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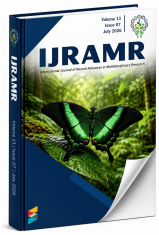

REVIEW ARTICLE

DRUG REPURPOSING: MECHANISMS, CASE STUDIES, AND CHALLENGES

Darshan Chavan[1], Sachin Baviskar[1], Harsha Marathe[1], Manoj S. Mahajan[2*], Aman B. Upaganlawar[3] and Chandrashekhar D. Upasani[4]

[1]Research Scholar, Department of Pharmacology, SNJB's Shriman Sureshdada Jain College of Pharmacy, Neminagar, Chandwad, Nashik, India; [2]Associate Professor, Department of Pharmacology, SNJB's Shriman Sureshdada Jain College of Pharmacy, Neminagar, Chandwad, Nashik, India; [3]Professor and Head, Department of Pharmacology, SNJB's Shriman Sureshdada Jain College of Pharmacy, Neminagar, Chandwad, Nashik, India; [4]Professor and Principal, Department of Pharmacology, SNJB's Shriman Sureshdada Jain College of Pharmacy, Neminagar, Chandwad, Nashik, India

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Corresponding author:
Darshan Chavan

ABSTRACT

Drug repurposing, also known as drug repositioning or reprofiling, has emerged as a highly transformative strategy in modern pharmaceutical research, providing an efficient and economical alternative to traditional de novo drug discovery processes. Traditional drug development pipelines require 10 to 15 years and financial investments exceeding two billion dollars, while repurposingmakesefficient use of pre-existing clinical safety, pharmacokinetic, and toxicological profiles. This strategy significantly compresses development timelines to 5 to 7 years and drastically cuts down research expenses. This comprehensive review examines the major core methodologies driving the field and categorizing them systematically into ligand-based drug-oriented, structure-based target-oriented, and network-driven disease-oriented approaches. It details how recent advancements in computational biology, artificial intelligence, high-throughput phenotypic screening, molecular docking, and multi-omics data analytics have collectively accelerated the precise identification of novel drug-disease correspondences. The paper provides an in-depth analysis of landmark historical case studies, including Sildenafil, Aspirin, Thalidomide, and Metformin, showing their successful clinical translation in different therapeutic areas, including oncology, psychiatry, immunology, and emerging infectious diseases like COVID-19.Despite many clinical advantages, widespread adoption faces critical bottlenecks. These include the inherent biological complexity of heterogeneous diseases, limited intellectual property protections for generic or off-patent medications, complex regulatory frameworks, and data integration limits. This review balances these major advantages against remaining structural challenges, highlighting that robust interdisciplinary collaboration between academia, pharmaceutical industries, public health bodies, and international regulatory agencies is absolutely imperative to systematically unlock the full therapeutic potential of existing chemical libraries and expand global healthcare resources. Drug repurposing stands as acrucial tool for fast-tracking therapeutic solutions and addressing global health inequities.

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INTRODUCTION

Drug repurposing, also called as drug repositioning, is a most important strategy in modern pharmaceutical research that involves identifying new therapeutic and curable uses for already approved or existing drugs.

This approach has gained considerable attention because it offers several advantages over traditional drug discovery. The development of a new drug usually requires many years of research, high financial investment, and extensive clinical trials to establish safety and efficacy.

In contrast, repurposed drugs possess well-established pharmacokinetic characteristics, safety profiles, and toxicity data, which significantly reduce the time, cost, and risk related to the drug development process. Drug repurposing has indicated appreciable success in many therapeutic areas such as cancer, cardiovascular diseases, infectious diseases, neurological disorders, and metabolic disorders. Various drugs that were originally implemented for one disease have subsequently shown advantageous effects in the treatment of other conditions(1). For example, the drug Sildenafil was originally examined for angina but was later certified for erectile dysfunction and pulmonary arterial hypertension. Similarly, Thalidomide, once withdrawn due to safety concerns, has been successfully repurposed for the treatment of multiple myeloma and other inflammatory diseases. These examples verified how existing drugs can provide new therapeutic opportunities (2). The latest advances in genomics, proteomics, bioinformatics, and computational biology have further accelerated the process of drug repurposing. Network pharmacology, molecular docking, and data-driven analysis are examples of modern methods that make it easier for researchers to determine possible drug-disease correspondence. Scientists may now examine biological pathways, illness causes, and curative targets thanks to these technologies, increasing the likelihood of finding new symptoms for presently available medications (3).

Drug repurposing is also especially invaluable in addressing rare diseases and developing health threats where rapid treatment options are instantly needed. Repurposed medications offer an effective plan to create exclusive treatments and increase patient results since they can enter clinical trials more rapidly. A useful, economical, and inventive approach to drug research is complete drug repurposing. This approach substantially enlarged treatment options and improved global healthcare by increasing the therapeutic potential of currently available medications (4).Drug repurposing, also called as drug reprofiling, is a creative approach aimed at finding new therapeutic uses for existing drugs. This set-up has emerged as an important alternative to old drug discovery processes, which are mainly time-consuming, costly and which has high rate of failure (5). Drug repurposing allows existing drug authorized researchers to capitalize on familiar pharmacological and safety profiles of these substances, remarkably quickening the development process and lowering related expenses. The process of drug repurposing focuses on identifying new applications for drugs that are already approved or detached, rejected or experimental.

This approach attaches the potential of drugs to act on diverse targets or shared disease pathways, thereby opening up the chance to address complex and emerging diseases. In recent years, the use of reprofiling Drugs potentially quickened, resulting in treating conditions such as Alzheimer's disease with repurposed drugs potentially expedited the identification of new prevention or treatment for AD dementia and mild cognitive impairment (6). Moreover, drug repurposing has been successfully applied in the field of antiviral research, providing new therapeutic options for diseases like Dengue, Ebola, ZIKA, and other various infectious diseases. This approach is particularly valuable in rapidly addressing the emergence of viral infection and the resistance observed against existing antiviral therapy. It is also used to find a new therapeutic use.

A newly developed drug is used to treat various diseases and disorders. It is a very useful and effective method, which is time-consuming and expensive. The method of finding new drugs by classical means is unsafe, overpriced and time-consuming. It is better because the medication decreases the high cost of long-term progress and washout associated with old drug discovery. It has the added advantage of being put away for 5-7 years, on average, in drug development time. Basically, one-third of old repurposed drugs or medication newly reprofiling industrial Companies comprises up to 30% of United States Food and Drug Administration (FDA) accredited medication and vaccines. Recent advances in Computational biology, artificial intelligence, systems pharmacology and biological data analytics have played an important role in other methods that are growing in drug repurposing, like high-throughput screening platforms and phenotypic assays in drug repurposing for research approach (7).This project is obtaining increasing consideration due to high cost, time and drug deviation associated with traditional drug discovery, which typically takes over a decade and billions of dollars to bring a new drug to market. The concept of drug repurposing is not new; it is an ancient observation that has led to the recognition of new synonyms of existing drugs. Classic examples mainly include sildenafil citrate, originally made for angina but repurposed for erectile dysfunction and later pulmonary arterial hypertension and thalidomide, originally introduced as a sedative but later repurposed for multiple myeloma and leprosy. All these are some old repurposed drug examples. Drug repurposing used in drug discovery and development is a demanding and gradual process. It holds the existing pharmacodynamics, pharmacokinetics and safety profile of approved drugs (8).

Table 1. Summarizes the key differences between the Traditional (De Novo) Drug Discovery and Drug Repurposing(9).

Parameter	Traditional (De Novo) Drug Discovery	Drug Repurposing
Development Time	10-15 years	5-7 years
Estimated cost	$ 1-2.6 billion	$ 300 million
Safety Data	Generated from Scratch (Phase 1)	Already available from prior approval/ trials
Probability of success Rate	~10 %	~ 30%
Regulatory Pathway	IND/ NDA process	Approval from the FDA and/or EMA.
Key Failure Point	Efficacy & Safety	Efficacy
Primary IP Advantage	Novelty (Composition of Matter IP)	Reduced Risk, Time, & Cost
IP protection	Strong composition-of-matter patents	Often limited to new-use or formulation patents; weaker commercial incentive

Landmark Case Studies in Drug Repurposing

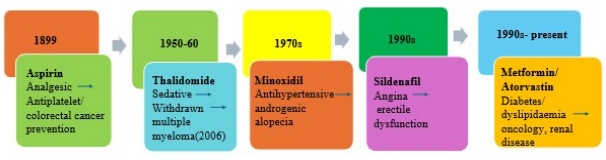

Figure 1. Timeline of Landmark Drug Repurposing Examples

Sildenafil: Sildenafil is a phosphodiesterase inhibitor that was mainly developed to treat angina and heart failure. It basically works on vasodilation.

But the participants in clinical trials utilize this. Compounds marketed with side effects such as headache, a few participants show penile erection. In 1993 1st clinical trials using sildenafil for the treatment of erectile dysfunction in healthy participants lacking cardiovascular diseases. After 5 years, sildenafil was certified for the treatment of patients with erectile dysfunction in America and Europe. Moreover, sildenafil was certified to be useful in the treatment of the pulmonary arterial hypertension disease process in 2005 (10). Target is inhibition after that, CGMP increases result in vasodilation, which improves blood flow and has an effect on nitric oxide transduction and inflammation. Other off-target effects include some activity on PDEC (retina), which is applicable for visual side effects and minor effects on other phosphodiesterase's at higher doses or effects. Major contraindications include nitrate (risk of hypotension and caution should be used with strong CYP3A4 inducers. A clinical trial gave sildenafil to pregnant women (to improve foetal growth), which affected neonatal pulmonary complications and death. It is one of the most prominent examples of successful drug repurposing. During the initial Phase I and Phase II clinical studies conducted in the early 1990s to evaluate the drug as a potential treatment for angina, researchers found that its impact on relieving chest pain was minimal and failed to meet expectations for cardiovascular benefit (11). As shown in Figure 1.

Aspirin: Acetylsalicylic acid, also called aspirin, holds a central place in the history of modern therapeutics and remains one of the most widely studied drugs in medicine. Introduced at the end of the 19th century, it rapidly became a standard treatment for pain, fever, and inflammation due to its ability to modulate biochemical pathways involved in prostaglandin production (12). Its earliest molecular action is the irreversible inhibition of cyclooxygenase (COX) enzymes, specifically COX-1 and COX-2, which regulate the formation of prostaglandins and thromboxane. This irreversible effect, especially on COX-1 in platelets, explains its long-recognized antithrombotic property. As scientific awareness developed, aspirin shifted from being only an analgesic and antipyretic to becoming the backbone of cardiovascular prevention. Low-dose therapy is now widely used to limit platelet aggregation and to contribute to the prevention of myocardial infarction, ischemic stroke, and certain manifestations of atherosclerotic disease. The drugs that inhibit platelet thromboxane production more strongly than endothelial prostacyclin synthesis are key to this protective effect (13). In the last few ten-year periods, research has expanded into the potential anticancer effects of acetylsalicylic acid. Long-term use has been connected with decreased incidence of colorectal cancer and, to some extent, prostate cancer (14). These effects are thought to originate from its anti-inflammatory actions, variation of COX-2–driven pathways, and possible influences on cellular proliferation, apoptosis, and immune responses in the tumor surrounding. Although ongoing studies aim to define ideal doses and populations that may benefit, aspirin continues to be described as an important model of how a single molecule can evolve from a simple analgesic to a drug with broad prophylactic and therapeutic potential (15).As shown in **Figure 1.**

Thalidomide: Thalidomide was used as a sedative and anti-nausea drug for pregnant women. In the 1960s, it was established to treat severe birth defects, mainly in limb phocomelia and other internal organ deformities or irregularities. This drug was separated from the market due to increased drug toxicity testing, mainly for developmental toxicity. Nowadays, it is used in combination with other drugs, used drugs like dexamethasone, to prevent or treat a type of blood cancer. It is also used to treat moderate to severe skin lesions associated with Hansen's disease (leprosy). In 2006, it was repurposed as a first-line agent in the treatment of multiple myeloma. Thalidomide is a drug with a mixed and historically significant profile in modern pharmacology and regulatory science (16). First introduced in the late 1950s as a sedative and antiemetic, it was widely marketed to pregnant women for the management of morning sickness because it was shown to be safe and non-addictive. However, within a few years, clinicians around the world observed a dramatic increase in severe congenital abnormalities among infants born to mothers who had taken the drug during early pregnancy. These defects included limb depletion anomalies such as phocomelia, along with a wide range of internal organ deformity (17). The magnitude of this tragedy led to the abolition of thalidomide from global markets in the early 1960s and became a driving force behind modern drug-safety regulations, especially those related to teratogenicity and developmental toxicity testing. Despite its damaging effects in pregnancy, thalidomide later emerged as a valuable therapeutic agent when its immunomodulatory and anti-inflammatory properties were recognized (18). Beginning in the late 20th century, it was reintroduced under strict controls for the treatment of erythema nodosum leprosy, a painful inflammatory complication of Hansen's disease. Forward research represents its significant anti-angiogenic and anti-tumor activity, leading to a major switch in its clinical role. In 2006, thalidomide was formally repurposed as a first-line therapy for multiple myeloma, particularly in combination with agents such as dexamethasone (19). As shown in **Figure 1.**

Metformin: Metformin, a widely used medication for controlled type 2 diabetes, has been increasingly acknowledged for its potential in drug repurposing, particularly in oncology. The existing descriptions highlight that metformin is known for its moderate efficacy, low side effects, and high appropriateness, making it a strong candidate for therapeutic applications beyond its traditional role as an anti-diabetic agent (20). These expectations are frequently highlighted in scientific discussions because they offer an advantage in repositioning metformin for a new indication. In recent years, metformin has attracted attention for its possible anticancer properties. According to epidemiological studies, metformin may reduce cancer risk and mortality, although ongoing research is examining the exact mechanisms involved. The available information highlights that metformin is thought to influence cancer cell metabolism and exhibit direct and indirect effects by changing systemic energy dynamics. These perceptions form a central part of the current scientific viewpoint regarding why metformin might be effective in cancer-related applications (21). Additionally, research mentions that metformin's potential prolongs the tumor. It has shown the ability to hinder tumor growth by activating AMPK pathways and inhibiting mTOR pathways, both of which are fundamental for cellular proliferation. This point is regularly used as an example of metformin displaying antitumor actions that support drug repurposing within oncology. The significance of AMPK initiation and mTOR inhibition remain an important part of explaining how metformin could contribute to tumor growth suppression. The potential for drug repurposing using metformin also includes oral cancers such as oral squamous cell carcinoma. Preclinical studies have

indicated that metformin reduces cancer cell proliferation and modulates critical pathways involved in cancer development. This strengthens the idea that metformin's influence on metabolic and signaling pathways is not limited to a single cancer type. Overall, repurposing metformin has contributed to substantial progress in understanding its therapeutic potential across multiple cancers. The repositioning efforts are supported by promising preclinical findings and clinical trials, strengthening metformin's role in both diabetes management and cancer treatment. Metformin is reported in several reviews to activate AMPK-dependent and AMPK-independent mechanisms**,** both of which contribute to its metabolic and anticancer effects (22). Many studies show that metformin reduces insulin and IGF-1 transduction**,** which can decrease cancer cell growth because these pathways are connected with tumor progression in insulin-resistant states. Metformin is known to suppress hepatic gluconeogenesis**,** and this reduction in glucose availability can indirectly influence tumor metabolism, especially in cancers dependent on glycolysis (23,24). As shown in **Figure 1.**

Minoxidil: Minoxidil is basically known as an antihypertensive vasodilator and as a topical agent for hair growth, but it has become a main example of drug repurposing. Review studies usually focus on minoxidil, which was originally present as an oral therapy for aiding hypertension, with its hair-growth effects uncovered as a secondary observation during clinical use. This unexpected advantage led to its repositioning as a treatment for androgenetic alopecia and other hair-loss disorders. Minoxidil has been widely used in dermatology because of its capacity to quicken hair follicles, extend the anagen phase, and amplify circulation in the scalp. In drug repurposing research, minoxidil has been investigated for additional roles after dermatology and cardiovascular therapy (25). Several respective reviews report that minoxidil displays actions on potassium channels, prostaglandin pathways, and cellular proliferation, which has inspired inspection into conditions where these mechanisms are applicable. Studies have surveyed its potential effects on wound healing, where minoxidil may increase vascular perfusion and support tissue healing processes. Research has also highlighted its influence on dermal papilla cells, fibroblasts, and keratinocytes, recommending that minoxidil may have broader applications in skin rebirth(26). Minoxidil has been assessed for antifibrotic effects, with some findings showing that it may decrease collagen accumulation and inhibit fibroblast activity. This has created interest in reprofiling it for disorders identified by fibrosis (27). As shown in **Figure 1.**

Atorvastatin: Atorvastatin, a mostly described statin for lipid lowering, has been explored for drug repurposing after its primary use in reducing low-density lipoprotein cholesterol (LDL-C). While atorvastatin's lipid-lowering efficacy is well accepted, with dose-dependent outcomes resulting in 36% to 53% decreases in LDL-C, emerging evidence suggests potential curative applications linked to its molecular mechanisms beyond cholesterol control. Drug repurposing involves identifying new uses for existing drugs based on their pharmacological properties, safety profiles, and emerging mechanistic insights. This economical approach helps speed up drug development for unfulfilled medical needs by using approved drugs like Atorvastatin(28). One promising area for its new use is in the treatment of diabetic nephropathy. Studies differentiate atorvastatin from non-statin lipid-lowering agents such as ezetimibe, revealing that atorvastatin attenuates kidney injury more effectively, possibly through inhibition of histone deacetylases (HDACs). HDAC inhibition by atorvastatin leads to epigenetic modification, improving defense gene expression in kidney cells, which may underlie its nephroprotective effects beyond lipid decreases(29). Additionally, atorvastatin's pharmacogenetic connection may influence its therapeutic and adverse effect profiles, a factor that could be mobilized in personalized medicine approaches during repurposing. For example, atorvastatin plasma levels and endurance are managed by genetic variations in CYP3A4 and ABCB1, recommending that patient genotype may direct a repurposing strategy to decrease side effects and improve efficacy. Although atorvastatin and other statins are primarily used to lower cardiovascular risk, their pleiotropic effects—anti-inflammatory, immunomodulatory, and epigenetic, offer prospects for repurposing in other illnesses that share pathways, such as fibrosis and chronic inflammation(30). As shown in **Figure 1.**

Key Approaches for Drug Repurposing: The main Approaches for drug repurposing are computational, experimental, and drug-centric methodologies, which have been successfully applied in several disease domains, particularly cancer, neurological disorders, infections, and metabolic diseases.

Computational Methods: Computational methods have emerged as a fundamental part of drug repurposing efforts, using large-scale biological, chemical, and clinical data to predict novel drug–disease relationships. The main computational techniques are:

Molecular docking and virtual screening: These tools simulate drug-target interactions to estimate binding affinity and potential efficacy against new targets. Progress in combining machine learning and deep learning improves prediction accuracy and prioritize candidates efficiently (31).

Network-based methods: By evaluating biological networks like protein-protein interaction networks and disease-gene-drug networks, researchers can discover off-target effects or common pathways that drugs can change, indicating repurposing opportunities.

Omics data integration: Combining genomics, transcriptomics, proteomics, and metabolomics permits identification of disease signatures and drug effects at a systems level, and matching drugs to diseases based on molecular profiles (32).

Artificial Intelligence (AI) and Large Language Models (LLMs): AI-based algorithms allow for deeper analysis of complex datasets, generating hypotheses and predicting new drug indications. LLMs can pull textual data, such as literature and clinical records, to identify potential candidates for repurposing. Examples of such computational approaches are in silico screening platforms specifically for repurposing, combining docking, machine learning, and pathway assessment to identify drug candidates across multiple diseases, including cancer, infectious diseases, and metabolic disorders (31).

Experimental and Phenotypic Screening: In addition to computational predictions, experimental methods are used to

empirically test drug effects in biological models. Phenotypic screening evaluates drugs' impact on cellular or organismal phenotypes without prior assumptions about the specific target, providing a direct measurement of therapeutic potential, particularly in complex diseases like cancer.

Other experimental methods include

Re-engineering protein targets: Altering existing drugs or their targets to enhance efficacy and specificity in new indications.

Nanotechnology-based delivery systems: Enhancing bioavailability or targeting repurposed drugs to specific tissues.

These approaches are vital to validate computational predictions and explore mechanisms underlying drug action in new contexts (31,32).

Drug-Centric and Knowledge-Based Strategies: Drug-centric methods focus on detailed knowledge of a drug's mechanism of action, Polypharmacology, and safety profile to recognize logical new indications. Knowledge-based analyses use clinical observations, epidemiological data, and real-world evidence, such as electronic health records, to detect unforeseen therapeutic effects or side benefits of drugs under routine use. Examples of successful repurposing from such strategies include aspirin for colorectal cancer prevention and itraconazole for basal cell carcinoma, representing the translation of mechanistic insights into clinical use (31).

Table 2. Data Sources and Databases used in Drug Repurposing (32)

Category	Databases	Use
Chemical/ Drug	DrugBank, PubChem, ChEMBL	Chemical structures, drug targets, bioactivity data
Disease/genomic	OMIM, GWAS Catalog, TCGA	Disease-gene associations, cancer genomics
Gene expression	GEO, Connectivity Map (CMap), LINCS L1000	Drug- and disease-induced transcriptomic signatures
Clinical/real-world data	Electronic health records, insurance claims databases	Observational signals of off-label drug effects
Clinical trials	ClinicalTrials.gov, EU Clinical Trials Register	Ongoing/completed repurposing trials

Methodology of Drug Repurposing: The methodologies used in DR can be divided into three broad groups depending on the quantity and quality of the pharmacological, toxicological and biological activity. These are mainly (i) drug-oriented, (ii) target-oriented, and (iii) disease/therapy-oriented. As shown in **Figure 2.**

Drug- Oriented (Ligand- based) Methodology: Drug-oriented drug reprofiling is a remarkable approach to drug development that looks for new therapeutic uses for approved, over-the-counter, or discontinued drugs (33). This method uses medicament with known pharmacological properties, a set up mode of action, and realize safety profiles rather than developing completely new compounds from expansion (34).

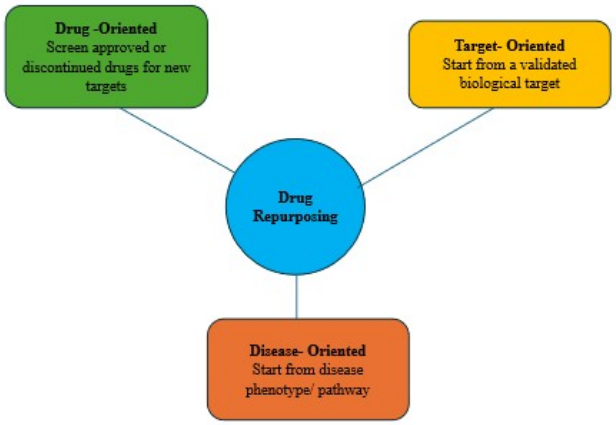

Figure 2. Methodology of Drug Repurposing

Researchers can substantially cut the development timeline, decrease costs, and lower risks by starting with substances that have already passed crucial phases of clinical testing. This method is particularly advantageous for addressing unfulfilled medical needs, rare diseases, and new health challenges that require faster solutions. Drug-oriented repurposing includes essential screening of known drugs using experimental tests, numerical modelling, and biological data analysis to uncover earlier unknown interactions with new disease targets or pathways (35). Many existing drugs interact with various biological systems, potentially providing unexpected benefits beyond their original uses. Furthermore, regulatory approval for repurposed drugs can be quicker because much of the toxicological and pharmacokinetic data is already available. This not only speeds up clinical translation compared to traditional drug research pipelines but also increases the chances of success. Overall, drug-oriented drug repurposing is an inventive, cost-effective, and time-saving method that maximizes the therapeutic potential of existing pharmaceutical compounds while minimizing development risks (34,35). As shown in Figure 3.

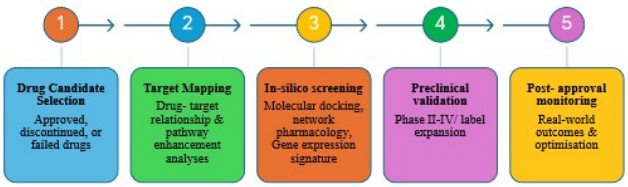

Figure 3. Generalised workflow of Drug- Oriented (Ligand-based) Methodology

Selection of drug candidates: The procedure started by discovering better drugs from already approved medications, discontinued compounds, or drugs that failed for reasons separate from safety. Preference centres on existing knowledge about pharmacokinetics, bioavailability, drug-target interactions, and established safety limits. Using drugs with well-documented profiles helps decrease development time and risk. Compounds that act on various biological pathways, known as pleiotropic or multi-target drugs, are especially important because they may be effective across different diseases. This approach increases the chance of achievement while lowering costs compared to developing entirely new drugs from scratch (34).

Mechanism-Based Target Mapping: Currently, the molecular actions of selected drugs are being tested to uncover common pathways shared with other diseases. Drug–target

relationships are identified through the use of biochemical and pharmacological databases, pathway enhancement analyses, and systematic review of scholarly articles. By comparing these interconnected researchers can detect overlaps in ligands (molecular signaling or biological processes) across different conditions. Identifying such shared mechanisms issues a strong scientific basis for drug repositioning, as it is recommended that a drug effective in one disease may also regulate applicable pathways in another, carry its potential use past the original indica tions(34).

In-Silico Screening and Computational Analysis: Computational approaches play an important role in drug repurposing by authorizing well organized identification of new curative uses for existing compounds. Techniques such as molecular docking and virtual screening simulate drug–target interactions to predict binding affinity and selectivity. Pharmacophore modelling helps define key organizational features required for biological activity. In addition, network pharmacology examines complex relationships among drugs, targets, and disease pathways. Gene expression signature matching relates drug-induced and disease-related profiles to uncover potential therapeutic overlaps. Together, these in silico methods reduce cost, time, and risk in discovering alternative drug synonyms (35).

Preclinical Experimental Validation: Encouraging drug candidates found using computational methods are then tested in laboratory and animal studies. Cell-based experiments, enzyme inactivation tests, and disorder-relevant animal models are conducted to assess their therapeutic potential and understand how they work. These experiments help verify that the candidates show biological activity in the targeted disease conditions.

Clinical Translation and Regulatory Pathways: Substantiated drug candidates can move faster into clinical testing because their safety has already been established. As a result, they often enter later-stage clinical trials rather than starting from early phases. Regulatory authorities may also allow faster approval routes, such as enlarging an existing drug label or using accelerated approval programs, which can substantially decrease the time needed to bring the therapy to patients.

Post-Approval Monitoring and Optimization: After a drug goes through approval for a new use, ongoing post-marketing monitoring is carried out to ensure its long-term safety and effectiveness. Data from real-world clinical practice and patient outcomes are examined to improve treatment guidelines and ensure optimal use in routine care.

Target- oriented Methodology: High-throughput and high-content screening (HTS/HCS) are used in in vitro and in vivo studies to evaluate large numbers of compounds against biological systems rapidly. These approaches generate quantitative data on molecular interactions, cellular responses, and phenotypic changes. Alongside experimental screening, in-silico methods are widely applied to predict interactions between proteins, drugs, and biomarkers before laboratory testing. Drug-oriented (ligand-based) strategies focus on known active compounds. Screening is performed by comparing new molecules with existing drugs or chemical libraries based on structural similarity, pharmacophore features, or biological activity. This approach does not require detailed knowledge of the molecular target and is useful when target structures are unknown. In contrast, target-based (structure-based) strategies begin with a well-characterized biological target, such as a protein or receptor. Molecular docking and virtual screening are used to identify compounds that bind specifically to the target's active site. This method relies on accurate target information and is effective for designing highly specific therapeutics(33,34).

Disease-oriented: Drug repurposing can be built up when additional, detailed information about a disease is available. Knowledge of a drug's known side effects, adverse reactions, and off-target symptoms often provides important clues about different therapeutic uses, as these accidental effects may reflect interactions with biological pathways applicable to other diseases. Likewise, disease phenotypes and clinical declarations help in understanding how drugs affect biological systems beyond their primary symptoms. Advances in omics technologies, such as genomics, proteomics, and metabolomics, generate large datasets that express how pharmaceuticals modulate gene expression, protein networks, and metabolic profiles. Combining these datasets allows researchers to identify shared molecular signatures between drugs and diseases, thereby spotlighting new therapeutic opportunities. Computational approaches play a central role in this process. Pathway and network-based analyses are used to establish disease-specific molecular pathways and interaction networks. These models help identify key regulatory nodes, critical targets, and interconnected protein molecules involved in cellular functions. By mapping drug actions onto these networks, researchers can better understand drug-target relationships and predict novel indications. Overall, such an integrative plan of action improves insight into disease mechanisms and supports rational drug repurposing (33–35).

Applications across Therapeutic Areas

Challenges and Limitations in Drug Repurposing

Sr. No.	Drug	Original Indication	Repurposed For	Citation
1	Auranofin	Rheumatoid arthritis	Breast, Ovarian, lung cancer & acute lymphoblastic leukemia	(36).
2	Sunitinib	Renal carcinoma	Pancreatic tumor	(37).
3	Metformin HCL	Type 2 diabetes	Breast cancer	(38).

Drug Repurposing among Anti-depressant drugs

Sr. No.	Drug	Original Indication	Repurposed For	Citation
1	Dapoxetine	Depression and Psychological disorders	Premature ejaculation	(39).
2	Sibutramine	Depression	Anti-obesity	(40).

Drug Repurposing for Covid-19

Sr. No.	Drug	Original Indication	Repurposed For	Citation
1	Ivermectin	Anti-viral	Covid-19	(41).
2	Chloroquine	Malaria	Covid-19	(42).
3	Remdesivir	Anti-viral	Covid-19	(43).

Additional examples of drug repurposing

Sr. No.	Drug	Original Indication	Repurposed For	Citation
1	Melatonin	Sleep cycle regulates	Immunomodulator	(44).
2	Spironolactone	Antihypertensive	Diuretics	(45).

Drug repurposing is a strategy for identifying new therapeutic uses for existing drugs, and it holds significant potential to accelerate drug development, reduce costs, and provide effective treatments across various conditions, notably cancer. However, this approach has several important challenges and limitations that influence its efficacy, implementation, and broader adoption in clinical practice.

Biological and Clinical Complexity: A major challenge in drug repurposing, particularly in cancer, stems from the inherent biological complexity and heterogeneity of the disease. Cancer's molecular diversity complicates the development of universally effective therapies, as heterogeneity influences drug response and the emergence of resistance mechanisms. This complexity necessitates comprehensive mechanistic insights and robust predictive biomarkers to ensure the successful repositioning of drugs for new indications. Clinical trial design signifies another obstacle. Repurposed drugs often require new clinical evaluations to establish efficacy and safety in the novel indication. Difficulties in patient selection, endpoints, and regulatory expectations can complicate the design of these trials. Moreover, clinical validation is important to overcome biases and confirm therapeutic benefit, but trial costs remain high, specifically when large-scale or combination therapy trials are needed to address monotherapy limitations (46,47).

Intellectual Property and Commercial Incentives: One of the most important barriers to drug repurposing is the lack of strong intellectual property (IP) protection and commercial incentives, mainly for off-patent or generic drugs. Limited patent life or the absence of exclusivity rights reduces the appeal for pharmaceutical companies to invest in costly repurposing development and clinical trials. This issue results in a relatively low industry interest in repurposing projects despite their potential societal benefits. Policy and regulatory frameworks often lag, offering insufficient protection for repurposed indications, which further discourages private investment. Thus, public funding and non-profit organisations usually drive early-stage research, but these groups often lack the resources or regulatory engagement to advance repurposed drugs to clinical authorisation successfully (46).

Regulatory Barriers and Uncertainty: Directing different regulatory pathways shows a complex challenge. Regulatory agencies require rigorous evidence to approve drugs for new indications, including efficacy, dosing, and safety data, which can be expensive and time-consuming to generate. The absence of clear or harmonized guidelines for repurposed drugs complicates their market authorization. In addition, 'off-label' use, prescribing approved drugs for unapproved indications, is common but ethically and legally complex, raising concerns about patient consent, safety monitoring, and liability.

Data Quality and Integration Challenges: The rising role of computational methods and artificial intelligence (AI) in drug repurposing introduces its own limitations. These techniques require high-quality, comprehensive multi-omics, pharmacological, and clinical datasets. Issues such as data incompleteness, heterogeneity, lack of standardization, and interpretability of AI models hinder reliable drug candidate identification and validation. Furthermore, computational predictions must be experimentally and clinically validated, highlighting the need for integrated pipelines combining bioinformatics, experimental assays, and clinical research. The complexity and cost of such integrated efforts show additional challenges (46).

Financial and Infrastructural Limits: Repurposing is generally more cost-effective than de novo drug discovery, but it still requires substantial investment, mainly for confirmatory clinical trials. Funding limitations severely restrict the progress of many promising repurposing candidates, especially in academic and non-profit settings where resources are rarer. Infrastructure gaps, including insufficient collaboration networks, regulatory support, and knowledge-sharing platforms, further impede efficient repurposing. Enhanced partnerships across academia, industry, health technology assessment bodies, and regulatory agencies are needed to overcome these barriers (48).

Ethical and Equitable Access Concerns: Ethical challenges include ensuring equitable access to repurposed therapies, particularly in low- and middle-income countries (LMICs), where healthcare disparities limit clinical trial participation and drug availability. Moreover, issues of informed consent arise when using drugs off-label, and transparency in sharing clinical trial data and conflicts of interest are essential (49,50).

Glossary of Abbreviations

Abbreviations	Full Forms
ABCB1	ATP-Binding Cassette Subfamily B Member 1 (Drug transporter gene)
AD	Alzheimer's Disease
AI	Artificial Intelligence
AMPK	Adenosine Monophosphate-Activated Protein Kinase
cGMP	Cyclic Guanosine Monophosphate
CMaP	Connectivity Map
COX	Cyclooxygenase (e.g., COX-1, COX-2)
CYP3A4	Cytochrome P450 Family 3 Subfamily A Member 4 (Drug-metabolizing enzyme)
DR	Drug Repurposing
EMA	European Medicines Agency
FDA	United States Food and Drug Administration
GEO	Gene Expression Omnibus
GWAS	Genome-Wide Association Study
HCS	High-Content Screening
HDACs	Histone Deacetylases
HTS	High-Throughput Screening
IGF-1	Insulin-like Growth Factor 1
IND	Investigational New Drug
IP	Intellectual Property
LDL-C	Low-Density Lipoprotein Cholesterol
LINCS L1000	Library of Integrated Network-Based Cellular Signatures L1000
LLMs	Large Language Models
LMICs	Low- and Middle-Income Countries
mTOR	Mammalian Target of Rapamycin
NDA	New Drug Application
OMIM	Online Mendelian Inheritance in Man
PDEC	Phosphodiesterase Type 6 (specifically in retinal cone cells, sometimes referenced generally as PDE6 or PDEC)
TCGA	The Cancer Genome Atlas

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