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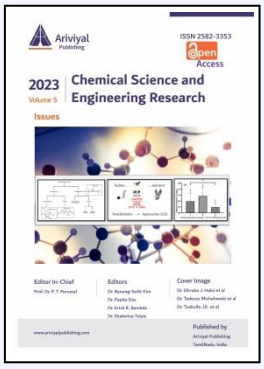

Impact of Drug Repurposing on New Drug Discovery: A Review

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Abstract: Drug repositioning, commonly known as drug repurposing, is a process of identifying new therapeutic use(s) for already used, available, or old medications. It is an efficient strategy for discovering or synthesizing medicinal compounds with novel pharmacological or therapeutic applications. Usually, drug discovery has relied on a de novo design technique, which is expensive and takes years to produce a medicine before it can be sold. By implementing the drug repositioning method in their drug research and development programmes, numerous pharmaceutical companies have been creating new medications in recent years in response to the identification of novel biological targets. This strategy is extremely efficient, saves time, is cost effective, and has a minimal failure risk. It raises the effectiveness of a medicine by maximizing its therapeutic value. As a result, drug repositioning is a successful alternative to the standard drug discovery procedure. Pharmacological repositioning combines activity-based, experimental, and in silico, computational techniques to develop/identify new rational applications for drug compounds. As the efficacy and safety of the original drug have previously been thoroughly explored and approved by regulatory bodies, redirected based on a feasible target molecule to cure diseases that are very rare, difficult to treat, and untreated. Repositioning drugs offers a greater return at a reduced risk.

Keywords: Drug repurposing; therapeutic indication; in silico repositioning; drug discovery; target-based screening; orphan disease; activity-based repositioning

1. Introduction

Drug repositioning, drug re-tasking, drug reprofiling, drug rescue, drug recycling, drug redirection, and therapeutic switching are other names for drug repurposing (DR). It can be described as the process of identifying new pharmacological applications from old/ existing/ failed/ investigational/already marketed/FDA authorized medications/pro-drugs, and the utilization of the newly generated drugs to treat diseases other than the drug's original/intended therapeutic use. It includes finding novel therapeutic applications for currently used medications, including licensed, discontinued, abandoned, and experimental ones.[1-3] Traditional Drug discovery is a lengthy, expensive, risky, and demanding process. The Eastern Research Group (ERG) reported that it typically takes 10-15 years to produce a new medicine.[4] However, the average success rate for developing new molecular entities is only 2.01%.[5] By reducing the high financial cost, longer design phase, and increased risk of failure, the unique strategy of drug repositioning has the potential to be used in place of traditional drug discovery programmes. It confers a decreased chance of failure, where a failure rate of about 45% is related with safety or toxicity issues in traditional drug discovery programmes, with the added benefit of saving up to 5-7 years in typical drug development time.[6-7] Additionally, compared to traditional approaches, drug repositioning requires less expenditure in research and development. For many nations, drug repositioning removes financial barriers. Utilizing a drug repositioning strategy reduces the cost of developing a new drug from $12 billion to just $1.6 billion. The trend of finding new disease targets, particularly for existing and older medications, has drawn attention to this novel idea. The attempt of drug developers to meet demand, particularly for illnesses without effective treatments or that are otherwise expensive to treat, is what gives drug repositioning its bright outlook. Profit, of course, is a crucial element in this situation. The most fruitful starting point for the development of a new treatment is an existing drug, according to Nobel winner pharmacologist James Black.[6] For example, sildenafil originally developed for the treatment of hypertension and angina pectoris, has currently been used to treat erectile dysfunction.[1]

2. Traditional drug Discovery vs. Drug Repurposing

The Traditional method of drug discovery entails the de novo identification of new molecular entities (NME), which has five stages: preclinical discovery, safety review, clinical research, FDA review, and

Table 1. Differences between activity- and in silico- based approaches of drug repositioning

Activity-based approach	In silico-based approach
Experimental screening (in vitro and in vivo)	Computational screening (virtual)
Assay for target- and cell- and organism-based screening	based on protein target screening
Requires no knowledge of the target proteins' structures or the phenotypic characteristics of drug-induced cells or diseases.	Target protein structural data as well as data on drug-induced changes in cell/disease phenotypes are required.
time- and labor employment	Time and labor efficient
lower percentage of screening-related false positive hits	higher percentage of screening-related false positive hits

post-market safety monitoring by the FDA. It is an expensive, time-consuming technique that has a significant risk of failure.[8] Drug repositioning, on the other hand, only has four stages: compound identification, compound acquisition, development, and FDA post-market safety monitoring.[9] The benefits of drug repurposing over traditional drug discovery methods are realised due to the availability of previously obtained pharmacokinetic, toxicological, clinical, and safety data at the outset of a repurposing development project. According to estimates, the time and expenditures needed to create a repositioned medicine range from 3 to 12 years (compared to 10 to 17 years in a standard discovery programme), guaranteeing the repositioning company significant time and financial savings. The following are some additional benefits. While the development of medications for fast developing and re-emerging infectious diseases, difficult-to-treat diseases, and neglected diseases (NTDs) is the core focus of the drug repositioning method, treating chronic and complicated diseases is the primary focus of traditional discovery programmes. Due to the accessibility of bioinformatics or cheminformatics approaches, massive omics (proteomics, transcriptomics, metabolomics, genomics, etc.) data, and database resources, disease targeted-based repositioning methods can be used to explore the unidentified mechanisms of action of known/existing drugs, such as unidentified targets for drugs, unidentified drug-drug similarities, new biomarkers for diseases, etc.[10]

3. Strategies of Drug Repurposing

On-target and off-target are the two basic DR methods. In on-target DR, a medication molecule's well-known pharmacological action is applied to a new therapeutic indication. In this approach, the drug's biological target is the same, but the disease is different. Since the medicine operates on the same target and has two distinct therapeutic effects, an on-target profile is shown, for instance, in the repositioning of minoxidil (Rogaine). Minoxidil was changed from a medicine that prevented hair loss and was a vasodilator for hypertension. As an antihypertensive vasodilator, minoxidil has the ability to open potassium channels and enlarge blood vessels. This pharmacological activity facilitates its usage in the treatment of male pattern baldness by allowing more oxygen, blood, and nutrients to the hair follicles (androgenic alopecia). On the other hand, the pharmacological mechanism in the off-target profile is not known. Drugs and drug candidates work on novel targets outside of their therapeutic indications. Consequently, the objectives and the signs are both fresh. A classic illustration of the off-target profile is aspirin (Colsprin). Aspirin has long been used as an NSAID to treat a variety of inflammatory and painful conditions. Additionally, it prevents platelets from performing their regular functions, which reduces blood coagulation (clot formation) (antiplatelet drug). As a result, it is applied to the management of heart attacks and strokes. It has also been claimed that aspirin is now being used in yet another novel way to treat prostate cancer.[11]

4. Approaches of Drug Repurposing

The experiment-based approach and the in silico approach are two alternate and complimentary methods for drug repositioning (Table 1).[12,13]

5. Methodologies of Drug Repurposing

Depending on the quantity and quality of the pharmacological, toxicological, and biological activity information that is available, the approaches used in DR may be categorised into three major classes mainly (i) drug-oriented, (ii) target-oriented, and (iii) disease/therapy-oriented. The drug-oriented technique assesses the structural properties of drug molecules, biological functions, harmful impacts, and toxicities. With the help of cell/animal tests, this technique is intended to identify compounds that have biological effects. This kind of repositioning approach is based on conventional pharmacology and drug discovery principles, where investigations are often carried out to ascertain the biological effectiveness of pharmacological molecules without really being aware of the biological targets. With this orientation profile, significant gains in DR have been made via chance or clinical observation, such as with the discovery of sildenafil.[14] Target-based methodologies include virtual high-throughput screening (vHTS) of drugs or compounds from drug libraries or compound databases, such as 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 a specific protein molecule or an interest biomarker. Compared to drug-oriented methods, this strategy has a significantly higher success rate for drug development since the majority of biological targets directly correspond to disease pathways and processes.[15] When more knowledge about the disease model is available, the application of the illness/therapy oriented technique in DR is pertinent. Given the availability of information provided by proteomics (disease specific target proteins), genomics (disease specific genetic data), metabolomics (disease specific metabolic pathways/profile), and phenotypic data (off-target mechanism, pharmacological targets, disease pathways, pathological conditions, adverse and side effects, etc.) regarding the disease process, DR can be guided by the disease and/or treatment in this case. Therefore, it necessitates building specialised disease networks, recognising genetic expression, taking into account critical targets, and identifying disease-causing protein molecules connected to cell and metabolic pathways of interest in the disease model.[16]

Table 2. Examples of some repositioned drugs from approved and investigational drugs

Drug, pharmacological category	Original indication	New indication	Status of development
Amphotericin B (AMB), Anti-fungal antibiotic	Fungal infections	Leishmaniasis	Established
Dimethyl fumarate, Anti-allergic	Psoriasis	Multiple sclerosis (MS)	Established
Duloxetine, SSNRI	Depression	Generalized anxiety disorder, fibromyalgia, chronic musculoskeletal pain, neuropathic pain	Established
Everolimus, Immune suppressant	Immune suppressant	Pancreatic neuroendocrine tumours	Established
Fluorouracil, Antimetabolite, Anti-cancer	Cancer	Breast cancer	Established
Fluoxetine, Antidepressan	Depression	Premenstrual dysphoria	Established
Gabapentin, Anti-epileptic	Epilepsy	Neuropathic pain	Established
Galantamine, AChE inhibitor	Neuromuscular paralysis	AD	Established
Ibudilast, PDE inhibitor (Antiasthmatic)	Asthma	Neuropathic pain	Established
Imatinib, TKI (Anti-cancer)	ALL, CML	GIST	Established
Isoniazid, Antitubercular	Tuberculosis	Certain types of tumours	Established
Methotrexate, Antimetabolite (Anti-cancer)	Cancer	Rheumatoid arthritis, Psoriasis	Established
Miltefosine, Antileishma	Cancer	Leishmaniasis, Amoeba infection	Established
Mifepristone, Antiprogestin	Termination of pregnancy in combination with misoprostol	Cushing's syndrome	Established
Minoxidil, Vasodilator (Antihypertens)	Hypertension	Androgenic alopecia	Established
Orlistat, Anti-obesity agent	Obesity	Cancer	Established
Propranolol, β-Blocker	Hypertension	Migraine	Established
Retinoic acid	Acne	Acute leukaemia	Established
Ropinirole, Anti-Parkinsonian drug	PD	Restless leg syndrome	Established
Sildenafil, PDE inhibitor	Pulmonary arterial hypertension, Angina pectoris	Erectile dysfunction	Established
Simvastatin, Hypolipidemic	CVDs	Lung cancer	Established
Thalidomide, Immune modulator	Immunomodulation, Morning sickness (discontinued)	Leprosy, Multiple myeloma	Established
Topiramate	Fungal infections	IBD	Established
Valproic acid, Anti-epileptic	Epilepsy	migraine headache, Manic depression (bipolar disorder)	Established
Valsartan, ARB (Anti-hypertensive)	Heart attack, Hypertension	AD	Established
Zidovudine, Anti-viral	Cancer (clinical trial discontinued)	AIDS/HIV	Established

6. Examples of Repositioned Drugs[17-19]

Examples of some repositioned drugs from USFDA approved and investigational drugs are given in table 2.

7. Opportunities and Challenges

Medication repositioning speeds up drug development and lowers costs, in contrast to typical drug discovery programmes, which are lengthy, complex, and expensive to produce. Repositioning medications is another low-risk tactic. Drug repositioning performance has been greatly enhanced by computational or machine learning methods. Utilizing experimental methods (such as target protein-based screening, cell-based assay, testing in animal models, and clinical trials) that provide direct evidence-based understanding of linkages between medications and diseases is more dependable and believable than using computational methods. The term "mixed methods" refers to the modern practice of combining computational and experimental approaches to find new uses for established medications. In this procedure, clinical trials and biological experiments are used to validate the computer techniques. With greater access to databases and technical advancements, the mixed approach to repositioning provides a logical and thorough examination of all potential repositioning options. Additionally, compared to traditional drug discovery, drug repositioning requires less R&D effort. As a result, drug repositioning gives many pharmaceutical companies the chance to produce treatments with lesser investments.[20,21]

Opportunities for more quickly and efficiently developing repositioned pharmaceuticals are provided by the mixed approach of DR. Numerous illnesses need new medications to be treated in order to address prospective market demand and economic effects, according to the market. For instance, there is a sizable potential market to investigate for medications developed to treat uncommon or neglected diseases.

Therefore, there is a chance for drug repurposing to treat uncommon, untreated, orphan diseases or diseases that are challenging to cure. Over 6000 rare diseases go untreated because they are so rare. Five percent of them are being studied. There is a sizable market to be explored for rare diseases. Repurposing old drugs to treat both common and rare diseases is increasingly emerging as an appealing area of research due to the use of drug molecules with reduced risk of failure at shorter time and lower cost development, which is advantageous given the high attrition rates, significant costs, and slow pace of drug discovery and development.[22-26]

As a result, prospects for drug repositioning typically include a number of challenges. A significant obstacle to repositioning is finding a new therapeutic use for an existing medication. Drug repositioning, however, is a difficult process that takes into account a variety of elements, including technology, business strategies, patents, investment, and market needs. There are a number of difficulties, such as selecting the proper therapeutic area for the drug under study and problems with clinical trials, such as the need to conduct new trials from scratch if the results from clinical or preclinical trials for the original drug or drug product are stale or unsatisfactory.[27-28]

8. Promising Novel Uses in Drug Repositioning

Drug repositioning can be accomplished in a number of ways, including by using alternative delivery methods, combining two already-approved medications for a new indication, and improving or changing current formulations.[24] For example, research on the modified medicine carbamazepine ER (extended-release) has produced positive results, with 6 vs 36 of 48 individuals suffering from side effects after receiving Carbamazepine ER as opposed to the conventional IR (immediate-release).[29] Medication repositioning occasionally recovers financial losses from the initial unfavorable outcome of drug development and offers a significant return on investment. For instance, the once contentious Thalidomide, which was once developed as a sedative, is now mostly utilized in the treatment of certain cancers. Together with its Celgene-produced derivative Lenalidomide, it was effective in generating more than $2.8 billion in worldwide sales. Comparing this to conventional novel chemical entity (NCE)/new molecular entity (NME) medications revealed a higher return on investment.[24] The NCE/NME medications follow the conventional drug development process, in which newly discovered compounds go through clinical testing before receiving FDA clearance to treat illness. The potential for treating illnesses has been greatly expanded by the investigated innovative uses in medication repositioning, bringing the gap between therapy and disease one step closer to elimination. Additionally, it improves the standard of care, particularly for highly modified illnesses, newly discovered disease outbreaks, and extremely resistant and rare diseases.

9. Conclusions

Drug repositioning continues to retain great interest and potential for pharmaceutical corporations and academics in terms of fresh discoveries and giving out-dated medications a new lease of life, despite the downsides and stigmas. The discovery of drug compounds, especially by chance observations, has a long history in the dug repurposing. It has opened up a new path in recent years for the creation of novel therapeutics based on already-available/approved medications. With the identification of pharmacological compounds with unidentified therapeutic indications, strategic drug repositioning has sparked innovation. Drug repositioning strategies are becoming more and more popular since they significantly minimize R&D expenses, increase success rates, cut down on research time, and lower investment risk. The implementation of novel ways of repositioning strategy in the drug discovery programme for practically all human diseases is made possible by these advantages, which are advantageous to discovery scientists, drug researchers, consumers, and pharmaceutical corporations. By investigating novel disease/metabolic/signalling pathways, off-targets and target-specific mechanisms, genetic expression profiles for even genetic disorders, the medication repositioning technique has proven to be highly helpful in establishing the undiscovered mechanism of action of pharmaceuticals. For better drug repositioning, more indepth understanding is required to be executed with integrated approaches between computational and experimental methods to ensure high success rates of repositioned drugs. Drug repurposing can however, be used effectively in the discovery and development of new medications with fresh and potent therapeutic applications for human illnesses.

Conflicts of Interest

The authors declare no conflict of interest.

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