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Accelerate drug repurposing with in-silico molecular modelling techniques, tools and databases: A comprehensive review

Vanisri. M, Sreesivasakthi. A, MuthuKaviya. M, Roja Jayashankar, Salai Dhivyathai. N, Rajaganapathy. K * and Srinivasan.R

Department of Pharmacology, Faculty of Pharmacy, Bharath Institute of Higher Education and Research, Selaiyur, Chennai 600073, Tamil Nadu, India.

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Abstract

Exploring innovative ways to accelerate drug repurposing through in-silico molecular modeling techniques, tools, and databases is paramount in modern pharmaceutical research. Exploring the vast landscape of drug repurposing presents both a challenge and an opportunity in the realm of pharmaceutical research. With the escalating costs and time-consuming nature of developing new drugs from scratch, the urgency to identify novel therapeutic uses for existing compounds has never been more pressing. Readers can expect a detailed exploration of how computational methods are revolutionizing drug repurposing efforts, offering insights into accelerated drug discovery and development timelines. This comprehensive review dives deep into the opportunities and challenges of leveraging computational approaches to identify new therapeutic uses for existing drugs and this article highlights the potential of in-silico methods to revolutionize drug discovery by repurposing existing compounds efficiently and cost-effectively, ultimately leading to faster development timelines and improved patient outcomes and will be focused for *In-silico* molecular modeling techniques, tools, and databases as powerful allies in expediting this crucial process.

Keywords: Drug repurposing; In-silico molecular modeling; Biological databases; Molecular docking; Reverse docking; Pharmacophore mapping

1. Introduction

Unlocking the hidden potential of existing drugs and finding new therapeutic uses can revolutionize the field of medicine. This is where drug repurposing approaches and strategies using in-silico methodologies come into play. In a world where novel drug discoveries are often time-consuming, expensive, and prone to failure, repurposing existing drugs offers a promising alternative drug repositioning and repurposing is a groundbreaking approach in the field of pharmaceutical research, offering a cost-effective and time-efficient strategy for discovering new therapeutic uses for existing drugs [1-5]. One of the earliest instances of repurposing can be traced to the discovery of aspirin, originally used for pain relief and now widely prescribed for its cardiovascular benefits. Throughout the 20th century, serendipitous findings led to the repurposing of existing drugs for new indications, demonstrating the value of exploring untapped therapeutic potentials [6-10].

Pharmaceutical companies spend around $2.6 billion in developing a drug through to market approval. To minimize risk and development time, the Drug repositioning identifies new indications for known drugs. In-silico tools play a pivotal role in accelerating the identification of novel therapeutic uses for existing drugs [11-12]. By leveraging computational methods and algorithms, we can efficiently sift through vast amounts of data to identify potential drug candidates with previously unrecognized medical applications. Computational approaches have been applied to the

* Corresponding author: Rajaganapathy. K

drug- repositioning pipeline. In silico drug target identification, which involves numerous distinct algorithms for identifying disease-associated genes and proteins, is the first step in the drug discovery pipeline. Reverse docking, first proposed in 2001, refers to the computational docking of a specific small molecule of interest to a protein structure database [13-14].

The drug repurposing through in-silico molecular modeling tools is revolutionizing the field of drug discovery. As researchers strive to find new therapeutic uses for existing drugs, the power of computational approaches offers a promising solution to expedite this process. In this review, we delve into the realm of in-silico techniques, databases, and tools that are reshaping how we identify novel treatment options for existing drug [15].

2. The Drug Repurposing and repositioning Via In-silico Computer based Approaches

Drug repositioning involves shifting the use of experimental or approved medications to new indications. A few successful repositioning examples are the sedative thalidomide, which is currently approved to treat leprosy and multiple myeloma, the cytotoxic anti-cancer agent gemcitabine, which was initially developed as an antiviral, and sildenafil, which was originally developed for heart disease and was repurposed for erectile dysfunction. The drug-repositioning pipeline has been studied using In-silico computational methods. The initial stage in the drug discovery process is called In-silico drug target identification, which entails using many different algorithms to find genes and proteins linked to illness (Liu et al., 2010) and the In-silico target identification was followed by Reverse docking for drug repurposing of existing molecules, which was first proposed in 2001, refers to the computational docking of a specific small molecule of interest to a protein structure database (Chen, Zhi, 2001) [16].

Drug repurposing, also known as drug repositioning or drug reprofiling, is the process of identifying new therapeutic uses for existing drugs that are already approved for other indications. This innovative approach presents a cost-effective and time-efficient strategy to combat diseases by repurposing drugs with established safety profiles.

In-silico molecular modeling is a cutting-edge computational technique used in drug discovery to predict the behavior and interactions of molecules. By simulating chemical structures and biological processes, researchers can expedite the identification of potential drug candidates with higher accuracy and efficiency. This sophisticated approach allows scientists to visualize how drugs bind to specific targets at the molecular level, enabling them to optimize drug design before proceeding with costly experimental trials. In-silico modeling offers a powerful tool for exploring diverse chemical space, unlocking new avenues for drug repurposing, and accelerating the development of innovative therapeutic solutions.[17]

2.1. Leveraging Protein Databases for Drug Repurposing

Protein databases play a pivotal role in drug repurposing by providing valuable information on the structures and functions of proteins. By exploring these databases, researchers can identify potential drug targets, predict protein-ligand interactions, and design new therapeutic strategies. Leveraging these resources allows for a more efficient and cost-effective approach to discovering novel uses for existing drugs. Through comprehensive data mining and analysis of protein databases, scientists can uncover hidden connections between drugs and diseases, leading to innovative treatment options and improved patient outcomes. The wealth of information contained within these repositories empowers researchers to make informed decisions in drug repurposing efforts, ultimately accelerating the pace of discovery in the pharmaceutical industry [18].

Exploring the vast realm of molecular modeling and docking, researchers often face the challenge of accessing quality protein databases for their studies. In-silico protein databases serve as invaluable resources for understanding protein structures, predicting interactions, and designing novel therapeutics. When venturing into the realm of drug repurposing, the exploration of target databases plays a crucial role in identifying potential candidates for repositioning. These databases house a wealth of information on target proteins, their structure, function, and interactions with ligands. By delving into these repositories, researchers can uncover hidden gems and overlooked targets that hold promise for repurposing existing drugs to treat new diseases. By delving into protein databases, scientists can unravel the complexities of protein structures, uncovering insights that drive advancements in drug discovery and disease research. The wealth of data stored within these databases empowers researchers to decipher the molecular mechanisms underlying biological processes, opening doors to new possibilities in the realm of molecular modeling and drug design.

Protein databases form the foundational pillars of molecular modeling, serving as vast repositories of structural and functional information crucial for understanding protein behavior. These databases house a diverse array of proteins

from various organisms, enabling researchers to explore and analyze protein structures, sequences, and interactions with precision. By harnessing the wealth of data within protein databases, scientists can unravel complex biological processes, predict protein structure-function relationships, and design novel therapeutics more efficiently. The interconnected nature of these databases fosters collaboration and knowledge-sharing within the scientific community, propelling advancements in drug discovery and structural biology toward brighter horizons. When delving into the vast realm of in-silico protein databases for molecular modeling, navigating through these repositories with precision is essential. Sequence alignment tools such as Clustal Omega and MUSCLE play a pivotal role in comparing and aligning protein sequences to identify conserved regions and structural motifs. By employing sophisticated algorithms, researchers can uncover evolutionary relationships and functional similarities among proteins, paving the way for insightful molecular insights. Moreover, understanding the nuances of sequence alignment facilitates the identification of critical residues and domains that contribute to protein structure and function. Through meticulous exploration of protein databases like UniProt and PDB, researchers can extract valuable information on sequence variations across species, aiding in the elucidation of evolutionary patterns. This process not only enhances our understanding of protein structure-function relationships but also inspires novel avenues for drug design and therapeutic interventions [19].

2.2. Exploring BLAST for Protein Sequence Search

When delving into the realm of protein databases for molecular modeling, one powerful tool at our disposal is the Basic Local Alignment Search Tool (BLAST). BLAST allows researchers to search vast repositories of protein sequences to find homologous proteins that share structural and functional similarities. This enables scientists to identify potential templates for homology modeling and gain insights into the evolutionary relationships between proteins [20].

By utilizing BLAST for protein sequence searches, researchers can uncover hidden connections between seemingly unrelated proteins, shedding light on their shared ancestry and evolutionary paths. This not only aids in understanding protein structure-function relationships but also opens up new avenues for drug discovery and enzyme engineering. The ability to navigate through the genetic tapestry of proteins using BLAST brings a sense of excitement and possibility to the field of molecular biology, where each sequence uncovered holds the potential for groundbreaking discoveries [21].

2.3. Leveraging Protein Databases for Homology Modelling

Homology modeling, also known as comparative modeling, is a powerful technique used to predict the three-dimensional structure of a protein based on its similarity to known protein structures. Protein databases play a crucial role in homology modeling by providing templates that share sequence similarity with the target protein. By leveraging these databases, researchers can generate accurate structural models that aid in understanding protein function and designing novel therapeutics.

Through homology modeling, researchers can bridge the gap between sequence and structure, allowing for the rational design of mutant proteins or the exploration of protein-ligand interactions. Protein databases such as PDB and SWISS-MODEL offer a wealth of structural information that can be utilized to create reliable homology models. This approach not only accelerates drug discovery efforts but also contributes to our fundamental understanding of biological systems, bringing us closer to unlocking new treatment modalities and advancing scientific knowledge.

In drug discovery and Drug Repurposing, homology modeling serves as a powerful tool to predict the 3D structure of a target protein based on its amino acid sequence. By comparing this model with known structures, researchers can identify potential binding sites for drug molecules. This method accelerates the process of designing new therapeutics with improved efficacy [22].

Homology modeling not only aids in understanding the structural basis of drug-target interactions but also facilitates the prediction of ligand binding modes. By incorporating this predictive approach into drug discovery pipelines, researchers can expedite the identification of lead compounds for repurposing. The synergy between computational homology modeling and experimental validation results in more efficient and targeted drug development strategies.

Homology modeling plays a pivotal role in drug discovery by predicting protein structures based on known templates. **SWISS-MODEL** is a widely-used database offering automated homology modeling services with high accuracy**. MODELLER** is another powerful tool that excels in generating reliable protein models through comparative modeling techniques, aiding in rational drug design.

Moreover, **Phyre2** stands out for its user-friendly interface and ability to predict protein structures even for sequences with no close homologs. These essential homology modeling databases and tools provide researchers with invaluable

resources to expedite the drug repurposing process, offering hope for the discovery of novel therapeutic interventions [23].

2.4. Utilizing Databases for Active Site Prediction

When it comes to drug repurposing through in-silico molecular modeling, the crucial step of predicting active sites is paramount. By harnessing ligand databases, researchers can explore a plethora of small molecules that bind to target proteins. These databases provide a rich source of information on known ligands, aiding in the identification of potential binding sites and guiding drug repurposing efforts toward promising candidates.

Through the utilization of ligand databases for active site prediction, researchers embark on a journey of discovery and innovation. The intricate dance between ligands and protein targets unfolds, offering insights into potential drug interactions and new therapeutic avenues. This process not only enhances the efficiency of drug repurposing strategies but also cultivates a sense of excitement as novel connections between compounds and proteins are unveiled.

One of the key aspects of molecular modeling is predicting the active sites of proteins accurately. By utilizing protein databases that house information on known active sites and binding pockets, researchers can leverage this data to predict and analyze the potential binding sites within a protein molecule. This predictive ability is crucial in drug design and understanding molecular interactions at a microscopic level.

Through advanced algorithms and computational tools, researchers can sift through vast amounts of structural data stored in these databases to pinpoint regions within a protein that are likely to play a significant role in its biological function. This process not only aids in identifying potential drug targets but also allows for the design of novel molecules that can interact specifically with these active sites, potentially leading to the development of new therapeutic interventions with enhanced efficacy and specificity [24].

3. Accessing Ligand Databases for Molecular Docking

When it comes to molecular docking studies, accessing comprehensive ligand databases is crucial for identifying potential small molecules that can bind to a target protein. These databases contain an array of chemical compounds with detailed structural information, making them invaluable resources for virtual screening and drug discovery. The chemical structure (Ligand) is used for drug likeliness prediction based on pharmacophore modeling. The pharmacophore analysis is predicted based on the Lipinski rule of 5 parameters using the **molinspiration tool**. The molinspiration can predict the miLogP (octonol/water partition coefficient), topological polar surface area (TPSA <130), n atoms number of atoms (<80), molecular weight (MW<500Da), number of hydrogen acceptor (nON<5), number of hydrogen donor (nOHNH<10), violations from Lipinski's rule, number of rotatable bonds (nrotb<12), and volume of the molecule helps to screen the compounds. chemical structures (Ligand) are used for drug likeliness prediction to understand the biological activity with the effective distribution and metabolism in the body. The In-silico drug likeliness prediction and ADMET analysis represent the discovery of lead molecules with predicted biological activity. The molinspiration tool measures the miLogP value (logarithm of the compound's partition coefficient between *n*-octanol and water) which measures the compound's hydrophilicity. The highest logP values indicate lower hydrophilicity and thus poor absorption and permeability in the membrane. TPSA indicates the total polar surface atoms present in the compounds. The increased TPSA is associated with reduced membrane permeability, higher TPSA belongs to better substrates for p-glycoprotein. Molecular weight increased the absorption rate and most of the drugs have the lowest molecular weight. Hydrogen bond donors and acceptors will help to understand the hydrophilic interaction of O-N and OH-NH groups.

Researchers can explore ligand databases like ZINC, PubChem, and ChEMBL to find suitable ligands for molecular docking simulations. By leveraging these vast repositories of chemical compounds, scientists can enhance the efficiency of their drug design process and uncover promising leads for developing novel therapeutics. The wealth of data available in these databases empowers researchers to make informed decisions and accelerate the pace of discovering new drug candidates through in-silico methods [25].

4. Conducting Molecular Docking and Reverse Docking for Drug Repurposing

Molecular docking is a crucial computational technique wherein the interactions between small molecules (ligands) and target proteins (receptors) are predicted and analyzed. This process aids in identifying potential drug candidates by evaluating their binding affinity and orientation within the receptor's active site. Reverse docking, on the other hand, involves screening a library of compounds against multiple target proteins to repurpose existing drugs for new

therapeutic indications. This innovative approach accelerates drug discovery by efficiently exploring the interactions between diverse ligands and protein targets, leading to exciting possibilities for discovering novel treatment options.

Molecular docking predicts the preferred orientation of one molecule to a second when bound to each other to form a stable complex. This method plays a pivotal role in drug discovery, helping researchers analyze and optimize ligand-protein interactions with high precision [26].

By simulating the behavior of molecules at the atomic level, molecular docking provides valuable insights into how potential drugs interact with target proteins. The binding process involves a delicate interplay of electrostatic interactions, hydrogen bonding, van der Waals forces, and hydrophobic interactions. These molecular interactions determine the strength and specificity of the ligand-protein complex. Understanding and manipulating these interactions hold the key to unlocking novel drug targets and therapeutic avenues, paving the way for groundbreaking discoveries in pharmaceutical research. This enables scientists to design new drugs or repurpose existing ones more efficiently, ultimately leading to the development of novel therapeutic solutions for various diseases.

Within the intricate realm of molecular docking, diverse bonding interactions between ligands and proteins play a pivotal role in determining the stability and efficacy of drug molecules. These interactions encompass hydrogen bonding, hydrophobic interactions, electrostatic forces, and van der Waals forces. Each molecular interaction contributes uniquely to the binding affinity between the ligand and protein, forming a complex network of intermolecular forces that dictate the specificity and strength of their connection. Understanding these various bonding interactions not only sheds light on the mechanism of drug-receptor recognition but also paves the way for designing potent therapeutics with enhanced efficacy and reduced side effects [27].

As researchers delve deeper into the realm of molecular docking, navigating the active site of a protein structure becomes a crucial aspect. The active site often likened to a lock waiting for its key, is where the magic happens. It is within this microcosm that ligands interact with proteins, forming intricate bonds that hold the key to unlocking new therapeutic possibilities. Imagine yourself as an explorer venturing into uncharted territory, equipped with sophisticated tools that allow you to navigate the twists and turns of the active site with precision and finesse. Every crevice and contour within the protein's binding pocket holds secrets waiting to be unraveled. By understanding the nuances of the active site, researchers can strategically design ligands that fit snugly into place, triggering a cascade of events that could lead to groundbreaking drug discoveries [28].

In the realm of molecular docking, scoring functions play a pivotal role in evaluating and ranking ligand-protein interactions based on their affinity and stability. These functions encompass various parameters such as energy terms, geometric fit, and desolvation energies to assess the binding potential of a given complex. The intricate process of decoding these scoring functions involves meticulous analysis of each contributing factor to determine the overall fitness of a ligand within the protein's active site. By deciphering these numerical values and algorithms, researchers can gain insights into optimizing drug design strategies and identifying potential lead compounds with enhanced binding affinities, fostering innovation in pharmaceutical research [29].

4.1. Leveraging Molecular Docking for Drug Repurposing

One of the most promising applications of molecular docking is in the realm of drug repurposing. By utilizing computational tools to predict interactions between existing drugs and new target proteins, The various molecular docking toolsare **shown in Table: 1**researcher can identify potential therapeutic uses for approved medications beyond their original indications. This approach not only accelerates the drug discovery process but also offers a sustainable and cost-effective strategy for developing novel treatments. Through molecular docking simulations, scientists can explore the binding affinities and mechanisms of action between repurposed drugs and target molecules, paving the way for innovative therapeutic solutions. By repurposing existing drugs for new indications, researchers can leverage established safety profiles and pharmacokinetic properties, expediting clinical trials and ultimately bringing life-saving treatments to patients faster. This transformative approach underscores the power of computational methods in driving drug discovery toward a more efficient and patient-centric future [30].

Table 1 Tools Used for Molecular Docking

S.no	Tools Used for Molecular Docking	Description
1	Autodock Vina	It's one of the fastest and most widely used open-source docking engines. It is a turnkey computational docking program based on a simple scoring function and quick gradientoptimization conformational search.
2	Glide	Glide offers the full range of speed vs. accuracy options, from the HTVS (high-throughput virtual screening) mode for efficiently enriching million compound libraries to the SP (standard precision) mode for reliably docking tens to hundreds of thousands of ligands with high accuracy to the XP (extra precision) mode where further elimination of false positives is accomplished by more extensive sampling and advanced scoring, resulting in even higher enrichment.
3	SMINA	Docking with Smina is done from the command line and is very easy to script, thanks to the possibility of calculating the box from an existing ligand. The –autobox_ligand and –autobox_add switches define a docking box that is 8Å greater than the ligand specified. The –exhaustiveness 16 switch tells Smina to spend more time finding the best scoring binding mode of the ligand in the binding site; the default is 8.
4	Discovery Studio (Catalyst)	Discovery Studio is a software suite for simulating small molecule and macromolecule systems.
5	OpenEye Omega	OMEGA was designed with the large libraries required for computer-aided drug design. It generates multi-conformer structure databases with high speed and reliability. OMEGA performs rapid conformational expansion of drug-like molecules, yielding a throughput of tens of thousands of compounds per day per processor.
6	Maestro Suite	It's a streamlined portal for structural visualization and access to advanced predictive computational modeling and machine-learning workflows for small molecule drug discovery.
7	PLANTS	Parallel Molecular Docking using PLANTS software
8	GOLD	GOLD is the validated, configurable protein–ligand docking software for expert drug discovery.

4.2. Harnessing Reverse Docking for Drug Repurposing

Reverse docking is a powerful computational technique used in drug discovery to identify new indications for existing drugs. By virtually screening approved drugs against a target protein, reverse docking allows for the repurposing of drugs to treat different diseases. This method leverages existing drug libraries efficiently, potentially reducing costs and time in drug development. Through reverse docking, researchers can uncover hidden therapeutic potentials of known drugs beyond their original intended use. This approach offers a sustainable and economical strategy in the pharmaceutical industry by finding novel applications for existing medications. By repurposing drugs through reverse docking, we can enhance treatment options, accelerate drug discovery processes, and ultimately improve patient outcomes [31].

Reverse docking software plays a pivotal role in drug discovery by predicting potential binding sites on protein structures for small moleculesThe various reverse docking toolsare **shown in Table: 2**. Among the notable software available, AutoDock Vina stands out for its efficiency and accuracy in identifying suitable binding sites. Vina is user-friendly and offers robust algorithms for accurate predictions, making it a preferred choice for researchers in the field. Another prominent software worth exploring is idock, known for its high-throughput virtual screening capabilities. Idock utilizes advanced computational techniques to expedite the process of identifying protein-ligand interactions

efficiently. Its user-friendly interface coupled with powerful algorithms makes it an indispensable tool for researchers aiming to streamline the drug discovery process.

Embark on a journey through the realm of molecular docking software, each a powerful tool in the hands of researchers. AutoDock stands out for its user-friendly interface and robust algorithms, making it ideal for beginners. For advanced users, SwissDock offers unparalleled accuracy and customization options for intricate simulations. Delve into the world of MOE, known for its comprehensive suite of tools that cater to all aspects of molecular docking analysis. Vina shines with its exceptional speed and efficiency in generating reliable binding poses. Lastly, GOLD continues to be a preferred choice with its versatile parameters and reliable performance across diverse molecular systems [32].

Table 2 Tools to be used for Reverse Docking for Drug Repositioning

S.no	Tools used for Reverse Docking for Drug Repurposing	Description
1	SurflexDock	A program designed to predict interactions between a target protein and compounds from a database by fitting them together with their surfaces to create plausible complexes.
2	Raccoon2	Tool for virtual reverse screening providing support for database queries along with feature enrichment analysis capabilities
3	SybylX Suite	Includes three modules designed specifically for virtual reverse screening: High Throughput Searching (HTS) module, Lead Optimization (LO) module, and Super Screening (SS) module
4	Glide XP	A module of Schrödinger Suite optimized specifically for reverse virtual screening scenarios involving thousands or millions of compounds through highly parallelized searches executed on GPUs or CPUs clusters.
5	ICM Explorer	Integrated into Accelrys Discovery Studio software suite, which includes, among others, a de novo library building tool focused on synthesis protocols design automation features.; - SYBYL X by Tripos is an advanced Software Tool used in Reverse Docking Studies
6	AutoDock Vina	Reverse docking software

4.3. Enhancing Drug Repurposing with Molecular Dynamic Simulations

Molecular dynamic simulations play a pivotal role in the realm of drug repurposing, offering valuable insights into the behavior of drug molecules within biological systems over time. By simulating the interaction between drugs and target proteins at an atomic level, researchers can predict drug efficacy and side effects more accurately. This sophisticated computational approach allows for the exploration of diverse binding conformations, aiding in the identification of novel therapeutic uses for existing drugs [33].

Through molecular dynamic simulations, researchers can unravel intricate details about drug interactions that are often challenging to capture experimentally. The dynamic nature of these simulations provides a comprehensive understanding of how drugs bind to their targets and how this binding may change under different conditions. By harnessing the power of molecular dynamics, scientists can expedite the process of drug repurposing, leading to the discovery of innovative treatment options and potentially accelerating advancements in healthcare [34-35].

5. Applying Pharmacophore Modelling in Drug Repurposing

Exploring the intricate realm of pharmacophore mapping and drug repurposing unveils a world where science meets innovation to revolutionize the landscape of medicine. As researchers delve deeper into this fascinating field, new possibilities emerge that promise to reshape the way we approach drug discovery and development. Pharmacophore modelling is a powerful technique in drug repurposing that focuses on identifying key structural elements necessary for a molecule to interact with its target. By analyzing the common features of known active compounds, pharmacophore models can be created to guide the discovery of new drug candidates with similar properties.This

approach not only accelerates the drug discovery process but also allows for the exploration of diverse chemical space for potential therapeutic interventions. By leveraging pharmacophore modelling in drug repurposing efforts, researchers can uncover hidden relationships between compounds and targets, leading to novel treatment options and ultimately improving patient outcomes [36].

Pharmacophore, a pivotal concept in drug design, embodies the essential features of a molecular structure that are responsible for its biological activity. It serves as a map guiding medicinal chemists to develop new drugs with enhanced efficacy and reduced side effects. By discerning the key interactions between a drug molecule and its target receptor, pharmacophore elucidates the crucial elements necessary for therapeutic success. Delving deeper into the principle of pharmacophore unveils a profound understanding of molecular recognition and ligand binding. This intricate dance between chemical entities dictates the specificity and potency of drug-receptor interactions. Through unraveling the nuances of pharmacophore, scientists can sculpt innovative pharmaceutical interventions that hold promise in treating complex diseases and improving patients' quality of life [37].

Table 3 Tools Used for Pharmacophore Mapping

S.No	Software used for Pharmacophore mapping	S.No	Software used for Molecular Docking Mediated Pharmacophore mapping
1	Schrodinger Suite	1	AutoDock Vina - An open-source software program used for protein-ligand docking simulations
2	Discovery Studio	2	Schrodinger Suite – A software package for macromolecular structure determination, including molecular docking and pharmacophore mapping tools
3	Ligand Scout 4	3	Glide - Software application from Schrodinger used for molecular docking simulations and pharmacophore mapping
4	CS Chem Space Analyzer	4	MOE – Molecular Operating Environment - All-inclusive integrated modules Toolbox that combine 3D visualization and modeling, chemistry, high-performance computing, informatics, and collaboration tools.
5	Hyper Chem HL Chem	5	PyRx for Visualization
		6	Autodock Vina for Protein-Ligand Docking
		7	Schrodinger Maestro for Preparing 3D Structures
		8	LigandFit from Tripos Sybyl for Docking Studies

5.1. Transforming Medicine through Pharmacophore Mapping and Drug Repurposing

Harnessing the power of pharmacophore mapping and drug repurposing has the potential to revolutionize the field of medicine. By identifying common structural features that are essential for a drug's biological activity, pharmacophore mapping enables researchers to design more effective drugs with fewer side effects. This approach not only accelerates the drug discovery process but also holds promise for personalized medicine, where treatments can be tailored to individual patients based on their unique pharmacophore profiles. Furthermore, drug repurposing, which involves finding new therapeutic uses for existing drugs, offers a cost-effective and time-efficient strategy to address unmet medical needs. Through innovative applications of pharmacophore mapping, scientists can uncover hidden potentials in well-established medications and introduce novel treatments for various diseases. This remarkable synergy between technology and creativity is reshaping the landscape of healthcare, paving the way for groundbreaking advancements that have the potential to improve countless lives. Pharmacophore mapping serves as a powerful tool in the realm of drug discovery, offering a strategic approach to identify essential chemical features required for interactions between ligands and biological targets. By utilizing pharmacophore models, researchers can expedite the screening process of potential drug candidates, leading to more targeted and efficient drug development. Through the meticulous analysis of molecular structures and interactions, pharmacophore mapping enables scientists to gain valuable insights into the key binding interactions that drive therapeutic effects. This innovative approach not only streamlines drug discovery processes but also opens doors to uncovering novel drug targets and designing more effective treatments with enhanced specificity and reduced side effects [38]. A closer look at drug repurposing, also known as drug repositioning or drug reprofiling, is a strategic approach that involves finding new uses for existing drugs outside their original

medical indications. This innovative concept hinges on the idea that a drug developed for one specific purpose may exhibit therapeutic benefits in treating different diseases or conditions. By exploring the underutilized potential of approved drugs, researchers can accelerate the discovery of novel treatment options and significantly reduce both time and costs associated with traditional drug development. Through comprehensive analysis of molecular structures and biological activities, researchers can identify existing compounds with untapped therapeutic potential through drug repurposing initiatives. This approach not only offers a more efficient path to introducing new treatments into clinical practice but also provides hope for patients by expediting access to safe and effective medications. Embracing drug repurposing as a viable strategy in pharmaceutical research opens up a world of possibilities for enhancing patient care and addressing unmet medical needs with creativity and resourcefulness. Pharmacophore mapping is revolutionizing the field of drug discovery by unlocking the hidden potential of existing drugs. By dissecting the molecular structure and identifying key pharmacophoric features, scientists can repurpose drugs for new therapeutic uses. This innovative approach breathes new life into forgotten or underutilized medications, offering hope for novel treatments and improved patient outcomes.

The various pharmacophore mapping tools are shown in Table: 3 Through meticulous pharmacophore mapping, researchers can uncover unforeseen connections between drugs and diseases, paving the way for unexpected breakthroughs in healthcare. The ability to repurpose existing drugs not only accelerates the drug development process but also offers a sustainable solution for addressing unmet medical needs. This strategy not only saves time and resources but also highlights the boundless possibilities that lie within our current arsenal of medications [39].

By harnessing the power of pharmacophore mapping and drug repurposing, healthcare is experiencing a transformative shift. This innovative approach not only accelerates the drug discovery process but also holds the promise of addressing unmet medical needs in a more efficient and cost-effective manner. The ability to repurpose existing drugs by identifying novel therapeutic targets through pharmacophore mapping has the potential to revolutionize treatment paradigms and improve patient outcomes. Through the integration of cutting-edge technologies and computational tools, pharmacophore mapping is paving the way for personalized medicine and precision therapeutics. The synergy between medicinal chemistry, bioinformatics, and data science in this realm is reshaping the landscape of healthcare delivery. Embracing this revolutionary paradigm shift empowers researchers and clinicians to explore new avenues for drug development, leading to a brighter future where diseases can be tackled with greater precision and efficacy [40].

As we gaze into the horizon of pharmaceutical innovation, the future holds immense promise for pharmacophore mapping and drug repurposing. The evolving landscape of computational chemistry and artificial intelligence is poised to revolutionize the way we identify pharmacophores and repurpose existing drugs. With advanced algorithms and machine learning techniques, researchers are now able to sift through vast databases at unprecedented speeds, opening doors to novel drug discoveries and therapeutic applications. The synergy between pharmacophore mapping and drug repurposing is paving the way for personalized medicine tailored to individual genetic profiles. By harnessing the power of big data analytics and molecular modeling, scientists are on the brink of unlocking new avenues for targeted therapies and precision medicine. This convergence of technology and biopharmaceuticals offers a beacon of hope for patients worldwide, ushering in an era where diseases once deemed incurable may find remedies in unexpected places [41].

5.1.1. Complete List of In-silico Drug Repurposing Databases

Embark on the journey of drug repurposing with these cutting-edge in-silico databases designed to accelerate the discovery of novel therapeutic applications for existing drugs. Dive into comprehensive repositories such as DrugBank, ChEMBL, and PubChem to explore a vast array of chemical compounds and their biological activities, fostering innovation and efficiency in drug development [42]. The various lists of In-silico Database resources are shown in Table 4.

Uncover hidden gems within specialized platforms like Repurposing Hub and Open Targets that provide valuable insights into drug-target interactions and disease associations. Embrace the power of virtual screening tools offered by ZINC Database and Swiss Target Prediction to identify potential candidates for repurposing, paving the way for transformative breakthroughs in pharmaceutical research. Let these databases be your guiding light in the quest for repurposed medicines that hold immense promise for improving human health [43-44].

5.1.2. Computational Approaches in Drug Repurposing

Computational approaches have revolutionized the field of drug repurposing by leveraging advanced algorithms and data analytics to identify new therapeutic uses for existing drugs. Through virtual screening, molecular docking, and network pharmacology analysis, researchers can efficiently sift through vast databases of compounds to uncover hidden

potentials. This innovative methodology not only accelerates the drug discovery process but also reduces costs and minimizes risks associated with traditional trial-and-error approaches [45-47].

By harnessing the power of artificial intelligence and machine learning, computational approaches empower scientists to make informed decisions based on complex biological interactions. With predictive modeling and quantitative structure-activity relationship (QSAR) studies, researchers can predict drug-target interactions with high accuracy, paving the way for targeted therapies and personalized medicine. The synergy between technology and biopharmaceutical research holds immense promise in unlocking novel treatment avenues while optimizing resource utilization for a brighter future in healthcare [48-50].

Overcoming Challenges in Computational Drug Repurposing

One of the significant challenges in computational drug repurposing is the vast amount of data to analyze and interpret accurately. Integrating diverse data sources, such as genomics, proteomics, and clinical information, requires sophisticated algorithms and computational power. Researchers must navigate through this data landscape efficiently to identify potential drug candidates for repurposing. Furthermore, ensuring the reliability and reproducibility of computational predictions poses another hurdle. Validation of in-silico findings through experimental studies is crucial but can be resource-intensive. Collaborative efforts between computational biologists, chemists, pharmacologists, and clinicians are essential to validate and refine computational models for accurate drug repurposing outcomes [51-55].

Ethical Considerations in Drug Repurposing

When delving into the realm of drug repurposing, ethical considerations play a crucial role. It is imperative to assess the ethical implications of repurposing drugs originally intended for one condition to treat another. Ensuring patient safety, informed consent, and transparency in decision-making processes are paramount in upholding ethical standards in drug repurposing endeavors. The ethical landscape of drug repurposing also involves issues of equity and access. Striving to balance profit motives with humanitarian concerns is essential in ensuring that repurposed drugs reach those most in need, regardless of socioeconomic status. Collaborative efforts between stakeholders must be guided by ethical principles to navigate the complex terrain of drug repurposing ethically and responsibly [56-57].

5.1.3. The Future Landscape of Drug Repurposing

Drug repurposing, also known as drug repositioning or drug reprofiling, is a remarkable strategy that involves discovering new therapeutic applications for existing drugs. This approach offers a plethora of advantages, including reduced costs and accelerated timelines in drug development. By repurposing drugs, researchers can bypass many of the traditional hurdles associated with developing novel compounds from scratch.

Moreover, drug repurposing holds great promise in addressing unmet medical needs and rare diseases. The ability to leverage existing drugs for new indications not only saves time and resources but also brings hope to patients who may have limited treatment options. The power of drug repurposing lies in its potential to transform the pharmaceutical landscape by unlocking hidden potential in familiar medications, ultimately leading to improved healthcare outcomes [58-59].

In-silico drug design has emerged as a transformative force in the field of drug discovery, enabling researchers to virtually screen and design new compounds with unprecedented speed and accuracy. By harnessing computational simulations and algorithms, scientists can explore vast chemical space, predict molecular interactions, and optimize drug candidates before even setting foot in a laboratory.

This revolutionary approach not only accelerates the drug development process but also minimizes costs and reduces reliance on traditional trial-and-error methods. In-silico drug design empowers researchers to make informed decisions based on data-driven insights, leading to more targeted therapies and potentially life-saving treatments for complex diseases [60].

In the realm of drug repurposing, the future holds great promise as advancements in in-silico drug design and computational approaches continue to revolutionize the field. With the exponential growth of available data and computational power, researchers are now able to explore vast libraries of compounds and predict potential drug candidates with unprecedented speed and accuracy. Furthermore, collaborative efforts between academia, pharmaceutical companies, and regulatory bodies are fostering a culture of sharing knowledge and resources in drug repurposing initiatives. This collective approach not only accelerates the discovery process but also ensures that promising repurposed drugs reach patients faster, offering new treatment options for a variety of diseases. The future

landscape of drug repurposing is indeed bright, paving the way for innovative solutions to challenging medical problems [61].

Table 4 List of various biological databases for data repurposing

Database	Data type(s)	Short description	Last update	URL	Reference
ADReCS-Target	Interactions involving drugs, adverse events, genes and proteins.	A drug-gene-protein interaction database that also contains information on the toxicity and adverse events of chemicals and medications	2017	http://bioinf.xmu.edu.cn/ADReCS-Target	(Huang et al., 2018) [62]
BindingDB	Interactions involving drugs, targets, genes and proteins	An index of measured drug-like small-molecule binding affinities	2016	https://www.bindingdb.org/bind/index.jsp	(Gilson et al., 2016) [63]
BioGRID	Interactions involving drugs, targets and proteins	An edited website listing drug-chemical-gene-protein interactions	2018	http://wiki.thebiogrid.org	(Chatr-Aryamontri et al., 2017) [64]
ChEMBL	General drug information, disease indications, drug-target interactions, mechanisms of action	A chemical library of bioactive compounds with characteristics similar to those of drugs, carefully curated	2017	https://www.ebi.ac.uk/chembl/ws	(Davies et al., 2015) [65]
ChemProt-3.0	Interactions involving drugs, side effects, diseases, targets, genes and proteins	A repository for data on chemical-protein interactions	2018	http://potentia.cbs.dtu.dk/ChemProt/	(Kringelum et al., 2016) [66]
Comparative Toxicogenomics Database (CTD)	Interactions involving drugs, diseases, targets, genes and proteins	A database including information on toxicity and gene-protein-disease relationships	2018	http://ctdbase.org	(Davis et al., 2017) [67]
CTD2 Dashboard	Interactions involving drugs, targets, genes and proteins	A database of observations on cancer from research sites that are members of CTD2	2017	https://ctd2-dashboard.nci.nih.gov/	(Aksoy et al., 2017) [68]
DGIdb 3.0	Interactions involving drugs and gene	A repository containing data on interactions between drugs and genes, as	2018	www.dgidb.org	(Cotto et al., 2018) [69]

		well as the druggable genome			
DrugBank 5.0	Interactions involving drugs, side effects, disease indications, targets, genes and proteins, mechanisms of action	A database with detailed molecular details on medications, their targets, interactions, and mechanisms	2018	www.drugbank.ca	(Wishart et al., 2018) [70]
DrugCentral	Interactions involving drugs, side effects, disease indications, targets, genes and proteins, mechanisms of action	A website that provides general medication information, interactions between drugs and targets, pharmacological action, bioactivity, approvals, and pharmaceutical items	2018	http://drugcentral.org	(Ursu et al., 2017) [71]
ECOdrug	Evolutionary data, drug-target interactions	A database linking medications with the preservation of their targets in many species	2018	http://www.ecodrug. Org	(Verbruggen et al., 2018) [72]
IntAct	Interactions involving drugs, targets and proteins	A database of molecular interactions that is curated via direct data uploads and literature.	2018	http://www.ebi.ac.uk/ intact	(Orchard et al., 2014) [73]
KEGG Databases	Interactions involving drugs, pathways, targets, genes and proteins	A collection of databases with sections dedicated to systems, genetic, chemical, and health data	2018	http://www.genome. jp/keg	(Kanehisa et al., 2016) [74]
Pharos	Interactions involving drugs, pathways, targets, genes and proteins	A link between medications, targets, and illnesses	2018	https://pharos.nih. gov/idg/index	(Nguyen et al., 2017) [75]
PDBBind	Interactions involving drugs, targets and proteins	A database that offers experimental binding affinity information for PDB-listed biomolecular complexes	2017	http://www.pdbbind. org.cn/	(Liu et al., 2017) [76]
PDID	Interactions involving drugs and proteins	A data on protein-drug interactions are included in a database.	2015	http://biomine.cs.vcu. edu/servers/PDID/ index.php	(Wang et al., 2016) [77]

PharmGKB	Interactions involving drugs, pathways, genes and diseases	A well-curated website with details on medications, dosage recommendations, drug labels, and interactions between pharmaceuticals and genes	2018	https://www.pharmgkb.org/	(Whirl-Carrillo et al., 2012) [78]
STITCH	Interactions involving drugs, targets and proteins	An index of compound-protein interactions	2018	http://stitch.embl.de	(Szklarczyk et al., 2016) [79]
SuperDRUG2	Interactions involving drugs, side effects, targets, genes and proteins	A website that offers marketed and authorized medications	2018	http://cheminfo.charite.de/superdrug2	(Siramshetty et al., 2018) [80]
SuperTarget	Interactions involving drugs, targets and proteins	A database including details about routes, ontologies, and drug-target interactions	2012	http://insilico.charite.de/supertarget	(Gunther et al., 2007) [81]
IUPHAR/BPS Guide to Pharmacology (GtoPdb)	Interactions involving drugs and targets	A database including details about the biological targets of approved medications and other tiny compounds	2016	http://www.guidetopharmacology.org/	(Southan et al., 2016) [82]
Therapeutic Target Database (TTD)	Interactions involving drugs and targets	A Database of medicinal protein and nucleic acid targets, together with details on pathways and medicines and ligands that are targeted towards each target	2018	http://bidd.nus.edu.sg/group/ttd/ttd.asp	(Li et al., 2018) [83]
ChemSpider	3D structures of chemicals/ drugs	A database that mostly contains chemical structures	2015	http://www.chemspider.com/	(Pence & Williams, 2010) [84]
ZINC 15	3D structures of chemicals/ drugs	A database with 3D structures of compounds that resemble drugs	2018	https://zinc15.docking.org/	(Sterling & Irwin, 2015) [85]
SWEETLEAD	3D structures of chemicals/ drugs, general drug information	A database that is computer-aided in the discovery of pharmaceuticals, containing licensed drugs, regulated compounds, and herbal isolates	2013	https://simtk.org/home/sweetlead	(Novick et al., 2013) [86]

Side Effect Resource (SIDER)	Adverse events, side effects	A source with details on medications and their adverse effects	2015	http://sideeffects.embl.de/	(Kuhn et al., 2016) [87]
ClinicalTrials.Gov	Clinical trials	A global online portal offering up-to-date information about clinical trials	2018	https://clinicaltrials.gov/	
DrugPath: A Database of Drug-Induced Pathways	Drug-induced pathways	A database mostly comprising routes caused by drugs	2014	http://www.cuilab.cn/drugpath	(Zeng et al., 2015) [88]
Connectivity Map (CMap)	Gene expression profiles	A collection of biological signals at the genome scale	2018	http://clue.io/cmap	(Lamb, 2007; [89] Lamb et al., 2006; [90] Subramanian et al., 2017) [91]
ArrayExpress	Gene expression profiles	A database containing information from high-throughput functional genomics studies, such as medication response	2018	https://www.ebi.ac.uk/arrayexpress/	(Kolesnikov et al., 2015) [92]
Gene Expression Omnibus (GEO)	Gene expression profiles	A significant genomics databank	2018	https://www.ncbi.nlm.nih.gov/geo/	(Barrett et al., 2013) [93]
PubChem	General drug information		2018	https://pubchem.ncbi.nlm.nih.gov/	(Kim et al., 2016) [94]
DailyMed	General drug information, drug labels and indications	FDA medication labels and indications	2018	http://dailymed.nlm.nih.gov	
eRAM	rare diseases	Encyclopedia of rare disease annotations for precision medicine	2018	http://www.unimd.org/eram/	(Jia et al., 2018) [95]
Orphanet	Rare diseases and orphan drugs	An orphan drug and rare disease resource	2018	http://www.orpha.net	
repoDB	Repurposed drugs	Includes details regarding the triumphs and failures of medicine repositioning.	2017	http://apps.chiragjpgroup.org/repoDB/	(Brown & Patel, 2017) [96]
Repurposed drug database	Repurposed drugs	Data source about traditional and novel drug applications	2018	http://drugrepurposingportal.com/repurposed-drugdatabase.php	(Shameer et al., 2017) [97]
FAERS	Side effects	A database including records on adverse events, medication errors, and	2017	https://www.fda.gov/Drugs/Guidance ComplianceRegulatory Information/	(Fang et al., 2014) [98]

		complaints about the quality of products.		Surveillance/ AdverseDrugEffects/	
Offsides	Side effects	A source with details on medications and their adverse effects	2012	http://tatonettilab. org/resources/ tatonetti-stm.html	(Tatonetti et al., 2012) [99]
ACTOR	Toxicity	A database including data on the toxicity of chemicals	2015	http://actor.epa.gov	(Judson et al., 2008) [100]
WITHDRAWN	Withdrawn and orphan drugs	A list of medications that have been removed or stopped	2015	http://cheminfo. charite.de/withdrawn	(Siramshetty et al., 2016) [101]

6. Conclusion

As we conclude our exploration of in-silico molecular modelling databases and tools for drug repurposing, one cannot help but marvel at the immense potential and possibilities this innovative approach holds for revolutionizing the field of drug discovery. The convergence of advanced technology, vast data resources, and computational power offers a promising path towards identifying novel therapeutic uses for existing compounds, ultimately accelerating the drug development process. By embracing the power of bioinformatics and computational biology in repurposing drugs through in-silico methods, researchers are not only streamlining the discovery process but also contributing to a more sustainable and cost-effective approach to healthcare. As we look ahead with optimism, it is clear that the intersection of science, technology, and creativity will continue to drive breakthroughs in drug repurposing and pave the way for transformative advancements in medicine.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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