vital to overcoming existing barriers and improving patient care outcomes across diverse therapeutic areas.

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