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Drug Repurposing: Expanding Therapeutic Potential of Existing Drugs

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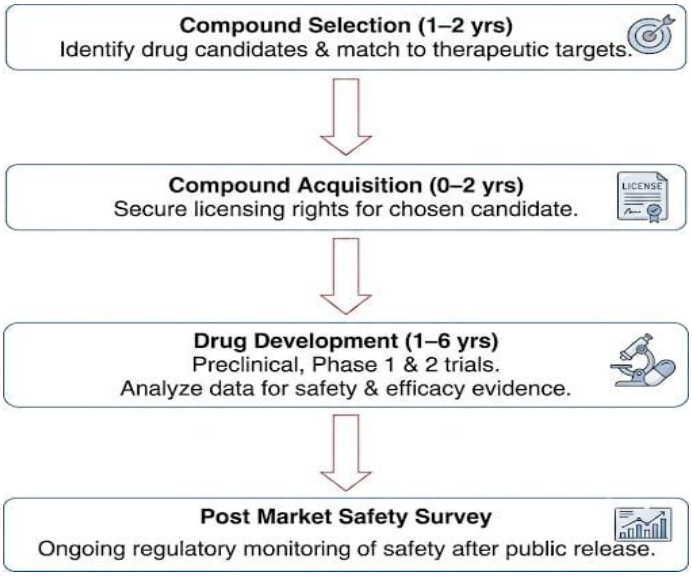
Abstract

Drug repositioning or drug repurposing is the process of finding new indications for existing drugs. More recently, the use of drugs already approved for other indications has become of great interest as an alternative to de novo drug discovery as it involves a shorter development time, lower development cost and reduced risk of development, while the drugs are already approved and have known safety and pharmacokinetic profiles. This review summarizes the origins, development and importance of drug repurposing, as well as its benefits over the traditional drug development process. The following drug repurposing strategies are introduced, such as the drug-centric, target-centric, disease-centric, experimental, computational and network pharmacology approaches. The contribution of pharmaceutical science to drug repurposing via formulation development, Pharmacological Evaluation, Medicinal Chemistry, and Biotechnology and Natural Products also is reviewed. In addition, the review highlights the current clinical uses of drug repositioning in the fields of oncology, cardiovascular diseases, neurological disorders, infectious diseases and metabolic disorders. Examples of successful drugs that have been repurposed include sildenafil, thalidomide, minoxidil, metformin and aspirin. The drug repurposing opportunities and challenges with regulatory considerations and patent issues are also explored. In conclusion, drug repurposing is a potentially valuable and low-cost approach to speeding up drug development, filling unmet medical demands, and enhancing therapeutic results.

1. Introduction

The process of finding an alternate therapeutic use for an existing drug or repositioning a drug that has been approved or studied for a different disease is called drug repurposing or drug

repositioning [1]. This strategy has been found to be an attractive alternative to the conventional drug discovery process because it involves the use of compounds that have a known pharmacokinetic, pharmacodynamic and safety profile, thus saving time, cost and risk in the development process [2]. The conventional drug discovery process is not only long and costly, but the attrition rates are high. The average time to develop a new drug is 10–15 years with costs of more than billions of dollars before becoming available in the market [3]. In addition, numerous drug candidates are not successful in the preclinical and clinical phases because they are not found to be effective enough or are deemed to be too toxic [4]. A possible way of addressing these challenges is drug repurposing where new indications are found for the currently available drugs, thereby avoiding some of the early stages in drug development [5, 6]. Many examples of drug repurposing for therapeutic applications have been successful and have demonstrated the importance of this approach in current drug design. Sildenafil was initially marketed as a drug for the treatment of angina pectoris but has since been approved for the treatment of erectile dysfunction and pulmonary arterial hypertension [7]. Likewise, an antihypertensive drug, minoxidil, was found to be effective against androgenetic alopecia. Thalidomide was previously discontinued because of its teratogenic effects, but has since been successfully used in the treatment of multiple myeloma and erythema nodosum leprosum [8,9]. The repurposing of drugs has become a hot topic in diverse therapeutic areas, including oncology, neurology, infectious diseases, cardiovascular disorders and rare diseases. The strategy offers an opportunity for quicker clinical translation, lower development expenses, and more accessibility of therapies for patients with unmet medical needs [10]. Moreover, the development of genomics, proteomics, molecular biology and systems pharmacology has enabled identification of new drug–disease relationships, thus further broadening the scope of repurposing [11,12]. This is reflected in the number of drugs that are being repurposed that enter into clinical use and drug research pipelines around the world. The strategy is not only useful to pharmaceutical companies for the extension of the life of existing drugs, but also has a great contribution to public health due to the speed of the effective drugs available [13,14].



Flowchart 1- Overview of the Drug Repurposing process

2. History and Evolution of Drug Repurposing

The practice of drug repurposing has a long history in drug research and the rationale that guides such work is mainly based on the discovery of unexpected pharmacological activities of an existing drug. Many drugs were found to have beneficial effects outside the scope of their initial indications by serendipity and observation before the formalization of the idea of drug repurposing. The findings showed that one drug could affect several targets and have the potential to cure diseases [15]. Chance was the primary motivation for drug repurposing in the past. A few of the earliest and most commonly referenced are sildenafil. The initial use of the drug was for the treatment of hypertension and angina pectoris. In clinical trials, however, its beneficial effects on erectile function were noted, and it has been approved to treat erectile dysfunction. This chance finding led to the development of sildenafil being one of the most commercially successful repurposed drugs and the importance of investigating alternative drug uses of existing medicines being demonstrated [16]. Thalidomide is one of the other notable examples. Thalidomide was first used in the late 1950s as a sedative and anti-emetic in pregnant women, but was later removed from the market because of its high teratogenicity. This was an unfortunate event but additional research found that it had immunomodulatory and anti-inflammatory effects. Consequently, thalidomide was also successfully repurposed for the treatment of erythema nodosum leprosum and multiple myeloma, showing that previously abandoned drugs may still have important therapeutic use if administered in the correct ways [17]. As the science of drugs progressed, drug repurposing became a more systematic and evidence-based approach than a simple accident. The knowledge gained from disease mechanisms, drug targets and pharmacological pathways were first applied to the discovery of new indications for existing drugs. The emerging molecular biology, genomics, proteomics and systems pharmacology tools have been useful in understanding drug–target interactions and disease pathogenesis and in identifying potential repurposing candidates [18]. The development of drug repurposing has also been further fueled by the availability of huge clinical data, EHRs and large-scale biomedical databases. These resources can help researchers to analyze existing drugs more efficiently and find potential therapeutic opportunities. As such, drug repurposing has emerged as a major part of the current drug development process, especially for rare and orphan diseases, cancer, neurological diseases, and infectious diseases in which the need for quick therapeutic developments is great [19,20].

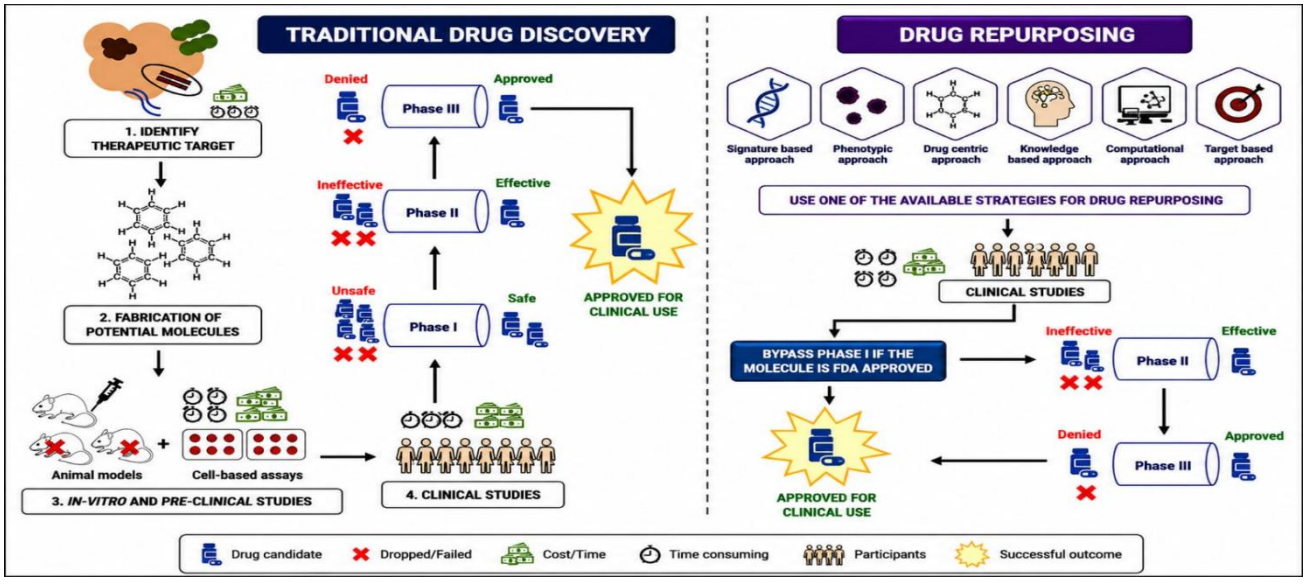


Fig.1 Comparison of Traditional Drug Discovery and Drug Repurposing

3. Need of Dug Repurposing

Repurposing can recognize new compounds as a result of a phenotypic advantage, rather than give a precise mechanism of action. This can be directly tested in preclinical animal models and this is more applicable to clinical applications and research. May advance straight to the Phase II clinical trials stage [21]. There is a minimum risk of failure with repurposed drugs [22]. Conventional drug discovery is a complex, lengthy and expensive process for the development of new drugs. It takes about 10-15 years and $1 billion on average to develop a new drug from the laboratory to market [23]. However, the safety effect of many drug candidates and their inadequate efficacy or unfavorable pharmacokinetic properties are major factors that cause failure during preclinical study phase or in clinical trials after significant investments [24]. One possible approach to circumvent these constraints is drug repurposing. The safety profile, dosage and pharmacokinetic properties of repurposed drugs are usually well described as they have already been extensively evaluated in both pharmacological and toxicological studies. This is much less time and resources than is needed to develop a new drug entity [25,26]. An increasing number of chronic and complex diseases, like cancer, cardiovascular disease, neurological disease, and infectious disease are also a major driver of drug repurposing [27]. Unfortunately, many of these diseases remain without good treatment and require novel therapeutic strategies. Drug repurposing provides a chance to discover new drugs based on old drugs and thus provide new drug treatment options and improve patient care [28].

Drug repurposing can be especially beneficial in the treatment of rare and orphan diseases. Pharmaceutical companies may not have the financial motivation to develop new drugs for these diseases because the number of patients involved are limited [29]. The use of repurposed drugs is an effective and affordable approach to meet the unmet medical needs in rare diseases [30]. In addition, the safety and toxicity of repurposed drugs are already known, and they are more likely to pass the screening process during clinical trials. This decreases chances of clinical failure at later stages and ensures quicker regulatory approval [31]. Accordingly, patients have access to effective treatment earlier, particularly in the event of an outbreak of a public health emergency or a fast-changing disease outbreak [32]. Besides the economic and clinical advantages, drug repurposing exploits the maximum therapeutic potential of drugs. A great number of approved medicines act on more than one biological target and pathway; they can be considered as strong candidates to seek new indications [33]. The potential of drug repurposing has also been expanded by the progress in biomedical research, which has greatly improved the capacity to discover such opportunities, making repurposing an essential element in today's pharmaceutical development [34,35].

4. Approaches and Strategies in Drug Repurposing

4.1 Drug- Centric Approach

One of the most popular strategies in drug repurposing is the drug-centric approach. This strategy involves a previously approved drug and investigating additional therapeutic uses, other than the approved indication. The rationale is that many drugs have multiple molecular targets and pathways, and this will provide opportunities for the application of these drugs in different disease states [36]. The drug-centric approach involves determining the pharmacological characteristics, mechanisms of action and safety of existing drugs or drugs in development. The characteristics are then studied to see if the drug can have a positive effect in diseases other than the one it was designed to treat. The pharmacokinetic and toxicological properties are well known, so the development process can be greatly hurried up [37].

The process of drug-centric repurposing frequently involves detection of secondary pharmacological effects, adverse events and clinical outcomes from routine clinical use of the drug. These observations could lead to the discovery of new therapeutic properties which can be explored in preclinical and clinical

studies. The method has led to several successful repurposing cases and is still an important means for finding new therapeutic opportunities [38]. The major benefit of the drug-based approach is the ability to shorten the time, cost and risk of traditional drug development. Researchers can bypass several early stage development processes, and move straight to efficacy evaluation for the new indication, by concentrating on drugs that have an established safety record. This approach is especially beneficial for diseases that are hard to treat or have a short lead time for effective treatment [39]. Although this drug-based strategy has its advantages, it can also be challenging. There are also many secondary pharmacological effects of a drug that may be beneficial, or at least not harmful, to its action as a therapeutic agent, but some of them are not. And, a drug that has been used in clinical practice a long time must undergo a significant amount of clinical validation before being approved as a drug for a new indication. Also, because of intellectual property considerations and a lack of commercial motivation, it may be difficult to develop repurposed therapies successfully [40].

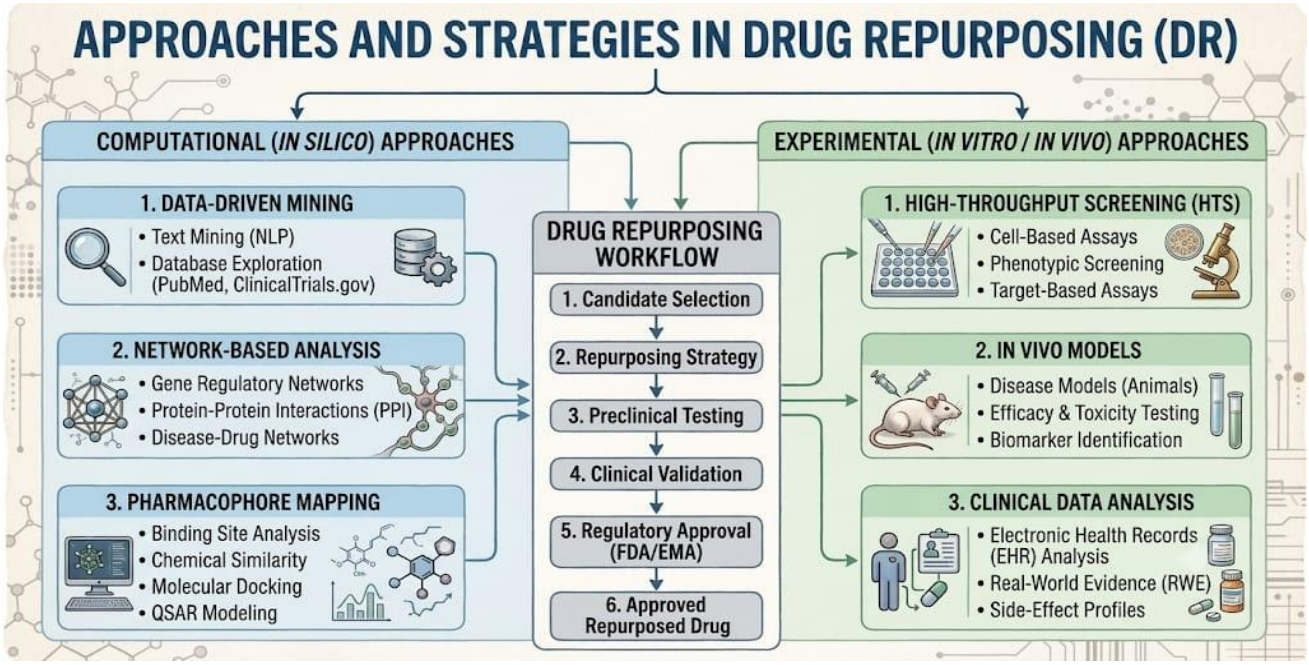


Fig.2 Approaches and Strategies in Drug Repurposing

4.2 Target-Centric Approach

A drug repurposing approach which targets particular biological targets to identify novel therapeutic indications. In this approach, a molecule known to target a specific disease is identified and current drugs that interact with that molecule are looked for to treat the disease. The basic idea behind it is that there are molecular pathways shared by many diseases and that a drug that is developed for one disease might have the same effect on another disease that is mediated by the target [41]. A detailed knowledge of the disease pathophysiology and molecular mechanism is essential for target-centric approach. A revolution in molecular biology, genomics, proteomics, and bioinformatics has helped to identify targets related to disease including enzymes, receptors, ion channels, and signaling proteins. When the target has been identified, then the existing drugs are screened to see if they react with the target and induce therapeutic effects [42].

The chief benefit of this approach is that it's scientifically based. The mechanism of action is directly related to a validated biological target,

which gives an accurate idea of the therapeutic outcome and decreases the uncertainty when developing a drug. In oncology, neurological diseases, cardiovascular diseases and inflammatory diseases, many molecular targets have been identified and such an approach has proven to be useful [43]. Target-centric repurposing can also help to speed up the development of treatments for rare diseases. A successful approach involves using existing drugs which have known interactions with their target, as it avoids the time-consuming process of discovering new compounds. Moreover, the molecular databases and the knowledge of the targets are improved, thus enhancing the efficiency of finding interesting candidates for repurposing [44]. But there is limitations to the approach. Numerous diseases are based on complex biological networks and modulation of a single target may not always lead to a substantial therapeutic effect. Furthermore, off-target effects may impact treatment efficacy and need to be investigated in preclinical and clinical studies [45].

4.3 Disease-Centric Approach

A disease-centric approach is a drug repurposing approach that aims at finding similarities between different diseases and using existing drugs to treat diseases that share similar pathological mechanisms. The disease-centric approach is unlike the drug-centric approach that takes a specific drug as a starting point, or the target-centric approach that takes a molecular target as its starting point; it begins with the disease and asks if drugs approved for one disease might be effective in another disease with similar biological characteristics [46]. The concept of this approach is based on the fact that many diseases share common molecular pathways, genetic factors, physiological abnormalities or clinical manifestations. If a disease has a similar pathogenic mechanism to another disease, then an effective drug can have therapeutic effects in another disease as well. New insights into disease biology and molecular medicine have greatly enhanced the identification of such links, and led to the discovery of new therapeutic applications of existing drugs [47]. The approach has worked well in certain diseases like oncology, neurology, immunology and infectious diseases. For instance, the medications used to treat autoimmune diseases have been studied in the context of inflammatory diseases due to common immune mediated mechanisms. In the same way, a few anticancer medicines have been used for rare diseases due to the commonality of cellular signaling pathways and genetic changes [48].

This method has the benefit of being able to apply the existing knowledge on the clinical course of disease and effectiveness of treatment. If there are commonalities between diseases, researchers can identify candidate drugs more quickly and efficiently and lessen the amount of screening that would otherwise need to be done in early stages of drug development. This can help to speed up therapeutic development and enhance treatment options for patients with unmet medical needs [49]. But there are difficulties in the disease focused approach as well. Diseases that look alike may be very different at the molecular level and this can impact on how well drugs work. Thus, comprehensive biological validation and clinical assessment are necessary prior to approval of a drug for a new indication. Additionally, there may be heterogeneous responses to therapy and patient-specific factors may affect therapeutic response and make repurposing difficult [50].

4.4 Experimental Approaches

Experimental methods are also important for drug repurposing as they give direct evidence on the therapeutic potential of a drug for a new indication. These methods include laboratory-based investigations to assess the biological activity, efficacy and toxicology of approved and/or investigational drugs in multiple disease models. Experimental drug repurposing has made a contribution

This is an important factor in the identification of new therapeutic applications and is a key element of the repurposing process [51]. High throughput screening (HTS) is one of the most common experimental techniques used. HTS is a technology that allows the screening of thousands of compounds to a biological target

or against a disease model. Drug libraries can be screened to discover specific compounds that have a therapeutic effect that has not been seen before. This has been a method for expediting discovery of repurposing candidates, and shortened the timeline for early phase drug development [52]. Another significant experimental approach is phenotypic screening that involves monitoring the change in the phenotype of cells or organisms after drug treatment. Phenotypic screening is conducted without the need for prior knowledge of the molecular target and can discover drugs that affect complex biological pathways. In the field of cancer, neurological diseases and infectious diseases, this approach has proven to be extremely helpful for identifying new therapeutic applications for current drugs [53]. Repurposed drugs are often tested in vitro by using the cultured cells, tissues or biochemical assays. These studies provide valuable information regarding drug efficacy, mechanism of action, cytotoxicity, and target interactions. For in vitro experiments, the results are often used as a basis for further in vivo studies [54]. In vivo studies are performed in animal models to evaluate pharmacological activity, safety, pharmacokinetics and therapeutic efficacy in physiological conditions after successful in vitro evaluation. Animal studies are important sources of information that guide repurposing of drugs that may be suitable for clinical trials and establish potential adverse effects before clinical trials are begun [55].

Experimental approaches also enable the identification of biomarker(s), validation of drug target(s), and the study of drug–disease interactions. These methods are very labor intensive and take a lot of time; however, they are essential for providing biological proof and cannot be replaced when determining the therapeutic potential of repurposed drugs. Experimental approaches thus remain a critical, if not crucial, means to turn repurposing hypotheses into clinically valuable therapies.

4.5 Computational Approaches

Computational techniques have proven to be effective tools in drug repurposing, as they can analyze vast biological, chemical and clinical data sets. These approaches involve the use of bioinformatics, cheminformatics, systems biology, and data-mining approaches towards the discovery of novel therapeutic targets of existing drugs. screening has been shown to be faster and less expensive than traditional experimental screening.

These approaches are not only cost-effective and time efficient, but they can also assess thousands of drug-disease associations at once [56]. A widely adopted computational approach is the database repurposing of drugs. Existing drugs, genes, proteins, diseases and clinical outcomes are analysed in publicly available databases, to look for novel associations between the different entities. The ability to combine several biomedical databases allows for the identification of attractive repurposing candidates and the generation of hypotheses for additional experimental validation [57]. The other significant method is gene expression profiling. This approach involves looking at the changes in gene expression profiles of a disease and those caused by drugs. Drugs that change or counteract disease-specific gene expression signatures could potentially be used to treat the disease. By using gene expression-based repurposing, a number of drug candidates have been identified for cancer, neurological diseases and inflammatory diseases [58].

In addition, computational drug repurposing is broadly used for molecular docking and virtual screening. Molecular docking is a predictive modeling approach that can be used to evaluate the binding affinity of a drug molecule to a biological target, thus enabling the prediction of potential therapeutic activity. Virtual screening can be used to rapidly screen large numbers of drugs against a specific target and thus speed up the process of identifying promising drugs for repurposing [59]. Further, omics technologies such as genomics, proteomics, metabolomics, transcriptomics, etc. have greatly contributed to drug repurposing studies. These technologies generate detailed understanding of disease mechanisms and drug effects, and identify new drug–target interactions and therapeutic possibilities. Modern applications of drug repurposing research have involved the

integration of omics data with computational analysis, which has increased the breadth of drugs that can be repurposed [60]. Although computational methods have many benefits, they are not without their drawbacks. Therapeutic applications need to be confirmed by predictions from computational analysis and experiments or clinical trials. Inaccuracies in prediction could also be caused by data quality, missing biological data, and methodological differences. However, computational tools remain essential to speeding up the drug repurposing process and to facilitate the creation of new therapeutic approaches.

4.6 Network Pharmacology Approach

Network pharmacology is a new way of drug repurposing, which combines pharmacology, systems biology, bioinformatics and network analysis to gain insight into the complex interactions among drugs, targets, pathways and diseases. In contrast to the one drug–one target approach, network pharmacology is a novel strategy that considers that numerous drugs possess multiple pharmacological targets and biological pathways. This whole picture approach has helped greatly in identifying novel therapeutic uses for existing drugs [61]. Network pharmacology is a method based on building and researching biological networks linking drugs, genes, proteins, signaling pathways and disease phenotypes. These interwoven networks can be used to find new drug–target relationships and new therapeutic avenues that cannot be seen through traditional approaches. These analyses can give valuable insights into the disease mechanism and aid in the identification of repurposable drugs [62]. Network pharmacology has the ability to solve the problems of complex and multifactorial disease, e.g., cancer, cardiovascular disease, neurodegenerative disease, and metabolic disorders. These diseases typically feature multiple molecular pathways, so network-based analyses can uncover drugs that can target multiple pathways, which in turn can lead to better therapeutic outcomes [63].

Network pharmacology can also be used for the discovery of drug combinations and synergistic effects. Analyzing drug/drug interactions and biological pathways can predict a combination of drugs and pathways that could yield better therapeutic results with less side effects. This can be very beneficial in oncology and in the management of infectious diseases, where combination therapy is often needed [64]. With the accumulation of more and more biological databases, protein–protein interaction networks, genomic data, and pathways information, the use of network pharmacology in drug repurposing has been rapidly developed. Advanced computational tools allow researchers to integrate a variety of sources of biological data, and produce comprehensive models that can help identify promising candidates for repurposing [65]. Although network pharmacology holds great promise, there are several issues and challenges in the field, such as data quality, network complexity, and the need for experimental validation. Future predictions from the network analysis need to be verified by laboratory and clinical studies before therapeutic applications can be set up. However, network pharmacology has emerged as a vital approach in contemporary drug repurposing and continues to play a crucial role in identifying novel therapeutic avenues.

5. Role of Pharmaceutical Sciences in Drug Repurposing

In the successful implementation of drug repurposing strategies, pharmaceutical sciences are playing an important role. Pharmaceutics, pharmacology, pharmaceutical chemistry, biotechnology, and pharmacognosy are the different disciplines involved in the identification, development and optimization of already existing drugs for new therapeutic applications [66]. The incorporation of these disciplines enables a full understanding of the drug action, safety, efficacy and formulation needs, which in turn increase the likelihood of the repurposing success [67]. The pharmaceutics field plays a significant role in drug repurposing in drug formulation development and optimization of drug delivery. For many of these drugs, their new uses necessitate changes to their dosage form, route of administration or delivery system in order to achieve the desired therapeutic effect. New

drug delivery technologies like nanoparticles, liposomes, and controlled-release drugs can increase the bioavailability of drugs, minimize toxicity, and increase adherence. Existing drugs can be optimized for their therapeutic effect in various disease settings (68,69). The understanding of pharmacology is important to the mechanisms of action of repurposed drugs. Detailed pharmacological studies allow to pinpoint other biological activities, side effects and pathways that can be utilized for new clinical applications. Understanding of pharmacodynamics and pharmacokinetics is crucial for assessing the effectiveness and safety of re-purposed drugs in various disease conditions and patient groups (70,71). Pharmaceutical chemistry aids the drug repurposing by studying the structure and physico-chemical characteristics of drug molecules. Structure–activity relationship (SAR) studies offer important clues into drug–target interactions and can be used to find compounds that may be useful for targeting new therapeutic targets. Existing drugs can also be chemically modified to achieve better therapeutic efficacy and selectivity and increased safety, making them promising to be used for other disease purposes (72). Biotechnology has become a key player in the field of drug repurposing in the current era. Recent progress in genomics, proteomics, transcriptomics and molecular biology has helped scientists to discover new disease pathways and therapeutic targets. These technologies allow new indications to be discovered for existing drugs, and aid in the development of personalized treatment approaches. Biotechnological tools also help in identifying biomarkers and in validating targets to enhance repurposing strategies (73,74). The research of natural products and their pharmacological activities is important to the field of Pharmacognosy, which is in turn very important to drug repurposing. Numerous compounds from plants have several biological activities, and can have potential for repurposing in several therapeutic areas. For instance, investigation of traditional medicinal agents and natural compounds has resulted in the discovery of a number of compounds with applications other than their traditional purposes [75]. In summary, the pharmaceutical sciences offer a scientific platform for drug repurposing activities including drug discovery, drug formulation, mechanistic studies, and clinical translation. Together, these disciplines have improved the efficacy and effectiveness of repurposing efforts and clearly shortened the time to effective therapies for patients who do not have an effective therapy available [76,77].

6. Clinical Applications of Drug Repurposing

6.1 Drug Repurposing in Cancer

Despite development of various effective and cheap therapeutic methods, cancer is still one of the most significant disease causes for morbidity and mortality in the world. High costs, long development timelines, and high failure rates at clinical trial stage are common challenges for conventional drug development for cancer [78]. Given that drugs already approved for other indications have safety profiles and pharmacologic data, drug repurposing is an attractive strategy in the area of oncology as it will help to expedite the clinical translation of a drug and will help to decrease its development costs [79]. Several non-oncology drugs have already shown that they have strong anticancer activity by different mechanisms; such as by inhibiting cell proliferation, inducing cell death, altering immune responses and disrupting signaling pathways involved in tumors [80]. For instance, thalidomide is a sedative which was successfully used to treat multiple myeloma because of its anti-angiogenic and immunomodulatory properties. Likewise, the antidiabetic drug metformin has demonstrated anti-cancer properties in the regulation of cellular metabolism and the inhibition of tumor growth in various cancers [81]. Drug repurposing has also helped to identify new therapeutic targets for hard-to-treat cancers. Current drugs can be screened alone or in combination with regular chemotherapy, in order to improve the effectiveness of treatment and overcome drug resistance. Moreover, re-used drugs might offer cost-effective treatment

options, especially in low- and middle-income countries where access to newly developed anticancer drugs may be restricted [82].

Cancer drug repurposing has been further fueled by recent developments in molecular biology, genomics and precision medicine [83]. Researchers can systematically assess drugs already in use for other diseases and in other forms of cancer for their anticancer properties, as pathways shared by different diseases are identified. These are becoming increasingly important in modern oncology and many repurposed drugs are now in clinical trials [84]. However, there are obstacles to widespread use of repurposed drugs in cancer therapeutics that include regulatory hurdles, IP protections, and the need for strong clinical data to support their use. However, drug repurposing remains as an excellent opportunity for adding to the arsenal of drugs available for cancer treatment and enhancing patient situation [85].

6.2 Drug repurposing in cardiovascular and lymphatic diseases.

Cardiovascular diseases (CVDs) are the top killers in the world and these include hypertension, heart failure, coronary artery disease, myocardial infarction and stroke [86]. Although remarkable progress has been made in the treatment of cardiovascular disease, substantial numbers of patients still suffer from suboptimal clinical outcomes, with the need for new therapeutic approaches. Drug repurposing has proven to be a useful strategy for the discovery of new cardiovascular therapeutics that are already known to be safe and have known PK profiles [87]. A number of drugs have been developed for non-cardiovascular uses that have been shown to have beneficial effects on cardiovascular disorders. Sodium–glucose cotransporter-2 (SGLT2) inhibitors are, for example, originally used to treat type 2 diabetes and have been demonstrated to have important cardiovascular advantages, such as decreased hospitalization for heart failure and cardiovascular mortality [88]. These results have broadened their therapeutic application, and now a large number of heart failure patients are being treated with them beyond the control of glycemic status [89].

Likewise, inflammatory drugs are interesting in cardiovascular medicine because inflammation is one important element of atherosclerosis and the progression of cardiovascular disease is well recognized. Repurposing drugs that have been developed to inhibit inflammatory pathways might offer further cardiovascular benefit and benefit long-term outcomes in high-risk individuals [90]. Drug repurposing has also been helpful in identifying drugs that could be used for treating cardiovascular diseases as they have beneficial effects on vascular function, oxidative stress, and metabolic abnormalities. Technological progress in cardiovascular research and molecular biology has allowed for the discovery of common pathways between cardiovascular and non-cardiovascular diseases and has increased the possibility of reusing existing drugs [91].

Drug repurposing in cardiovascular drug development has the following benefits: Lower drug development costs, faster time to market, higher chance of clinical success than de novo drug discovery. In addition, a wealth of safety information allows quicker clinical assessment and regulatory approval of new indications. Given the rising number of cardiovascular diseases and the need for successful therapeutic options worldwide, these benefits are of great significance [92]. Drug repurposing is a promising approach for cardiovascular drug discovery. Researchers can speed up the process of developing new applications for current drugs, reduce the time and expense of conventional drug discovery and development and help to enhance patient outcome

6.3 Drug Repurposing in Neurological Disorders

Neurological diseases are one of the most difficult diseases in medicine, because of their progressive course, pathophysiology and few options for treatment. Diseases like Alzheimer's disease, Parkinson's disease, epilepsy, multiple sclerosis and amyotrophic lateral sclerosis remain a huge burden on the patient and health care system around the world [93]. In recent years, the novel drug development for

neurological disorders has failed to achieve success, prompting new focus on drug repurposing as a method to find effective treatments utilizing drugs that already are available [94]. In the field of neurodegenerative disorders, drug repurposing has proven to be a very promising approach. A number of drugs have been developed for non-neurological conditions that have been shown to have neuroprotective, anti-inflammatory and antioxidant properties that may prove useful in neurological disorders. As an instance, glucagon-like peptide-1 (GLP-1) receptor agonists that initially were used to treat diabetes have demonstrated potential for the treatment of Alzheimer's and Parkinson's diseases [95] with the improvement of cognitive function and the reduction of neurodegeneration. Inflammatory and oxidative processes are pivotal in many neurological diseases. Therefore, anti-inflammatory drugs have been studied for their potential to slow the disease, and for their ability to improve clinical outcomes. Dual targeting of inflammatory pathways could provide new therapeutic approaches to neurodegenerative and autoimmune neurological diseases [96].

Also, existing drugs have been used for other diseases, such as epilepsy and multiple sclerosis, where they have shown beneficial effects on those diseases for which they were not originally developed. The identification of shared biological pathways of neurological disorders has been made possible by the progress in molecular neuroscience, thus opening new possibilities for the use of approved drugs [97]. Safety information from approved drugs can greatly speed up clinical evaluation in neurological diseases, which is lengthy and costly to develop drugs. In addition, repurposing may have the advantage of decreasing the cost of identifying completely new therapeutic targets and, importantly, give patients quicker access to treatments that work [98]. However, there are challenges because of the complexity of the central nervous system, insufficient penetration of some drugs into the CNS, and the requirement of extensive clinical trials to establish efficacy. However, drug repurposing remains a valuable approach to the identification of new indications for existing drugs in neurological diseases and to the enhancement of therapeutic effects in patients [99].

6.4 Drug Repurposing in Infectious Diseases

There are still new pathogens emerging, antimicrobial resistance spreading and some infections have no good therapy with infectious diseases being major health issues and challenges globally [100]. The process of drug discovery and drug development of novel drugs to treat infectious diseases often takes time and financial resources, hence drug repurposing is an attractive option for finding therapeutic agents quickly. Repurposed drugs have very well-established safety and pharmacokinetic profiles, so they can be evaluated more quickly than newly discovered drugs [101]. The theme of drug repurposing has been heavily investigated when it comes to viral infections. In recent outbreaks of infectious diseases, several drugs were tested for their possible antiviral activity, as their mechanism of action was known and clinical experience indicated possible activity. Pre-existing safety information allowed for expedient initiation of clinical research and highlighted the benefit of repurposing in a public health emergency [102]. With the emergence of antimicrobial resistance, there is a need for more antibacterial drug repurposing. A number of non-antibiotic drugs have been explored to help make antibiotics more effective, block bacterial virulence or disrupt bacterial survival pathways. These methods could be used to overcome resistance and increase the success of treatment in hard-to-eradicate bacterial infections [103].

Besides viral and bacterial infections, there is a possibility of drug repurposing in parasitic and fungal infections. There are several approved drugs that have shown unsuspected anti-parasitic or anti-fungal activity, which opens up possibilities to develop inexpensive drugs for NTDs. This is especially beneficial in resource poor areas where access to the new medicines could be limited [104]. Promising advances in molecular biology, genomics and pathogen

characterization have also taken infectious disease drug repurposing a step further. Better understanding of host–pathogen interactions has led to the discovery of drugs that target important pathways in the process of infection and disease. These advances have broadened the number of candidates that may be feasible to repurpose and boost the chances of discovering treatments that might be effective [105]. Even though there are benefits to drug repurposing in infectious diseases, there are still several difficulties including differences in clinical effectiveness, possible drug resistance, and thorough clinical validation. However, it is also a useful tool to promote the development of therapeutic products and to meet the urgent needs of global health, especially in the case of emerging infectious diseases outbreaks [106].

6.5 Drug Repurposing in Metabolic Disorders

Type 2 diabetes mellitus, obesity, dyslipidaemia, metabolic syndrome and non-alcoholic fatty liver disease (NAFLD) are all major health problems worldwide. This coupled with the risks for cardiovascular disease, kidney disease and other chronic complications [107]. While there are several therapeutic options available, the increasing prevalence of metabolic disorders has led to a need for better, more affordable therapies. A new direction for identifying new therapeutic uses for old drugs has been developed, called drug repurposing, for metabolic diseases [108]. The best examples of drug repurposing in metabolic disorders are the expanded uses of antidiabetic drugs outside of glucose control. Some drugs used in diabetes have shown to have a positive effect on body weight, cardiovascular health and renal function. The results have expanded their use in the clinic and its effectiveness in patients with multiple metabolic comorbidities [109]. The repurposing of drugs has also been an option when it comes to obesity management. Some drugs used in other fields have been found to be effective in appetite control, in energy expenditure, and in the metabolism of weight gain. These strategies could offer alternative treatment options for those who are not improving sufficiently with lifestyle changes [110].

Current anti-dyslipidemia drugs have been studied to ultimately improve lipid metabolism, decrease inflammation and increase insulin sensitivity for use in the dyslipidaemia and metabolic syndrome arena. Many metabolic abnormalities have overlapping biological pathways, so that drugs used for one metabolic disorder may be beneficial in other disorders, thus justifying repurposing approaches [111]. One of the most prevalent liver diseases globally, NAFL (non-alcoholic fatty liver) is a key area of drug repurposing. Multiple drugs have been studied and approved that show efficacy at decreasing the levels of fat accumulation, inflammation and fibrosis in the liver. This is especially relevant as there are few FDA approved medications that are effective for NAFLD or its more advanced stages [112]. Despite progress there are issues around the selection of optimal candidates, long-term safety and efficacy in large scale clinical trials. However, drug repurposing remains a useful tool to speed up the therapeutic development process in metabolic diseases and to tackle important unmet medical needs [113].

7. Examples of Repurposed Drugs

7.1 Sildenafil: From Angina to Erectile Dysfunction

In the history of pharmaceuticals, there are no more successful drug repurposing examples than sildenafil. It was first used by researchers to treat angina pectoris and other cardiovascular disorders [114]. It works by blocking phosphodiesterase type 5 (PDE5) which leads to an increase in cyclic guanosine monophosphate (cGMP), causing smooth muscle relaxation and vasodilation. In patients with angina, sildenafil was not highly effective as a treatment for anginal chest pain, but researchers noted another side effect in men—better penile erections. This finding prompted additional research on the drug as an ED therapy [115]. Later clinical trials have shown that sildenafil has a definite beneficial effect on erectile function in men suffering from ED

caused by different causes such as vascular, psychological and mixed causes. During sexual stimulation, this drug increases blood flow to the penile tissues, helping to become and stay erect [116.]. Due to its efficacy and good safety profile, sildenafil was approved by the regulatory authorities in 1998 to treat erectile dysfunction, and was launched under the brand name Viagra. The introduction transformed the management of erectile dysfunction and offered an easy-to-use oral therapy option for millions of patients worldwide [117].

The success of sildenafil has made it clear how critical it is to be aware of unexpected clinical observations during drug development. At first a disappointment in the field of cardiovascular treatment, this drug proved to be the most commercially successful pharmaceutical product of all time. The sildenafil experience has been used often as a paragon of serendipitous drug repurposing and has stimulated the search for new uses of the same drugs [118]. Sildenafil was subsequently found to have more uses than erectile dysfunction. The vasodilatory properties of sildenafil also led to its use to treat patients with pulmonary arterial hypertension; an example of how a single drug can be used successfully in multiple clinical applications. The greater utility has underscored the potential for existing drugs to be used in new ways to gain the greatest possible therapeutic benefit. The shift from anti-anginal to erectile dysfunction and pulmonary hypertension (PDH) use of sildenafil is remarkable in drug repurposing. This success shows the value of being careful not to overlook unexpected outcomes when assessing treatments, and how important it is to discovering new therapeutic options and having a meaningful effect on the lives of patients all over the world.

7.2 Thalidomide: Sedative to Multiple Myeloma Therapy

Another iconic example of drug repurposing is thalidomide. It was developed in the late 1950s as a sedative and anti-nausea agent to be used for treating morning sickness in pregnant women. The drug, however, was withdrawn from the market due to the association with serious congenital birth defects and became one of the largest drug safety failures in history [120,121]. Although this drug was historically known for its terrible side effects, later studies demonstrated that thalidomide also has immunomodulatory, anti-inflammatory and anti-angiogenic properties. It was discovered to be useful in the treatment of erythema nodosum leprosum (ENL), a very inflammatory condition of leprosy in the 1960s. It was with this discovery that it became a therapeutic agent again [122].

Additional studies revealed that thalidomide was able to block the growth of blood vessels that are essential to the progression of tumors, as well as to regulate immune responses that play a role in the development of tumors [123]. The properties sparked interest in using it in hematological malignancies such as multiple myeloma. Thalidomide was found to have therapeutic efficacy in patients with refractory multiple myeloma in clinical studies and was subsequently approved for this use [124]. The success of thalidomide repurposing also underpinned the development of newer drugs in the field of immunomodulation like lenalidomide and pomalidomide with better efficacy and safety profiles. These agents are playing an increasing role in current and future treatment for multiple myeloma and have also contributed to the increasing therapeutic effects of the discovery of thalidomide [125]. Thalidomide serves as an example of the fact that the action of a drug that was once considered to be unsafe can be successfully repurposed if the pharmacological properties of the drug are better understood and appropriate risk-management strategies are adopted. Thalidomide is still an important therapeutic agent for certain diseases today, but is available only under strict regulatory controls and monitoring programs [126].

7.3 Minoxidil: Antihypertensive to Hair Growth Promoter.

A successful drug repurposing is Minoxidil. Originally developed as an oral antihypertensive drug for the treatment of severe and resistant hypertension [127]. Drug causes strong Vasodilation by opening ATP-sensitive Potassium Channels in VSM which causes relaxation of blood vessels and lowers the blood pressure. An unusual side effect was frequently observed during the clinical use: excessive hair growth (hypertrichosis) [128]. When the growth of hair was seen unexpectedly, researchers looked into the idea of using minoxidil for the treatment of hair loss disorders. Later research showed that minoxidil applied to the scalp could increase hair activity, extend the anagen stage of the hair growth cycle and regenerate hair in men with androgenetic alopecia. The results of these investigations resulted in the formulation of topical minoxidil products for the treatment of hair loss [129]. Topical minoxidil was effective in both male and female pattern hair loss, and this was proved in clinical trials. It was demonstrated to have a beneficial effect on hair density, thickness of the hair, and to slow the progress of alopecia [130]. Minoxidil has been approved by the FDA to treat androgenetic alopecia and is one of the most commonly used treatments for hair loss in the world, because of its favorable safety profile and effectiveness [131]. How minoxidil works to grow hair is not quite certain. There are some suggested mechanisms, however: increase in blood flow to hair follicles, stimulation of proliferation of follicular cells, increase of vascular endothelial growth factor (VEGF) expression, and extending the hair growth cycle. All of these actions together help hair follicles to function better and regenerate hair growth [132].

7.4 Metformin: Beyond Diabetes

One of the most commonly used drugs to treat type 2 diabetes mellitus is metformin [133]. Metformin was first used as an antihyperglycemic drug and has a main effect of decreasing glucose production in the liver and enhancing insulin sensitivity. However, its therapeutic potential has been demonstrated over the years to be much greater than its blood sugar-lowering ability, and it has been a successful case of drug repurposing [134]. Metformin has been shown to have anti-inflammatory, anti-oxidant and metabolic regulatory effects that have been found to be useful in various diseases. One of the most extensively investigated areas is oncology. Several epidemiological studies have indicated a decreased risk of some cancers, and better treatment responses among diabetics on metformin treatment. These observations have prompted a great deal of interest in the use of metformin as an adjunct anticancer drug [135]. Metformin has also been found to be helpful in the treatment of polycystic ovary syndrome (PCOS), an endocrine disorder among women that is associated with insulin resistance, irregular periods and infertility. Metformin restores ovulatory function and enhances the reproductive function of affected women by increasing insulin sensitivity and decreasing hyperinsulinemia. It has, therefore, become an important treatment modality to manage PCOS [136].

Moreover, the use of metformin in healthy ageing and age-related diseases has been highlighted. Experimental and clinical studies indicate that the drug is able to affect aging-related pathways in cells such as the activation of AMP-activated protein kinase (AMPK) and the metabolism of mitochondria (energy producing units of the cell). These effects have spurred efforts to study the effects of metformin as a potential health span-prolonging and age-related disease-preventing drug [137]. Further evidence is emerging of the potential for metformin to benefit neurological disorders, cardiovascular diseases and metabolic-associated liver diseases. While many of the applications are still under investigation, the wide array of biological effects of metformin underscores its potential to be a therapeutic agent for other applications. [138]

7.5 Aspirin: Expanding Therapeutic Application

One of the oldest and most popular medicine drugs is aspirin. It was also first used as an analgesic, anti-pyretic and anti-inflammatory drug to treat pain, fever and inflammatory diseases [139]. Its effect is mainly due to irreversible COX enzyme inhibition, thus

reducing the production of prostaglandins and thromboxanes [140]. As years went by, it was found that aspirin has important antiplatelet activity. Aspirin interferes with platelet aggregation, suppressing the production of thromboxane A_2, at low doses and thus decreases the risk of developing a thrombus. As a result of this observation, it became a therapy for the prevention and management of cardiovascular diseases such as myocardial infarction, ischemic stroke and others with the mechanism of thrombosis. Low-dose aspirin is still an integral part of cardiovascular risk management in certain groups of patients today [141].

Aspirin has been studied a great deal for its cancer-preventing properties as well as its cardiovascular uses. Studies of aspirin's epidemiology and clinical effects have indicated that the use of aspirin in the long-term may lower the risk of certain cancers, including colorectal cancer. Mechanisms proposed are anti-inflammatory, cell proliferation modulation, and pathway inhibition. The results have led to a great deal of interest in the use of aspirin as a chemo preventive agent [142]. Aspirin also has been studied in a variety of other indications such as pregnancy-related complications, neurodegenerative diseases and inflammatory disorders. Numerous new therapeutic opportunities for the use of aspirin have been opened up by its broad biological activity even though its use in several applications is still under investigation. With its long history of clinical use and well characterized safety profile it is an interesting drug for repurposing research [143]. The history of aspirin's multiple therapeutic uses illustrates the change over time of a traditional medicine to a new therapeutic use. Aspirin, from its use as a pain killer, to its use in cardiovascular protection and prevention of cancer, is an example of how repurposed drugs are able to get the most out of the therapeutic utility of existing drugs. As it is still relevant today in modern medicine, it is important to investigate new indications for existing drugs [144].

DRUG	ORIGINAL INDICATION	REPURPOSED INDICATION
Sildenafil	Angina	Erectile disfunction, Pulmonary hypertension
Thalidomide	Sedative	Multiple myeloma, Leprosy complications
Minoxidil	Hypertension	Hair loss Treatment
Metformin	Type 2 Diabetes	PCOS, Cancer research
Aspirin	Pain and Fever	Prevention of heart attack and stroke
Dapagliflozin	Type 2 Diabetes	Heart failure
Empagliflozin	Type 2 Diabetes	Heart failure, Kidney failure

Table 1- Successful examples of Drug Repurposing

8. Regulatory and Patent Considerations

Factors other than scientific discoveries are also crucial for the successful implementation of drug repurposing, such as regulatory approval and intellectual property matters [145]. Repurposed drugs have several benefits over new drugs, such as speed of development and cost savings, but a variety of regulatory and patent issues can affect how well they can be commercialized and adopted in the clinic [146]. Pathways have been put in place by regulatory agencies like the U.S. Food and Drug Administration and the European Medicines

Agency which allow for the approval of repurposed drugs. These drugs frequently have extensive preclinical and clinical safety data and developers can often take this information instead of having to run as many studies as for a completely new drug entity. This can make a huge impact on the development costs and speed up patient access to therapies [147]. All these benefits come with the caveat of appropriate demonstration of safety and effectiveness in the target disease for regulatory approval of a new indication. Clinical trials will continue to be crucial in proving therapeutic effectiveness, establishing the recommended dose, and discovering any adverse effects for the new indication. Thus, the regulatory aspects still remain one of the major parts of the drug repurposing process [148].

Another important consideration is patent protection. Most of the repurposed drugs are off-patent, which means that their patent life has expired. This means that access and affordability are enhanced, but at the same time the commercial motivation to undertake expensive clinical trials to secure new indications is diminished. To combat this, the developers may pursue patents for new indications, formulations, dosage regimens, and/or new modes of administration [149]. Some countries have also implemented market exclusivity schemes and incentives for orphan drugs to incentivize investments in drug repurposing, especially for rare diseases. Such regulatory measures can offer temporary marketing advantages and other benefits that can compensate for the cost of developing a new product from a repurposed drug [150] and encourage innovation in this area. Drug repurposing is likely to grow as regulatory and patent issues are significant constraints but improvements in the regulatory and patent landscape, as well as increased public-private partnerships, are likely to have an impact. Promoting innovation and ensuring patient access and safety from effective therapies requires a balanced regulatory environment [151].

9. Opportunities and Challenges in Drug Repurposing

Opponents of drugs' use in new indications have identified a number of benefits that make drug repurposing an appealing approach to pharmaceutical research, when compared with conventional drug discovery. Since many drugs already exist, identification of new therapeutic uses can save the time, cost and risk of drug development [152]. Some of the safety data that is required for drug development is readily available because repurposed drugs have already been broadly studied for their pharmacological, toxicological and clinical properties. This can allow for quicker clinical testing and regulatory approval than can be achieved with newly discovered compounds [153]. The biggest advantage of drug repurposing is to address unmet medical needs. A large group of diseases, such as rare diseases, neurodegenerative diseases, infectious diseases and some cancers, remain without adequate treatment [154]. The use of old drugs is a useful and economical strategy to develop new drugs for these diseases. In addition, significant improvements in the capacity to identify promising repurposing candidates and discover novel drug–disease relationships, through genomics, proteomics, bioinformatics and systems biology, have enhanced the capacity to identify new drug–disease connections [155].

Drug repurposing is also of great importance in times of public health emergency and disease outbreaks. Since approved drugs have well-established safety characteristics, they can be quickly assessed for new diseases to help provide therapeutic interventions in a timely fashion. This benefit has spurred efforts around the world to utilize repurposing as a key component of emergency preparedness and response [156]. While drug repurposing has many advantages, there are some challenges. The lack of commercial interest in many repurposed drugs, including some that are no longer subject to patent protection, is one of the main challenges. Pharma may not be willing to invest in the expensive and lengthy clinical trials if there is uncertainty on market exclusivity or returns on investment are not high. This can be a problem to get promising

repurposing candidates into approved therapies [157]. Regulatory and scientific complexities are also a challenge. Safety data may be available but efficacy data to support the new indication will need to be obtained from detailed clinical studies. Also complicating the development efforts may be differences in dosage requirements, length of treatment, patients treated, and the various mechanisms of disease. Further, many potentially interesting repurposing candidates do not have clinical efficacy in large-scale trials [158].

10. Future Perspective

In the modern era, the use of drug re-purposing in the drug development process is anticipated to be more and more significant. With the increasing number of biological databases, clinical records, genomic information, and sophisticated computational tools available, it has become easier to identify potential repurposing candidates. The advances are helping researchers to identify new uses for many current medicines quicker than ever before. The collaboration of various disciplines such as pharmacology, biotechnology, medicinal chemistry, and clinical research will be valuable for future drug repurposing studies. Better understanding of the mechanisms of disease and drug–target interactions will aid in the discovery of treatments for complex and rare diseases. Furthermore, concerted efforts among academic institutions, health care providers, regulators and pharmaceutical firms will facilitate the development and approval of repurposed drugs.

Drug repurposing could be further improved by the use of personalized medicine, which would enable treatments to be adapted to individuals' genetic and molecular differences. This approach may have therapeutic benefits and minimize side effects. In addition, ongoing improvements in precision medicine and biomarker studies can aid in selecting patient populations with the greatest potential to gain benefit from repurposed treatments. While regulation, IP and clinical validation issues are still present, continued scientific and technological advances will surely further bolster the position of drug repurposing in health care. For this reason, drug repurposing is expected to continue to be a key approach for enhancing treatment options and meeting unmet medical needs in the future.

11. Conclusion

Drug repurposing can be a promising approach to finding new therapeutic uses for existing drugs. It has a number of benefits compared to traditional drug development, such as reduced costs, quicker development time, and safer drug profiles. Several re-purposing strategies have led to effective treatments in cancer, cardiovascular, neurological, infectious and metabolic disorders. Thanks to its ability to speed up the drug development process and increase treatment choices, drug repurposing continues to serve as a valuable tool in drug development despite the challenges it poses for regulatory agencies and businesses. In general, it's a potentially valuable method of enhancing health care systems and advancing pharmaceutical research.

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