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Short Communication

Drug repurposing: A futuristic approach in drug discovery

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ABSTRACT

Drug repurposing (DR), also known as drug repositioning, is a strategy aimed at identifying new therapeutic uses for existing drugs. It offers an effective approach to discovering or developing drug molecules with novel pharmacological or therapeutic indications. In recent years, pharmaceutical companies have increasingly embraced the drug repurposing strategy in their drug discovery and development programs, leading to the identification of new biological targets. This strategy is highly efficient, time-saving, cost-effective, and carries a lower risk of failure compared to traditional drug discovery methods. By maximizing the therapeutic value of existing drugs, drug repurposing increases the likelihood of success. It serves as a valuable alternative to the lengthy, expensive, and resource-intensive process of finding new molecular entities (NMEs) through traditional or de novo drug discovery approaches. Drug repurposing combines activity-based or experimental methods with in silico-based or computational approaches to rationally develop or identify new uses for drug molecules. It leverages the existing safety data of drugs tested in humans and redirects their application based on valid target molecules. This approach holds great promise, particularly in addressing rare, difficult-to-treat diseases, and neglected diseases. By utilizing the wealth of knowledge and resources available, drug repurposing presents an emerging strategy for optimizing the therapeutic potential of existing medicines. It offers a pathway to rapidly identify effective treatments and repurpose approved drugs for new indications, benefiting patients and healthcare systems alike.

1. Introduction

Drug repurposing, also referred to as drug repositioning, drug re-tasking, drug reprofiling, drug rescuing, drug recycling, drug redirection, and therapeutic switching, encompasses the identification of alternative pharmacological indications for existing drugs. This approach involves exploring the potential therapeutic uses of drugs that have already been developed, whether they are approved, discontinued, abandoned, or still in the experimental phase. The process of drug repurposing aims to identify new therapeutic applications for drugs that were originally intended for a different purpose or have failed in their intended use. It involves extensive research and experimentation to determine if a drug could be effective in treating diseases or conditions other than those it was initially designed for. The advantage of drug repurposing lies in the fact that existing drugs have already undergone preclinical and/or clinical testing for safety and efficacy, which reduces the time and cost associated with traditional drug development. By repurposing drugs, researchers can potentially find new treatments for various diseases more efficiently and rapidly. The identification of new therapeutic uses for existing drugs can be accomplished through various approaches, including computational analyses, high-throughput screening, data mining, and repurposing-specific experimental studies. These methods help researchers identify potential drug candidates and

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establish their effectiveness in treating different diseases. Overall, drug repurposing offers a promising avenue for expanding the applications of existing drugs, potentially providing new treatment options for patients while saving time and resources in the drug development process.[1–3]

Approximately 30% of drugs and biologics approved by the US Food and Drug Administration (FDA) are classified as repositioned drugs, according to reports. Recent estimates indicate that the market for repurposed drugs reached $24.4 billion in 2015 and is projected to grow to 31.3 billion by 2020. The concept of drug repositioning originated from serendipitous observations in the 1920s, and over the course of a century, various approaches have been developed to expedite this process. Several notable drugs that have emerged from drug repurposing include sildenafil, minoxidil, aspirin, valproic acid, and methotrexate.[4] Drug repurposing encompasses two primary strategies: on-target and off-target approaches. In on-target drug repurposing, the established pharmacological mechanism of a drug molecule is utilized for a new therapeutic indication. In this strategy, the biological target of the drug molecule remains the same, but its application extends to a different disease.

Drug repositioning can be approached through two alternative and complementary methods: the experiment-based approach and the in silico-based approach.[5] The experiment-based approach, also known as activity-based repositioning, involves screening original drugs to discover new pharmacological indications using experimental assays. This approach includes protein target-based and cell/organism-based screening in vitro and/or in vivo disease models, without requiring prior knowledge of the target protein's structure. Various strategies are employed within the experimental repositioning approach, such as target screening, cell assay, animal model, and clinical approaches[6,7]·On the other hand, in silico repositioning involves the virtual screening of extensive drug/chemical libraries using computational biology, bioinformatics, and cheminformatics tools. This approach relies on the molecular interactions between drug molecules and protein targets to identify potential bioactive compounds.[8] Both the experiment-based and in silico-based approaches offer valuable avenues for drug repositioning, providing researchers with different methodologies to identify novel therapeutic applications for existing drugs.In recent decades, the in silico approach has become increasingly popular and successful in drug discovery programs. Pharmaceutical companies and drug discovery research laboratories have effectively integrated in silico tools and techniques into their processes. This approach has proven particularly valuable in exploring structurally diverse chemical spaces, thanks to the wealth of information available in the public domain regarding chemical structures, bioactive compounds, protein structures, and pharmacophore models. The utilization of in silico methods has provided researchers with valuable insights and opportunities for drug discovery.[9]. The methodologies employed in drug repurposing (DR) can be categorized into three main groups based on the available quantity and quality of pharmacological, toxicological, and biological activity information. These groups are: (i) drug-oriented, (ii) target-oriented, and (iii) disease/therapy-oriented. The drug-oriented methodology focuses on evaluating the structural characteristics of drug molecules, their biological activities, adverse effects, and toxicities. This strategy aims to identify molecules with specific biological effects through cell-based or animal-based assays. The target-oriented methodology involves in silico screening or virtual high-throughput screening (vHTS) of drugs or compounds from drug libraries or compound databases. This can include ligand-based screening or molecular docking, followed by in vitro and in vivo high-throughput and/or high-content screening (HTS/HCS) of drugs against specific protein molecules or biomarkers of interest. This approach has shown a higher success rate in drug discovery compared to the drug-oriented method, as it directly targets disease pathways or mechanisms represented by biological targets.The disease/therapy-oriented methodology is particularly applicable when a greater amount of information is available about the disease model. It involves constructing disease networks, considering genetic expression, identifying key targets, and recognizing disease-causing protein molecules related to specific cell and metabolic pathways of interest in the disease model. By employing these different methodologies, researchers can explore drug repurposing from various angles, leveraging available data to identify potential therapeutic applications for existing drugs.[10–12]

2. Discussion

Several available repositioned methods discussed below:

Blinded search or screening methods involve the serendipitous identification of potential drugs through biological tests or experimental screens conducted on specific disease models. These methods offer the advantage of flexibility in screening a large number of drugs or diseases.

Target-based methods employ in vitro and in vivo high-throughput and/or high-content screening (HTS/HCS) of drug molecules against specific protein targets or biomarkers of interest. They also utilize in silico screening of compounds or drugs from extensive compound libraries, such as ligand-based screening or molecular docking. These methods have a higher likelihood of identifying useful drugs or drug leads compared to blinded search methods. Moreover, they require less time to complete the screening process.

Knowledge-based methods utilize bioinformatics or cheminformatics approaches to gather and analyze available

Table 1: Examples of some repositioned drugs already developed or currently under development from various approved (FDA) or marketed drugs and investigational new drugs (IND). Some repositioned drugs currently under clinical trials in COVID-19 are also included in the listp [13–18]

Drug, pharmacological category	Original indication	New indication	Status of development
Amphotericin B (AMB), Anti-fungal antibiotic	Fungal infections	Leishmaniasis	Already developed *
Aspirin, NSAID	Pain and inflammation	CVDs (Anti-platelet)	Already developed *
		Prostate cancer	Under development *
Amantadine, Anti-viral	Influenza	PD	Already developed *
Astemizole, Anti-histaminic	Allergic illness such as urticaria	Malaria	Under development *
Atomoxetine, Anti-depressant	Depression	Attention deficit, Hyperactivity disorder	Already developed *
Avermectin, Anthelmintic	River blindness, Elephantiasis	Tuberculosis	Under development *
Hydroxychloroquine, Anti-malarial	Malaria, RA	COVID-19	Under development *
Ibudilast, PDE inhibitor (Anti-asthmatic)	Asthma	Neuropathic pain	Already developed *
Imatinib, TKI (Anti-cancer)	CML, ALL	GIST	Already developed *
Nitroxoline, Anti-bacterial	UTI	Breast, bladder and pancreatic cancers	Under development *
Orlistat, Anti-obesity agent	Obesity	Cancer	Already developed *
Penfluridol/Pimozide, Anti-psychotics	Psychiatric illness	Breast cancer	Under development *
Sunitinib, TKI (Anti-cancer)	Imatinib-resistant GIST, RCC	Pancreatic neuroendocrine tumors	Already developed *
Tamoxifen, Anti-estrogen (Anti-cancer)	Breast cancer, Anticancer	Systemic lupus erythematosus	Already developed *
		NTDs like Leishmaniasis (in combination with miltefosine)	Under development *
Thalidomide, Immune modulator	Immunomodulation, Morning sickness (withdrawn)	Multiple myeloma, Leprosy	Already developed #
Topiramate	Fungal infections	IBD	Already developed *
Valproic acid, Anti-epileptic	Epilepsy	Manic depression (bipolar disorder), migraine headache	Already developed *
Valsartan, ARB (Anti-hypertensive)	Hypertension, Heart attack	AD	Already developed *
Zidovudine, Anti-viral	Cancer (failed clinical trial)	HIV/AIDS	Already developed

information on drug profiles, chemical structures of targets and drugs, drug-target networks, clinical trial data (including adverse effects), and signaling or metabolic pathways. These methods leverage the rich information content to predict unknown mechanisms, such as unknown drug targets, drug similarities, or new biomarkers for diseases.

Signature-based methods utilize disease omics data, specifically gene signatures derived from genomics data, with or without treatments. These methods help discover unknown off-targets or disease mechanisms. Genomics data are widely available in public databases, and computational approaches are employed to investigate changes in gene expression, enabling exploration of drug mechanisms at a molecular level.

Pathway- or network-based methods utilize disease omics data, available signaling or metabolic pathways, and protein interaction networks to reconstruct disease-specific pathways. These methods focus on identifying key targets for drug repurposing within specific networks, allowing for a more focused analysis compared to general signaling networks.

Targeted mechanism-based methods integrate treatment omics data, signaling pathway information, and protein interaction networks to describe unknown drug mechanisms of action. These methods not only discover mechanisms related to diseases or drugs but also identify those directly related to specific drug treatments for particular diseases. [19–21]

2.1. Repositioned drugsTable 1

Traditionally, drug repurposing has a long history of discovering drug molecules, often through serendipitous observations. However, in recent years, it has opened up new avenues in the development of therapies based on existing or approved medicines. The systematic and rational approach to drug repositioning has led to the

innovation of drug molecules with previously unknown therapeutic indications. This approach offers significant advantages such as reduced research and development costs, higher success rates, shorter research timelines, and lower investment risks, making it increasingly in demand. In the era of precision medicine, the strategy of drug repositioning has proven particularly useful in uncovering the unknown mechanisms of action of drugs. It allows for the exploration of novel disease, metabolic, and signaling pathways, as well as off-target effects and target-specific mechanisms, including genetic expression profiles for genetic disorders. Advancements in genomics have provided us with vast amounts of genomic and transcriptomic data, thanks to technologies like next-generation sequencing, microarray data, and transcriptomics. Integrating network biology and systems biology approaches can further enhance our understanding of these novel mechanisms of action by providing valuable insights into drug-target interactions at the molecular and genetic levels.

To achieve successful drug repositioning, a comprehensive understanding requires the integration of computational and experimental methods. This integrated approach can greatly improve the success rates of repositioned drugs. Ultimately, drug repurposing holds great potential in the discovery and development of new drugs with novel and effective therapeutic indications for various human diseases.

3. Source of Funding

None.

4. Conflict of Interest

None.

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