Chapter

Applications of Molecular Docking Techniques in Repurposing of Drug

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Abstract

The applications of molecular docking techniques have played a key role in paradigm change in the field of drug development by providing a potent toolkit for the investigation. In addition, drug repurposing of already approved medications and for a novel treatment that was not previously recommended is known as drug repurposing. During the critical situation, it has attracted a great deal of attention. Molecular docking techniques have emerged as a necessity to expedite the drug development process and medication requirements. They promote a validated and cost- and time-effective method of creating novel pharmaceuticals. Molecular docking technologies facilitate the prediction of the binding interactions between small molecules and target proteins. Researchers can more thoroughly evaluate the potential efficacy of well-calibrated pharmaceuticals against novel disease targets. We will explain in this chapter how molecular docking was initially used to help with the drug discovery process. Next, we demonstrate the emerging and newer uses and applications of docking, such as target fishing and profiling, polypharmacology, drug repurposing, and adverse effect prediction. We also discussed about the potential of this technique, future applications, and its combination with other emerging techniques like artificial intelligence.

Keywords: molecular docking techniques, repurposing, paradigm, validation, prediction, polypharmacology

1. Introduction

Drug repurposing, also known as drug repositioning, drug reprofiling, indication expansion, or indication shift, is the process of finding new uses for pharmaceuticals that were previously approved but shelved, abandoned, or classified as experimental. While not a novel approach, drug repurposing has gained significant traction in the last 10 years: over one-third of recent approvals have been associated with this technique, and these drugs today account for approximately 25% of the pharmaceutical industry's yearly income [1].

1.1 Definition, extent, constraints, and scientific underpinnings of medication repurposing

Drug repurposing is the methodical process of discovering new uses for already approved medications, sometimes in tandem with their release into the general public and eventual generic availability. According to Langedijk et al. [2], this data was gathered by searching PubMed on November 21, 2019, for titles or abstracts that included the phrases "Drug repurposing" for the publication year 2018.

The original definition of drug repurposing has expanded to include not just medications that have been made generic but also active ingredients that were removed off the market because of safety concerns, or those that failed the clinical phase owing to toxicity or insufficient efficacy. It does not, however, include materials that have not yet undergone clinical testing, such as those kept in chemical libraries for screening by academic and commercial research teams. Hit-to-lead chemistry is usually required for compounds from such libraries in order to maximize their medicinal effects. Moreover, it is thought that the selective optimization of side activities (SOSA), as put out by Professor Wermuth, goes beyond repurposing. In SOSA, the biological characteristics that cause side effects are identified and made better through chemical alteration, making it possible to suggest the altered medication for a new use. This is not the same as repurposing, which spares the drug's structural changes [3].

Repurposing, on the other hand, makes use of two main scientific pillars: (1) the discovery that several diseases have similar biological targets, made possible by the decipherment of the human genome, and (2) the notion of pleiotropic medications. Drug repurposing requires an understanding of the complex interactions that exist between diseases, medicines, and targets. *In silico* techniques such as data mining, machine learning, ligand-based, and structure-based methodologies are essential for clarifying these interactions [4].

This talk highlights the current capacity to understand diseases from a molecular perspective, including a range of aspects such as genetic components, biomarkers, signaling pathways, and environmental factors that contribute to their pathogenicity. Determining the degree of similarity across diseases that share molecular characteristics has become crucial thanks to computational approaches, in particular data mining [5]. The discovery that 48 genes and four signaling pathways are shared by diseases like Parkinson's and Alzheimer's serves as an example of this paradigm shift Dovrolis et al. [6]. Finding protein targets that cross over into other diseases suggests that a single drug could be effective against a variety of pathological conditions.

The principal therapeutic actions and concurrent adverse effects of modern pharmacological substances are well-described. Drugs have a variety of effects due to their complex pleiotropic interactions with primary and secondary biological targets. This complexity raises the possibility of using medications created for one condition to treat another, provided that one of their secondary targets is present in the new illness [7]. Furthermore, the discovery of similar targets among diseases not only raises the prospect of a common pharmacological intervention but also opens the door to the creation of medications with a variety of purposefully designed side effects. Pan-kinase inhibitors are a good example of this idea in oncology, as their various yet coordinated actions work together to increase clinical efficacy.

The analogy between diseases and drugs extends to the realm of phenotypic analysis, disregarding therapeutic indications. By subjecting drugs with different therapeutic purposes to scrutiny based on phenotypic similarity, it becomes conceivable to discern potential efficacy across divergent indications. Thus, a high similarity

score between two drugs prescribed for distinct diseases may signify their potential effectiveness in both scenarios [7]. This nuanced understanding of molecular and phenotypic intricacies not only broadens therapeutic possibilities but also underscores the potential for synergistic drug effects, elucidating a comprehensive approach to disease management and drug development.

1.2 Benefits of repurposing medications

Repurposing drugs has a number of related benefits. The main focus of these benefits is the simplification of the regulatory procedures involved in bringing a medicine that has already received approval onto the market, especially in countries like the United States. This strategy makes use of preexisting information, particularly on the drug's safety and toxicity, to speed up the first stages of repositioned drug development [8]. Consequently, this accelerated process not only reduces development timelines significantly but also incurs substantial cost savings, estimated to be over 80% according to Naylor and Schonfeld [9].

Moreover, the likelihood of successfully bringing a repurposed drug to market is notably enhanced, with a reported increase of 150% compared to the introduction of a novel drug, as highlighted by Thayer [10]. It is important to remember, though, that a drug's intended indication and the level of safety it requires are closely related. Tolerability of side effects is therefore correspondingly reduced when a medication is repositioned for a disease that is less severe or critical than its original prescription [11].

The alterations to the drug's composition, dosage, or mode of administration require a thorough reassessment of its safety profile in light of these changed circumstances. This effectively changes the repositioned medication into a new pharmaceutical product, highlighting the significance of careful inspection during this transitional stage.

2. Conventional drug discovery versus repurposing of drugs

The standard drug discovery process is characterized by five sequential stages, commencing with FDA review, followed by preclinical and discovery research, safety evaluation, and clinical investigation and concluding with post-market safety surveillance administered by the FDA. *De novo* identification of novel molecular entities (NME) is a crucial step in this approach. The protracted and resource-intensive nature of this approach heightens the likelihood of failure [12].

In contrast, drug repurposing involves a streamlined four-step progression: development, compound acquisition, compound identification, and FDA post-market safety monitoring, as illustrated in **Figure 1** [13]. The application of cheminformatics and bioinformatics technology, along with the readily available large biological and structural databases, has significantly reduced the time and cost commitment to drug development while also lowering the failure rate. Artificial intelligence (AI) technologies, structure-based drug design (SBDD), and *in silico* approaches are largely responsible for the modern acceleration of the drug repurposing process [13, 14].

Historically, the repurposing strategy using licensed drugs for new therapeutic indications has worked well, especially when it comes to coincidental discoveries. Compared to traditional drug discovery programs, which will be explained below, the

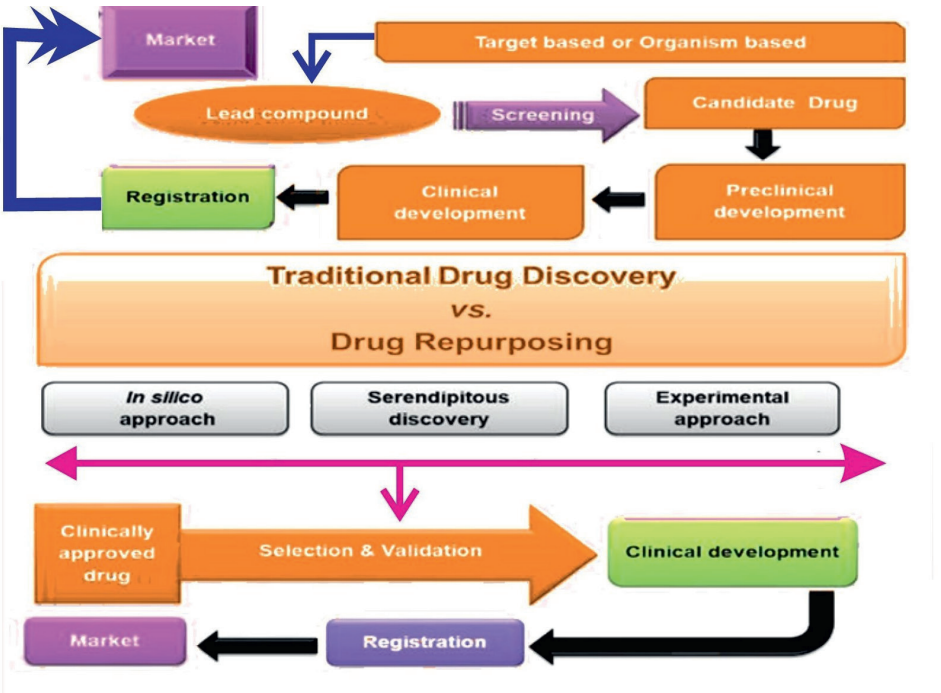

Figure 1.
Conventional drug discovery versus repurposing of drugs.

previously mentioned method seems to be rather helpful in the drug development domain. As an illustration, Pfizer repurposed sildenafil (Viagra), a phosphodiesterase-5 (PDE5) inhibitor, which was originally created to treat coronary artery disease (angina). This repurposing tactic may have helped save costs in addition to accelerating the development schedule. Phase II and III clinical trials are currently in progress, evaluating the feasibility of repurposing the oral antidiabetic medication metformin, commonly referred to as glucophage, as a treatment for cancer [15, 16].

Drug repurposing has various advantages over conventional drug development techniques. Interestingly, when compared to typical drug discovery programs, a significant decrease in the amount of time and money needed for research and development is seen. The conventional process for creating a new medication is estimated to span 10–16 years, whereas drug repurposing strategies may achieve this in a more time-efficient manner, ranging from 3 to 12 years. The financial implications are also noteworthy, with drug repurposing strategies costing as low as $1.6 billion, in stark contrast to the typical expenses associated with conventional drug development strategies, which can escalate to $12 billion. Furthermore, the identification of new pharmacological targets using drug repurposing strategies takes researchers only 1–2 years, with an average development period of 8 years for a repositioned medicine [17, 18].

The repurposing of pharmaceutical agents circumvents the customary 6–9 year timeline inherent in traditional drug development paradigms, facilitating a direct transition to preclinical evaluations and clinical trials. This departure mitigates cumulative risks, temporal expenditures, and financial outlays associated with drug development. Empirical evidence indicates that the approval timeline for

repurposed drugs is notably shortened to approximately 3–12 years compared to conventional drug development, resulting in a concurrent reduction in development costs by 50–60%.

The initiation of a drug repurposing initiative is characterized by the preexistence of an array of preclinical data, including pharmacological and toxicological information, as well as clinical efficacy and safety data. This buildup is the result of the drug candidate's previous development through the early phases, which include structural optimization and early preclinical trialing. Additionally, it is possible that the proposed medication has received regulatory approval and, as a result, has a clearly established safety and clinical efficacy profile. Because of this, this method significantly lowers development costs while also reducing the dangers related to early-stage failures, which are common in traditional approaches. This dual benefit raises the probability of clinical safety and the overall success rate of medication development [19, 20].

In the inaugural phase of a repurposing development initiative, the utilization of preexisting data encompassing pharmacokinetics, toxicology, clinical trials, and safety profiles confers distinct advantages over the conventional drug discovery paradigm. These advantages materialize in the form of expedited development timelines, reduced developmental expenditures, and mitigated risks of clinical failure. The temporal requirements for the development of a repurposed pharmaceutical are estimated to span between 3 and 12 years, a noteworthy reduction compared to the 10–17 years typically associated with traditional drug discovery programs. This temporal efficiency is concomitant with a substantial decrease in associated costs. The average expenditure for bringing a novel drug to market through conventional means is approximately $1.24 billion, whereas drug repurposing incurs an outlay equivalent to or less than 60% of traditional drug discovery costs. Such economic efficiencies result in considerable savings of both time and capital for the repurposing entity.

Moreover, the strategic emphasis of conventional drug discovery predominantly revolves around identifying therapeutics for chronic and intricate diseases. On the other hand, the drug repurposing strategy focuses its efforts on creating medications that are specifically designed to treat infectious diseases that are quickly becoming more prevalent, as well as diseases that are resistant to treatment and neglected illnesses (NTDs). This change in emphasis is in line with how healthcare requirements are changing. In addition, the development of cheminformatics and bioinformatics techniques, along with the large databases and repositories of omics data (metabolomics, proteomics, transcriptomics, genomes, etc.), enhances the use of disease-targeted repurposing techniques. These methods make it easier to investigate hitherto unrecognized mechanisms of action, such as unknown pharmacological targets, latent drug-drug interactions, and new disease biomarkers. The effectiveness and efficiency of drug repurposing initiatives are increased by the incorporation of these cutting-edge strategies [19].

3. Techniques for repurposing drugs

As shown in **Figure 2**, there are two primary DR strategies: off-target and on-target. When a medication molecule's established pharmacological mechanism is applied to a novel therapeutic indication, on-target drug delivery occurs. This approach targets a different disease with the therapeutic chemical using the same biological target [15, 16].

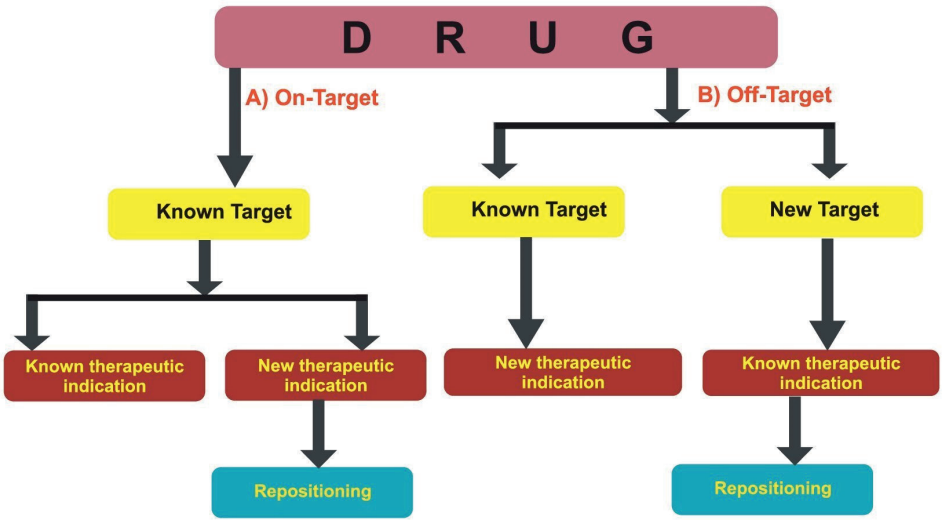

Figure 2.
Drug repurposing tactics: on- and off-target.

During the repurposing process, minoxidil (Rogaine) exhibits a pronounced on-target profile in which the medication acts on a same molecular target to produce two different therapeutic effects. Minoxidil was developed as an antihypertensive vasodilator before evolving into a medication for hair loss. Minoxidil acts as an antihypertensive vasodilator by modulating potassium channels and exhibiting vasodilatory qualities. This allows for increased blood, oxygen, and nutrition supply to hair follicles. The effectiveness of this medication in treating male pattern baldness (androgenic alopecia) is supported by its pharmacological activities. On the other hand, the off-target profile's pharmacological mechanism is still unknown. New therapeutic indications are being explored as a result of interactions between pharmaceuticals and drug candidates that are repurposing and novel targets outside of their initial scope. Thus, in the context of relocated minoxidil, both the molecular targets and therapeutic indications reflect new aspects [21].

The drug aspirin (Colsprin) is a great example of an off-target profile. Aspirin, which functions as a nonsteroidal anti-inflammatory medication (NSAID), has long been used to treat a variety of inflammatory and pain-related ailments. Additionally, it suppresses blood coagulation and acts as an antiplatelet drug by inhibiting the normal function of platelets. As a result, aspirin is useful in the treatment of heart attacks and strokes. Additionally, recent research has hinted at a potential treatment for prostate cancer based on aspirin.

4. Approaches of drug repurposing

Aspirin is a notable example of an off-target profile design (Colsprin). As a nonsteroidal anti-inflammatory medication (NSAID), aspirin has been used traditionally to treat a range of inflammatory and nociceptive disorders. It also inhibits the intrinsic properties of platelets, which prevents blood coagulation (clot formation), which is why it is categorized as an antiplatelet drug. As a result, aspirin is utilized in

the treatment of myocardial infarctions and cerebrovascular accidents. Additionally, recent publications have demonstrated an innovative use of aspirin in the treatment of prostate cancer [22, 23].

On the other hand, the *in silico* repurposing methodology makes use of cheminformatics, bioinformatics, and computational biology approaches to perform virtual screening of large drug/chemical libraries that are available in public databases. This method depends on identifying putative bioactive chemicals based on how the drug molecule and the protein target interact chemically (**Table 1**) [24].

Since it has shown such great promise in drug development efforts, the *in silico* methodology has become more and more popular in recent decades. With regard to the chemical structures of proteins, pharmacophore models, and bioactive chemicals, this approach makes use of the abundance of publically available data. Numerous pharmaceutical enterprises and research laboratories dedicated to drug discovery have successfully incorporated *in silico* tools and techniques, particularly for exploring diverse chemical spaces in the quest for novel therapeutic agents.

In comparison with experimental-based approaches, *in silico* repurposing offers several advantages, including a diminished failure rate, accelerated development timelines, and cost-effectiveness. However, a notable limitation of this approach is its dependency on precise structural information pertaining to drug targets. In instances where such information is unavailable, reliance on medication phenotypic or genotypic profiles relevant to the associated disease becomes imperative, as highlighted by Rosa and Santos [26]. The presented figure serves to symbolize various strategies employed in medication repurposing endeavors (**Figure 3**).

Recently, researchers and scientists have adopted an integrated approach that combines *in silico* and empirical methodologies in the quest to discover novel therapeutic indications for medications that have previously been approved for use. In this integrated model, clinical studies and preclinical biology experiments including both *in vitro* and *in vivo* evaluations combine to evaluate the results of computational approaches. Demonstrating superior efficacy compared to fortuitous discoveries, the concurrent and systematic application of computational and experimental modalities imparts a dependable and rational foundation for the exploration of new therapeutic applications. This hybridized strategy further affords opportunities for expeditious and streamlined repurposing of medications, establishing itself as a dependable and credible approach in pharmaceutical development [27].

Activity-based approach	***In silico*-based approach**
In vitro and *in vivo* experimental screening	Virtual or computational screening
Assays for screening cells/organisms and targets	Protein target-oriented screening
Requires neither drug-induced cell/disease phenotypic data nor target protein structural knowledge	Needs knowledge of the target proteins' structures as well as drug-induced cell or disease phenotypic data
Labor-intensive and time-consuming	Labor and time efficiency
Reduced false-positive hit rate during the screening process	Greater percentage of false-positive results while screening

Table 1.
Disparities between in silico- and activity-based methods for medication repurposing [24, 25].

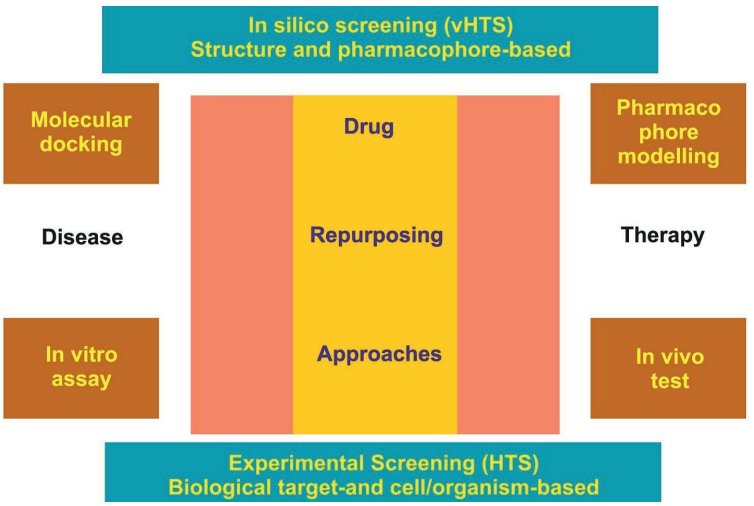

Figure 3.
Approaches of drug repurposing.

5. Methodologies of drug repurposing

Drug repurposing techniques can be roughly classified into three classes based on the quality and depth of available data on biological activity, pharmacology, and toxicology. The three main categories in which these approaches fall are (i) drug-centric, (ii) target-centric, and (iii) disease/therapy-centric.

The structural characteristics of therapeutic molecules, biological activity, side effects, and toxicities are all methodically evaluated in the drug-centric approach. This methodology seeks to discover substances with unique biological effects by means of experiments carried out on animals or cells. This repurposing paradigm emerged from studies that were largely focused on evaluating the biological efficacy of therapeutic compounds, frequently without a complete understanding of the underlying biological targets. Its roots are in conventional pharmacology and drug development concepts. The discovery of sildenafil through chance or clinical observation is one of the many noteworthy achievements in drug repurposing that the drug-centric strategy has historically produced [28]. This approach demonstrates how well it works to find new therapeutic uses for medications that already exist by using thorough evaluations of their pharmacological and biological characteristics.

Target-based methodology comprises high-throughput and/or high-content screening (HTS/HCS) of drugs against a target protein molecule or biomarker *in vitro* and *in vivo*, followed by virtual high-throughput screening (vHTS) or *in silico* screening of drugs or compounds from drug libraries/compound databases, such as molecular docking or ligand-based screening. This strategy has a substantially greater success rate in drug development than drug-oriented methods since most biological targets reflect the pathways or mechanisms causing disease [29].

In cases where the disease model has access to more data, the illness/therapy-oriented paradigm is appropriate in disease-research. In this case, decisions about disease-specific treatments can be informed by proteomics (disease-specific target proteins), genomics (disease-specific genetic information), metabolomics

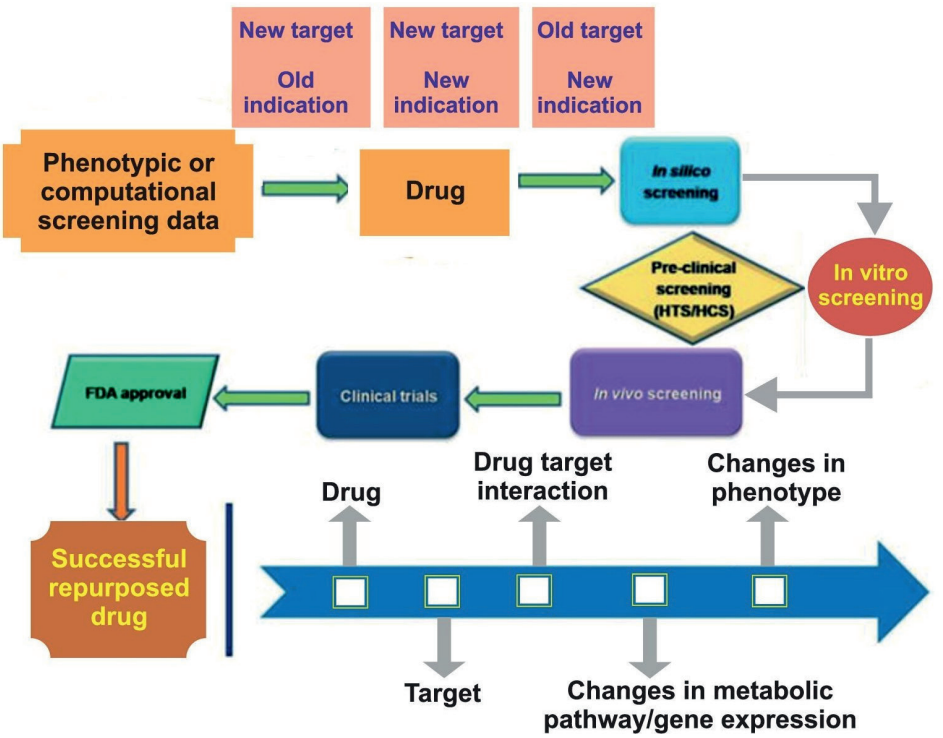

Figure 4.
The procedures and techniques used in medication repurposing.

(disease-specific metabolic pathways/profile), and phenotypic data (disease-specific disease processes, pharmacological targets, off-target mechanisms, pathological conditions, adverse and side effects, etc.). Consequently, it requires the construction of discrete disease networks, the discovery of genetic expression, the evaluation of significant targets, the identification of disease-causing protein molecules linked to cell and metabolic processes of interest in the disease model, and so on. **Figure 4** illustrates the steps and procedures required in repurposing medications.

The production of tiny medicinal compounds and biologics approved by the FDA is mostly accomplished through the application of target-based and drug-based phenotypic screening methods. Phenotypic drug screening methods identify therapeutic possibilities in small molecule libraries by means of fortuitous findings. Target-based strategies look for novel drugs by utilizing known target molecules. The treatment/therapy-based repurposing methodology and the disease-based strategies are comparable and presented in **Table 2** [30].

The following is a brief description of several of the available repurposing techniques shown in the **Table 2**.

5.1 Biological tests and experimental screens

Directed toward certain illness models and medications are used in blinded search or screening methods, whereby results are discovered by chance. These approaches' greater flexibility in screening a wide range of medications or illnesses is one of its advantages.

Techniques	Method type and category	Technique/particular strategy	Examples
Drugs			
Screening by phenotype	Target-based and blinded screening	HTS/HCS screening both *in vivo* and *in vitro*	For erectile dysfunction, sildenafil; for breast cancer, rituximab
Target 3D structure, chemical structure, medication, and ligand information	Using targets, cheminformatics	Ligand-based screening, fragment-based screening, molecular docking, and *in silico* screening	Etoposide (bladder cancer), fluorouracil (lung cancer)
Details about drug targets, chemical structure, target, and medication information	Based on knowledge, cheminformatics and Bioinformatics	Prediction of drug targets	Ketoconazole and simvastatin for breast cancer
Details of clinical trials and side effects	Based on knowledge, bioinformatics	Studies of drug similarity	—
FDA-approved labeling	Based on knowledge, bioinformatics	Studies of drug similarity	—
Disease-oriented			
Information on the available pathway	Based on knowledge, bioinformatics	Finding the cause of the sickness and addressing the main objectives	Vismodegib (cancerous skin)
Data on disease omics and genetics	Bioinformatics based on signatures	Using genomics and gene signatures to find important targets	—
Protein interaction network, accessible pathway information, and disease omics data	Network biology is either pathway- or network-based.	Examining disease-specific networks and pathways to find important targets	Dasatinib with sunitinib (brain tumor, breast cancer)
Therapeutic in nature			
Data on drug omics	Bioinformatics and/or network biology, signature-based or signature-and-network based	Examining gene signatures	Acute lymphoblastic leukemia (Sirolimus); neurological diseases (Fasudil)
Data on medication and disease omics	Bioinformatics based on signatures	Drugs and illnesses share similarities	Lung cancer: cetirizine; inflammatory bowel disease: topiramate
Protein interaction network, disease pathway, and drug omics data	Systems biology, network biology, and targeted-mechanism biology	Clarifying specific routes	Clomifene and daunorubicin (breast cancer)

Table 2.
A thorough summary of the various methods for repurposing medications along with relevant examples. A few currently in use medication repurposing methods [30, 31].

5.2 Target-based methods include

Ligand-based screening, molecular docking, and high-throughput and/or high-content screening (HTS/HCS) of therapeutic molecules for a target protein or biomarker of interest. They also do *in silico* screening of compounds or pharmaceuticals from huge chemical libraries. These strategies have a higher likelihood of finding drugs or drug leads than blinded search techniques. Furthermore, the entire screening process takes less time to complete.

5.3 Knowledge-based approaches

Use cheminformatics or bioinformatics procedures to gather data from clinical trials on drug profiles, chemical structures of targets and pharmaceuticals, drug-target networks, side effects, signaling, and metabolic pathways. The information level of knowledge-based approaches is sufficiently rich in comparison with target-based or blindfolded methods. Since the existing data may be predicted, it can also be used to anticipate novel and unknown mechanisms, such as novel disease biomarkers; medication targets that are not yet identified; or similarities between drugs.

5.4 Gene signatures created

From disease omics data (genomics data), with or without medicines, are used in signature-based techniques to identify unknown off-targets or unknown sickness processes. Genomic data can be accessed through public databases. One advantage of these methods is that they can be used to look into unknown drugs' mechanisms of action. Unlike knowledge-based approaches, signature-based approaches employ computational techniques to investigate pharmacological processes at the molecular level, such as variations in gene expression.

5.5 Pathway or network-based methods

Is made possible by route- or network-based approaches, which make use of strategies based on network analysis or pathway informatics. These methods make use of accessible signaling or metabolic pathways, protein interaction networks, and disease-omics data. One intrinsic benefit of these approaches is their ability to concentrate on a limited subset of proteins inside a particular network, as opposed to addressing a significant number of proteins distributed across several target molecules or signaling networks.

5.6 Targeted mechanism-based approaches

Integrate treatment omics data, existing knowledge of signaling circuits, and protein interaction networks to define the undiscovered mechanisms of action of drugs. In addition to being used to identify the processes connected to medications or illnesses, these techniques also have the advantage of being able to identify the mechanisms directly linked to the drug therapies for certain diseases [30–32].

6. Polypharmacology

Polypharmacology denotes the capacity of a pharmaceutical agent or compound to engage with multiple molecular targets within the physiological milieu. Conventional paradigms of drug discovery have historically emphasized the development of compounds that exhibit specific interactions with individual targets to elicit therapeutic effects. However, numerous pathological conditions manifest intricate biological networks and pathways, necessitating a shift toward interventions that concurrently target multiple components, thereby potentially augmenting therapeutic efficacy.

Molecular docking stands as a computational methodology integral to the realm of drug discovery and design. This technique entails the computational prediction of the optimal orientation and conformation of a diminutive molecule (referred to as a ligand) upon binding to a target macromolecule, typically a protein, resulting in the formation of a stable complex. The elucidation of these molecular interactions is pivotal for comprehending the binding dynamics between a pharmaceutical agent and its designated target, thereby facilitating the refinement of drug candidates to optimize efficacy and selectivity. The interconnection between polypharmacology and molecular docking within the drug discovery process is manifested in the following symbiotic relationship:

6.1 Identification of multiple targets

Within the realm of polypharmacology, investigators endeavor to discern and comprehend the interactions exhibited by a pharmaceutical agent with numerous targets implicated in a disease pathway. Molecular docking serves as a predictive tool for determining the binding affinity and mode of interaction between a ligand and various target proteins. The resultant information holds significance in the evaluation of a drug's potential to engage with multiple targets.

6.2 Optimizing polypharmacological agents

Computational methodologies, inclusive of molecular docking, play a pivotal role in formulating and refining polypharmacological agents. Through an understanding of molecular-level binding interactions, researchers can modify drug candidates to enhance their affinity for multiple targets.

6.3 Virtual screening for polypharmacological agents

Molecular docking frequently features in virtual screening processes, wherein extensive databases of chemical compounds are computationally sifted to discern potential drug candidates. Virtual screening can be customized to pinpoint compounds capable of interacting with multiple targets, thereby fostering the discovery of polypharmacological agents.

6.4 Understanding structure-activity relationships (SAR)

Molecular docking significantly contributes to Structure-Activity Relationship (SAR) studies by furnishing insights into how alterations in the chemical structure of a compound may impact its binding to diverse targets. SAR information assumes a pivotal role in optimizing drug candidates with polypharmacological potential.

6.5 Network pharmacology

Polypharmacology aligns closely with the concept of network pharmacology, which scrutinizes interactions among multiple targets and pathways within a biological network. Molecular docking, coupled with other computational methodologies, aids in the analysis of network pharmacology by forecasting and validating interactions within a complex biological system.

Molecular docking emerges as an invaluable instrument in the investigation and refinement of polypharmacological agents, affording insights into the molecular intricacies of interactions between drugs and their targets. This approach holds particular relevance in the context of intricate diseases where modulation of multiple targets is imperative for achieving efficacious therapeutic outcomes [31, 32].

7. The procedure of repurposing drugs

Medication repurposing is the methodical process of identifying and exploring new therapeutic uses for pharmaceuticals that already have a market. By exploring the possibility of using previously approved or experimental medications to treat conditions other than the ones for which they were initially approved, this novel strategy avoids the traditional method of *de novo* drug development. Adopting drug repurposing techniques could provide advantages in terms of timing and resources when compared to the traditional drug discovery process.

Molecular docking, which forecasts the binding affinities and spatial orientation of a small molecule, such as a possible medication candidate, with a target macromolecule, such as a protein, is one of the most significant computational techniques in drug discovery. In the subject of drug repurposing, molecular docking is essential because it might reveal possible interactions between current drugs and new therapeutic targets. The processes that are frequently used in medication repurposing are outlined here in an organized procedural overview that includes the function of molecular docking.

7.1 Target identification

Target identification aims to ascertain a fresh therapeutic target affiliated with a designated disease. This target may manifest as a protein, enzyme, or other molecular constituent participating in the pathogenesis of the disease.

7.2 Drug selection

This involves selection of established drugs anticipated to interact with the newly discerned target. These drugs may originate from diverse reservoirs, comprising approved drugs for disparate indications, investigational drugs, or previously unsuccessful drugs exhibiting promise against an alternative target.

7.3 Molecular docking

To simulate how the selected medications would interact with the target protein, molecular docking tools are used. To do this, the medications' affinities and binding mechanisms with the target must be predicted.

7.4 Scoring and analysis

The outcomes of the docking simulations are assessed using scoring functions to prioritize potential interactions. Elevated scores signify heightened binding affinities. Scrutinize the anticipated binding modes to elucidate the nature of drug-target interactions.

7.5 Validation

Validation through experimental means is imperative to affirm the forecasted interactions. This may involve *in vitro* investigations, such as biochemical assays, alongside *in vivo* studies gauging therapeutic efficacy in animal models.

7.6 Clinical testing

Clinical trials are conducted to evaluate the safety and efficacy of the repurposed medicine for its novel indication when preclinical findings show promise.

The advantages intrinsic to drug repurposing encompass the prospect of an expedited development timeline, diminished developmental expenditures, and the exploitation of preexisting safety and pharmacokinetic data. Nonetheless, challenges persist, including the procurement of intellectual property rights for novel applications and the potential manifestation of off-target effects.

Molecular docking, as a computational methodology, contributes to the preliminary screening and identification of conceivable drug-target interactions, facilitating the prioritization of compounds for subsequent experimental validation. It is imperative to underscore that while molecular docking affords invaluable insights, experimental validation remains paramount to substantiate the predicted interactions, ensuring both the efficacy and safety of repurposed drugs [24].

7.7 Drug repurposing opportunities

7.7.1 Uncommon and untreated illnesses

Repurposing pharmaceuticals is a compelling strategy, particularly when addressing rare and underdiagnosed illnesses that have unfavorable economic dynamics for the development of new medications. Under these conditions, the role of academic and nonprofit organizations becomes more significant in guiding the drug discovery process, supported by public policies and some regulatory actions intended to encourage research in these disease areas. These policies include financial awards, accelerated approval procedures, tax exemptions, and waivers of regulatory fees. Repurposed medications make up a significant percentage of the Drug for Neglected Diseases initiative (DNDi) clinical trial portfolio. Examples of these include miltefosine, fexinidazole, fosravuconazole, and AmbisomeTM. Fexinidazole is noteworthy for being the first medication developed for advanced-stage sleeping sickness to be taken orally in the previous three decades. DNDi was able to develop it for just USD 62.5 million, which is a small amount compared to the estimated $1 to $3 billion that is usually involved in *de novo* drug development [33].

Crucially, some of the obstacles that arise in commercial settings like worries about off-patent medications, for example, become less formidable when it comes to finding treatments for undertreated ailments. The fundamental motivation for

research into treatment solutions for these kinds of illnesses is not profit. As a result, efforts may be made to repurpose inexpensive, off-patent medications in order to guarantee widespread accessibility. Computational methods for predictive repurposing provide quick routes to testable ideas that can be translated into clinical applications in the field of uncommon diseases, which are frequently characterized by poorly known pathophysiology. Determining the genetic variants causing these ailments is made possible by large-scale genome sequencing projects, which speed up the development of medications that target the relevant proteins [34].

7.7.2 Precision medicine

Precision medicine represents an evolving paradigm that takes into account the individualized variations in genetic makeup, environmental exposures, and lifestyle factors to inform the selection or pursuit of tailored therapeutic interventions [35]. It is becoming clearer that several illnesses that were once thought to be solitary conditions really present as a spectrum of illnesses. Finding safer and/or more effective drugs is possible if they are designed to target particular subtypes within a larger pathological disease, or if they are matched to an individual's unique genomic, transcriptomic, proteomic, and metabolomic differences. The field of cancer is seeing a growing number of practical benefits from precision medicine. Exemplified by a recent case study of a patient with advanced colorectal cancer who was resistant to traditional chemotherapy and radiation and was exhibiting treatment-related damage [36], it emphasizes how important it is to repurpose drugs. To determine the expression of the V600E mutant BRAF protein and the MMR proteins (MSH2, MSH6, PMS2, and MLH1), the patient underwent immunohistochemistry investigation. Comprehensive genomic analysis revealed over 2000 genomic alterations, including point mutations, insertions, deletions, and copy-number variations. This included whole-genome sequencing of the pretreatment tumor and blood as well as whole transcriptome and whole genome sequencing of the metastatic tumor.

Genes that were differently expressed were found using transcriptome analysis; they included members of the proto-oncogene families FOS and JUN. These results validated the theory that renin-angiotensin system blockade can have therapeutic advantages. As a result, the patient experienced a dramatic and long-lasting response when the hypertension angiotensin II receptor antagonist irbesartan was repurposed as an anticancer medication. This is an example of how precision medicine can find new treatment approaches that are specific to the molecular details of each case.

7.7.3 Systems biology

An integrative viewpoint offered by systems medicine and network pharmacology challenges earlier drug discovery paradigms, particularly the target- and phenotypic-oriented methods connected to "rational" drug discovery. By employing network and metabolic control analysis as useful instruments, these approaches aid in the development of multi-target treatments or the choice of complementary drug combinations. The nifurtimox eflornithine combination therapy, which has been approved for inclusion in the World Health Organization's Model List of Essential Medicines for the treatment of advanced stages of the Gambiense form of sleeping sickness, provides a clear illustration of how this strategy can be used in practice.

Comparing this specific combination therapy to eflornithine monotherapy, there are benefits such as ease of administration, a shorter course of treatment, and possible defense against the development of resistant parasites. Interestingly, eflornithine, which was first developed for the treatment of cancer in the late 1970s, and nifurtimox, which was first approved for the treatment of American trypanosomiasis, have both undergone repurposing. Repurposing well-known medications as combination therapy is a well-trod path within the profession; the concept of combination drug repurposing adds another layer. Compared to single-drug therapy, the field of possible combination drug repurposing is far more expansive and difficult to exhaust due to the naturally combinatory nature of polypharmacy. Furthermore, when novel active compounds are identified, their potency is frequently found to be limited, which makes it difficult to use them in clinical settings right away since tolerated plasma drug concentrations are below limits that are effective. As an alternative to monotherapies, synergistic medication combinations have the potential to reduce the necessary therapeutic doses, which could increase the success rate of drug repurposing.

7.7.4 Cooperative models

Pharmaceutical corporations and academic institutions are beginning to realize how well they may work together to find new opportunities for repurposing existing products. Pharmaceutical companies have vast and significant chemical library warehouses that are frequently neglected and contain chemicals from failed or terminated medication prospects. These businesses also contribute to a great deal of experience in clinical development and translational research. Additionally, they provide access to screening technologies, which are generally difficult for most academic institutions to acquire and maintain. On the other hand, biotechnology companies and academic institutions make substantial contributions to the understanding of new fields in disease biology, which prepares the way for the creation of very creative drugs. Non-negligible benefits result from collaboration between these sectors, such as the development of human capacity through exchange of knowledge and training [19].

Potential approaches from the standpoint of intellectual property include investigating patent pools, implementing open licensing for the development of drugs targeted at underserved or uncommon diseases, and assisting academic institutions and staff in becoming patent owners of novel medical applications. To close the gap between stakeholders, innovative business models and collaboration are emerging. These models include financial sources like public money, venture capital, and nonprofit organizations. Certain medical fields, especially those related to uncommon illnesses, where medication repurposing plays a significant role, could benefit greatly from the application of these models.

8. Drug repurposing opportunities

After being approved by the United States Food and Drug Administration (US FDA) in 1998, sildenafil was brought to the pharmaceutical market and quickly became popular, according to Boolell et al. [37]. In a parallel setting, the well-known medication thalidomide experienced a reorientation. Thalidomide was first developed as a sedative by the German pharmaceutical company Grünenthal in 1957. However, when it was given to expectant mothers to treat morning sickness, it was shown to

have unanticipated teratogenic consequences. The ensuing discovery of severe birth abnormalities led to its discontinuation from distribution after being utilized in 46 nations, resulting in over 10,000 cases of limb and extremity deformities in newborns, with more than half succumbing within months of birth [38].

Over subsequent decades, research endeavors elucidated thalidomide's unanticipated anticancer properties. D'Amato and Folkman [39] observed its angiogenesis-inhibiting capabilities in animal experiments, opening avenues for further exploration. Further research, as demonstrated in studies [40, 41], revealed possible treatment advantages for multiple myeloma that was refractory and metastatic prostate cancer. These results culminated in the US FDA approving thalidomide and dexamethasone together for the treatment of multiple myeloma in 2006. Examples of many repositioned drugs that have been produced or are being developed from various FDA-approved or marketed drugs as well as investigational new drugs (IND) are displayed in **Table 3**. A few repositioned drugs that are now participating in COVID-19 clinical trials are also included.

Many datasets and software are publicly available for use in pathway analysis, proteomics, metabolomics, and genomics research. Numerous computational algorithms have previously been developed to expedite and streamline the repurposing process. A few notable databases utilized in pharmaceutical repurposing research are shown in **Table 4**.

9. Challenges associated with drug repurposing

Repositioners face significant challenges primarily stemming from the comparatively inadequate intellectual property safeguards applied to pharmaceuticals within this category. Such limitations can adversely impact the return on investment and act as deterrents for businesses engaged in their development [42]. Interestingly, repurposing drugs with the same active ingredient provides protection only in the form of a fresh application patent, which may be enhanced by a different formulation technique. This need results from the medication having previously been patented as a unique chemical entity. It is essential to recognize that the range of medicinal applications covered by application patents is systematically smaller than that of new chemical entities. This means that repositioners might have trouble stopping the off-label prescription of generic versions for applications that are patented. Additionally, the patents' legal standing may be weakened, especially in the event of any legal challenges claiming that the new indication was predicted based on scientific literature [11].

Notwithstanding these difficulties, companies that offer medications for orphan diseases that are defined in Europe as having a prevalence of little more than 5 in 10,000 may benefit more from them than from the relative drawbacks of patent protection. These benefits include a guaranteed duration of market exclusivity and fee reductions [43]. Notably, some companies, exemplified by Apteeus in France, specialize in "personalized" medication repurposing. In this approach, potential treatments are screened using patient cells originating from orphan diseases. This tailored strategy represents an innovative avenue within the repurposing landscape.

9.1 Difficulties in repurposing drugs

Repurposing drugs is promoted as a resource-efficient way to quickly produce new drugs. But oftentimes, academic researchers fail to fully address the necessary

Pharmacological category of drug	Uses	Novel uses	Developmental state
Ampicillin B (AMB), an antifungal medication	Fungus-related illnesses	The leishmaniasis	Developed already
NSAIDs and aspirin	Inflammation and pain	Antiplatelet CVDs	Developed already
		Prostate cancer	In progress
Antihistaminic astemizole	An allergic reaction, like urticaria	Malaria	In progress
Antidepressant atomoxetine	Depression	Hyperactivity and attention deficit	Developed already
Avermectin, a chelating agent	River-blindness and elephantiasis	Tuberculosis	In progress
Antibacterial antibiotic azithromycin	Infections with bacteria	COVID-19	In progress
Antidepressants, SSRIs, and bupropion	Depression	Giving up smoking	Developed already
NSAIDs, COX-2 inhibitors, and celecoxib	Inflammatory response	Colon and breast cancer	In progress
H2 receptor antagonist cimetidine	Stomach sore	Prostate, lung, and breast cancer	In progress
As an ALK inhibitor, crizotinib	Cancer (lymphoma; ALCL clinical study ongoing)	NSCLC	Developed already
Anti-inflammatory drug colchicine	Gout (arthritis gouty)	The pericarditis	Developed already
		COVID-19	In progress
Cardiotonic and Digoxin	CVDs, including heart attacks	Cancer of the Prostate	In progress
Acetaldehyde dehydrogenase inhibitor, disulfiram	Persistent alcoholism	Cancer	In progress
The immunosuppressant everolimus	suppressor of the immune system	Neuroendocrine tumors of the pancreas	Developed already
Antimetabolite, anticancer, and fluorouracil	Cancer	Breast cancer	Developed already
Antidepressant Fluoxetine	Depression	Dysphoria before menstruation	Developed already

Table 3.
Examples of pharmacological category of drug, uses, novel uses, and stages.

factors to guarantee that a medicine that has been repurposed is appropriate for a new application. The following discussion explores a number of issues related to drug repurposing.

9.2 Intellectual property and economic considerations

Legal obstacles impacting the patentability of new medical uses and/or the enforcement of patent rights may reduce the incentives for drug repurposing. While

Information Type	Database	Website
Chemical Structure	PubChem	http://pubchem.ncbi.nlm.nih.gov
	DrugBank	http://www.drugbank.ca/
	ChemSpider	http://www.chemspider.com
	ChemDB	http://www.chemdb.com
	Therapeutic Target Database(TTD)	http://bidd.nus.edu.sg/group/cittd/
Target 3D Structure	RCSB Protein Data Bank (PDB)	http://www.rcsb.org
	OCA	http://oca.weizmann.ac.il/oca-bin/ocamain
	Proteopedia	http://proteopedia.org
Drug-Target Information	Drugbank	http://www.drugbank.ca/
	Therapeutic Target Database (TTD)	http://bidd.nus.edu.sg/group/cittd/
	Pharmacogenetics Knowledge Base (PharmGKB)	http://www.pharmgkb.org/
	DrugMap Central (DMC)	http://r2g2drug.org/index.html
Protein Interaction Information	Human Protein Reference Database (HPRD)	http://www.hprd.org/
	Biological General Repository for Interaction	http://thebiogrid.org/
	Database of Interacting Proteins (DIP)	http://dip.doe-mbi.ucla.edu/dip/Main.cgi
	STRING	http://string-db.org/
Pathway Information	NCI Pathway Interaction Database (NCI-PID)	http://pid.nci.nih.gov/
	Kyoto Encyclopedia of Genes and Genomes (KEGG)	http://www.genome.jp/kegg/
	PathwayCommons	http://www.pathwaycommons.org/about/
Clinical Trial Information and Adverse Effects	Clinicaltrial.gov	http://clinicaltrials.gov
	AdverseReaction Database (Canada)	http://www.fda.gov/Drugs/
	SIDER	http://sideeffects.embl.de/
FDA Label Information	FDALABEL (US FDA)	http://www.fda.gov/ScienceResearch/
	DailyMed (US FDA)	http://dailymed.nlm.nih.gov/dailymed/about.cfm
	Structured Product Labeling (SPL)	http://www.dailymed.nlm.nih.gov/dilymed/about.cfm
Omics Data (Target/Drug)	NCBI-GEO	http://www.fda.gov/ForIndustry/DataStandards/
	Sequence Read Archive (SRA)	http://www.ncbi.nlm.nih.gov/geo/
	ArrayExpress	http://www.ncbi.nlm.nih.gov/Traces/sra/
	Cancer Cell Line Encyclopedia (CCLE)	http://www.ebi.ac.uk/arrayexpress/
	Sequence Read Archive (SRA)	http://www.broadinstitute.org/ccle/home

Table 4.
Information's, database, novel websites.

major pharmaceutical markets often allow patents for repurposed medicinal uses, several country laws initially present barriers to getting a patent for additional or secondary medical use. Furthermore, a plethora of potential off-label, unregistered uses for repurposing have been documented or are in clinical practice, despite the absence of controlled clinical trials endorsing such applications [34]. This existing knowledge, available to the public, may influence patentability and impede innovation. While it is feasible to secure a patent for a new indication for an off-patent medicine, challenges may arise if the new indication employs strengths and dosage forms already on the market. It may be necessary to use non-marketed strengths (ideally lower than those that were previously available) or a completely new formulation in order to fully maximize the benefits of drug repurposing [34, 44]. It is inappropriate to use more modern derivatives since they depart from the repurposing paradigm. In general, the European Union grants 2 years of market exclusivity and 8 years of data protection. If a second indication is created during the eight-year data exclusivity term, an extra year may be granted. On the other hand, the United States first provides 5 years, which can be renewed for an additional 3 years [45]. But these long times might not be favorable for achieving a sufficient return on investment; hence, different kinds of financial incentives are necessary to make drug repurposing profitable.

9.3 Availability of data and compounds

In the realm of drug development, the open-source paradigm is gradually gaining prominence, as noted in Ref. [19]. However, certain impediments persist, hindering public access to crucial data types, notably clinical trials. Accessibility concerns notwithstanding, challenges arise with data types such as image data, due to either their incompatibility with data mining, integration, or manipulation, or irregular provision [34]. The integration of disparate data types to enhance analytical capabilities proves computationally intensive [46].

The reluctance of certain pharmaceutical companies to disclose their chemical libraries, particularly failed drugs, poses challenges in diversifying potential applications and hinders drug repurposing efforts. Selectivity in partnership choices may create a fundamental obstacle, especially when a repurposed indication lies beyond the company's core disease area. Despite the potential value of shelved drugs as idle capital, missed opportunities, or postponed endeavors, the release of chemical libraries remains constrained. Effective facilitation and flexibility in administrative procedures are pivotal for compound distribution and material transfer agreement signatories. This holds true even when larger pharmaceutical companies express openness to crowdsourcing or collaboration with smaller entities such as boutique firms or academic groups. Complications may arise in cases involving compounds with generic active pharmaceutical components, particularly if the chemical is no longer available in the global market. The identification of a reliable vendor under such circumstances may prove challenging [46].

9.4 The area under consideration for drug repurposing

It is possible to argue that systematic efforts in medication repurposing could quickly exhaust the opportunities for repurposing pharmaceuticals for a particular ailment, despite the wide range of diseases requiring improved treatment approaches. The pool of candidates for repurposing is naturally small and grows yearly at a slow pace. For instance, a number of high-throughput screenings aimed at finding

repurposed drugs with trypanocidal qualities for possible use in the treatment of Chagas disease have been observed over time. But these screenings frequently ignore the results of earlier low-throughput screenings [47, 48] and are directed toward specific pharmacological targets, requiring subsequent experimental validation through *in silico* or wet screens (see, for instance, [49, 50]). An essential concern arises regarding the appropriateness of further repurposed-oriented phenotypic screenings focused on Trypanosoma cruzi. Similarly, one may question whether interest in drug repurposing would wane over time with the execution of a series of systematic screenings on established drug collections.

A quick solution to this conundrum could entail changing strategy to focus on unnamed target ailments. Examining medication combinations instead of possibly repurposed monotherapies may increase the likelihood of drug repurposing. An example of this paradigm's effectiveness in the field of infectious illnesses is the approval of nifurtimox eflornithine combination therapy for the treatment of second-stage African trypanosomiasis [51]. The following sections will explain how precision and system medicine, in their own unique ways, present a new opportunity to expand the use of drug repurposing.

Lastly, displays with goals may end up being more beneficial. It is necessary to investigate the full range of compounds from a pharmaceutical business that have the same active scaffold once an approved medicine has proven effective against an undisclosed target. Hundreds of these compounds are typically manufactured and used in hit-to-lead and lead-optimization processes to define structure-activity connections; a lead compound used for one therapeutic goal may not be the same for another condition.

9.5 Predicting drug-target interactions during medication repurposing *via* multiple targeting

Comprehending the various binding behaviors of medications and developing novel theories for medication repurposing require precise modeling of the interactions between pharmaceuticals and their target proteins. Computational methodologies for forecasting drug-target interactions have garnered significant attention, primarily due to the challenges and expenses associated with experimental identification of binding interactions. It has been determined that there are three main types of computational approaches: target-based, ligand-based, and machine learning-based methods [52].

In ligand-based techniques, the putative ligand is evaluated in connection with established active ingredients that are directed toward the putative protein. This comparison helps forecast binding interactions since ligand-based methods, including pharmacophore modeling and Quantitative Structure–Activity Relationship (QSAR), depend on the presence of active ligands linked to the protein target in order to be effective [53].

Target-based techniques, which include methods such as binding-site similarity and docking, are effective means of distinguishing between protein-ligand interactions according to the target's three-dimensional structure. The limited availability of target structures, especially for G protein-coupled receptors (GPCRs), results in limitations [47, 53].

Novel drug-target pairings can be predicted by machine learning approaches by utilizing commonalities between compounds and targets. These methods can be generally divided into two categories: machine learning based on features and learning

based on similarity. Additional subcategories of the similarity-based category include kernel-based, matrix factorization-based, and network-based approaches [48]. Machine learning techniques have the advantage of being quicker and more effective than docking procedures and data-intensive QSAR [49]. Nevertheless, popular databases have significant shortcomings, mainly because they include only true-positive interactions and leave out important information about the complex nature of drug–target interactions, like dose dependency and empirical affinities [50].

10. Conclusion

In summary, molecular docking is now a valuable tool in the drug repurposing market, offering a robust approach to discovering novel therapeutic applications for pharmaceuticals that have already received approval. Molecular docking is a promising avenue for drug development that could become more innovative and cost-effective in the future as technology advances and our understanding of molecular interactions deepens. In order to ensure that the potential of molecular docking for medicine repurposing is realized in an ethical and responsible manner, researchers need to keep improving and validating their techniques.

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