

Repurposing: A Review of a Cost-Effective and Time-Saving Drug Discovery

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ABSTRACT

Drug repurposing is a faster and safer approach in drug discovery that involves investigating already approved and marketed drugs for the treatment of conditions different from those for which they were originally prescribed, making it a cost-effective strategy. This review highlights both classical examples of drug repurposing, such as aspirin, dexamethasone, and propranolol, as well as recent applications, including therapies for COVID-19 and treatments for rare diseases. The evolution from traditional drug discovery methods to computational approaches, encompassing artificial intelligence, biological networks, transcriptomics, and literature mining, is explored. These approaches facilitate rapid screening, drug-disease network analysis, and other processes that enhance the efficiency and quality of drug discovery outcomes. Our findings emphasize how cutting-edge computational techniques, when integrated with established pharmacological knowledge, can expand therapeutic options across a wide spectrum of diseases, including neurological, infectious, cancer-related, and rare conditions. Drug repurposing thus represents a valuable resource for the medical field, offering the potential to enrich the drug market through computer-based and AI-assisted screening, supported by experimental and clinical research to validate and bring old drugs to new therapeutic applications.

Keywords: Drug repurposing; Drug discovery; Drug repositioning.

1. Introduction

Drug repurposing of approved drugs for both common and rare diseases has become an increasingly appealing strategy due to the high attrition rates, significant expenses, and slow progress associated with de novo drug discovery and development [1]. By using approved drugs with known safety profiles, this strategy significantly lowers overall development costs and accelerates the time required for clinical application [2]. Conversely, traditional drug discovery is a time-consuming and high-risk process that involves compound screening, assay development, target identification and validation, and extensive optimization to enhance efficacy and minimize toxicity [3]. Additionally, *in silico* drug repurposing further accelerates the process by testing multiple drugs against the biological signatures of known diseases using various computational methods [4].

1.1. Traditional de novo drug discovery and its challenges

Traditional drug discovery (Figure 1) involves both *in vitro* and *in vivo* testing to evaluate the safety of the drug and determine how the drug is absorbed, distributed, metabolized, and excreted by the body (ADME study) [5]. The data collected are reviewed to ensure the drug's safety before proceeding with human trials. This stage includes differentiating between toxic and effective doses (Therapeutic window) [6]. The Food and Drug Administration (FDA) then reviews the data obtained from clinical trials and evaluates whether the drug should be approved for public use or rejected [7]. Then the Food and Drug Administration (FDA) reviews the data obtained from clinical trials and evaluates whether the drug should be approved for public use or rejected [8]. The final stage is post-market safety monitoring, during which the approved drug is continuously monitored to track its long-term safety, effectiveness, and any adverse effects in the general population [9]. This process carries a high risk of failure, as many compounds fail during clinical trials, requiring extensive efforts to confirm their safety profiles and clinical efficacy [9].

Drug repurposing evades all previous processes, because the drug profile is already extensively studied.

1.2. Drug repurposing

Drug repurposing, also known as drug repositioning or drug recycling, is a technique of using an existing, approved, or marketed drug to treat conditions that differ from what the drug was initially prescribed for. It includes drug identification, evaluation of drug efficacy using preclinical models, and proceeding to phase II clinical trials. Drug repurposing gained considerable attention during the COVID-19 pandemic and was crucial in accelerating the drug discovery process and identifying rapid solutions to the overwhelmed healthcare system and the increasing drug demand [10]. The majority of drug repurposing has been opportunistic; once a medicine's off-target effect or newly discovered on-target effect is identified, it is often pursued for financial gain.

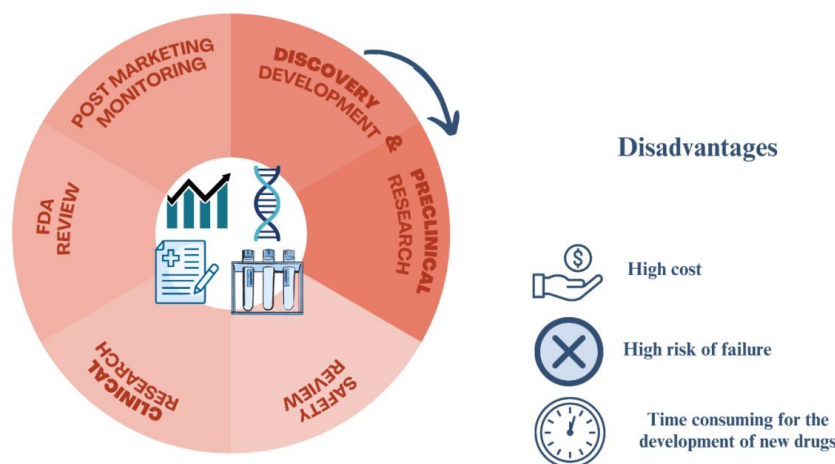


Fig. 1. Traditional drug discovery stages (discovery, preclinical research, safety review, clinical research, FDA review and post-marketing monitor) with disadvantages illustrated (high cost, high risk of failure and time consumption)

The following examples demonstrate the broad therapeutic applications of drug repurposing:

Amantadine

It was found that Amantadine had a therapeutic property against Parkinson's disease (PD) clinical features because it aids dopamine release and increases the time for its reuptake [11]. Moreover, it was then approved to be included in the medication strategy for dyskinesia in PD [12,13]. However, Amantadine was initially prescribed as an antiviral drug for influenza in 1966 [11].

Aspirin

Aspirin was first created as an anti-inflammatory, fever-reducing, and pain-relieving medication. It is a member of the nonsteroidal anti-inflammatory drug (NSAID) class and was commonly used to treat diseases like arthritis, headaches, and muscle soreness. Then, it was repurposed for the prevention of heart attacks, strokes, and other cardiovascular events because of its capacity to suppress platelet aggregation, or blood clotting, by permanently blocking the cyclooxygenase (COX) enzyme. This antithrombotic action lowers the formation of thromboxane A₂, a chemical that encourages platelet aggregation. In recent years, individuals who are recovering from a heart attack or stroke or who are at high risk of cardiovascular disease frequently take it in small doses [14,15].

Clonidine

Clonidine is a centrally acting sympatholytic drug that was developed in the 1960s. Clonidine works by lowering blood pressure, which is achieved by decreasing cardiac output and peripheral resistance. Its mechanism depends on the stimulation of alpha-adrenergic receptors [16]. In ADHD, it showed effectiveness in clinical trials, improving ADHD and its symptoms in children and adolescents [17].

Dexamethasone

In 1957, Dexamethasone was first developed, and in 1958, it was approved for the treatment of severe allergies and edema. It was used in COVID-19 treatment, and it was reported to dramatically decrease mortality in critical patients who needed ventilator assistance. Dexamethasone also may help in increasing nuclear power and facilitating medication entry to the nucleus [18]. Dexamethasone exerts its pharmacological effects by binding to cytoplasmic glucocorticoid receptors, forming a ligand-receptor complex that translocates into the nucleus. Once in the nucleus, this complex acts as a transcription factor, modulating the expression of glucocorticoid-responsive genes. Its anti-inflammatory properties are primarily attributed to the upregulation of phospholipase A₂ inhibitory proteins, such as annexins, which suppress the biosynthesis of pro-inflammatory mediators, including prostaglandins and leukotrienes. It was also found to be immunosuppressant as it inhibits neutrophil infiltration and suppresses lymphocyte proliferation, which can be repurposed for use after organ transplantation to reduce the risk of organ rejection by the immune system. It can also be prescribed for autoimmune diseases [19,20,21].

Dimethyl fumarate

The usage of Dimethyl fumarate (DMF) early in the 20th century was in the transportation of sofas as a fungicide, by including sachets containing it with the furniture. Its first medical mention was associated with "poison chairs" [22] and the skin burns some individuals had on their skin. In the 1950s, a German biochemist was suffering from Psoriasis vulgaris, and he utilized DMF for his condition, falsely believing that psoriasis was related to fumarate deficiency due to Krebs cycle dysfunction. This shifted the general theory of DMF from being a skin irritant to an effective therapeutic treatment. Finally, in 1994, the first DMF-based drug, Fumaderm®, was permitted in Germany for the treatment of severe psoriasis. This was then expanded to include moderate psoriasis in 2008. It proved to protect cells against oxidative stress by activating the Nrf2

(Nuclear factor erythroid 2-related factor 2) pathway, and it also proved to inhibit NF- κ B (Nuclear factor kappa-light-chain-enhancer of activated B cells), thus decreasing pro-inflammatory cytokines [23,24].

Disulfiram

Originally, Disulfiram was approved for chronic alcoholism treatment in 1951 due to its anti-aldehyde dehydrogenase (ALDH) activity [25,26]. It was under investigation for its anticancer properties and its tumor-suppressive mechanisms, including inhibition of aldehyde dehydrogenase (ALDH), which is highly expressed in cancer stem cells [27], in addition to interference with the NPL4 ubiquitin recognition factor and oxidative stress pathways [28].

Exenatide (Byetta)

Exenatide was primarily designed to treat type 2 diabetes. It is classified as a glucagon-like peptide-1 (GLP-1) receptor agonist or an incretin mimetic. It works by stimulating the pancreas to release insulin in response to food intake, suppressing excessive glucagon release from the liver, and slowing gastric emptying, which reduces appetite and aids in blood sugar control. Exenatide has demonstrated promise for weight loss, especially in non-diabetic obese individuals. Clinical studies have shown that patients taking exenatide lose significantly more weight than those taking other diabetes medications because it prevents blood sugar spikes, prolongs satiety, and hence decreases calorie intake [29,30].

Ketamine

In 1962, Ketamine was developed to replace Phencyclidine (PCP) while attempting to preserve its anesthetic properties, but without the notable side effects of PCP [31]. By 1965, it had been validated as a safe and effective anesthetic and analgesic. Ketamine received FDA approval as an intravenous anesthetic agent by 1970 [32]. Furthermore, Ketamine was redirected to treat depression and showed significant effectiveness in reducing depressive symptoms [33]. Its enantiomer's intranasal formulation, in combination with oral antidepressants, was approved by the FDA in 2019 for major depressive disorder that is resistant to treatment [34].

Metformin

Metformin, a widely used drug for type 2 diabetes, reduces the amount of glucose produced by the liver by blocking hepatic gluconeogenesis. Furthermore, it increases muscle peripheral glucose absorption, which improves insulin sensitivity [35]. However, it has shown significant attention for its anti-cancer properties, as Metformin inhibits the mitochondrial respiratory chain's complex I, lowers ATP (adenosine triphosphate) synthesis, and raises AMP (adenosine monophosphate) levels, inhibiting cell growth pathways such as mTOR (mammalian target of rapamycin) via both independent and AMPK (adenosine monophosphate-activated protein kinase)-dependent pathways, which interferes with the production of proteins and the growth of tumor cells, preventing cancer cell survival and proliferation [36,37]. In addition, it increases electron leakage by moderately inhibiting mitochondrial respiratory chain complex I, and ROS (reactive oxygen species) are produced inside the mitochondria as a result, as shown in (Figure 2) [38,39].

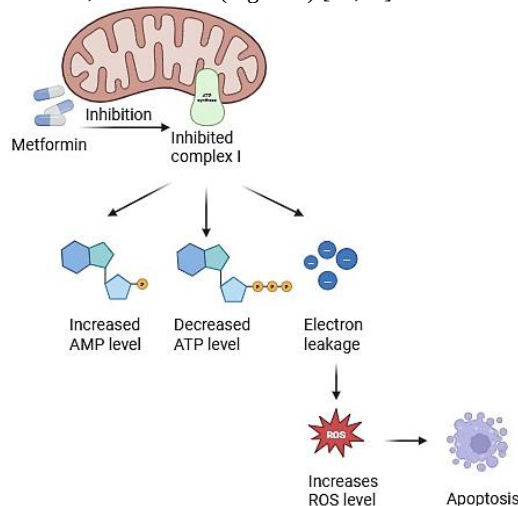


Fig. 2. The direct mechanism of action of metformin on mitochondria where it inhibits complex I thus increasing AMP level and decreasing ATP level, also causing electron leakage increasing ROS level leading to apoptosis

Metronidazole

Metronidazole was first marketed as an antiprotozoal drug in the 1950s. It acts on microorganisms when it is reduced inside the cells, producing free radicals that break down microbial DNA [40]. Ever since, it has been used as an antibacterial and antiprotozoal medication; furthermore, it has shown the ability to penetrate and accumulate in hypoxic tumors and was found to have anticancer properties [41,42]. It was proved to have a radiation-sensitizing action selectively on hypoxic tumor cells rather than normal cells; however, it has neurotoxic side effects [43].

Minoxidil

Minoxidil is a drug that has undergone both reformulation and repurposing. Minoxidil has been used as a potent antihypertensive oral drug. One known adverse effect of Minoxidil during therapeutic treatment is excessive hair growth. This finding led to the development of a topical form of Minoxidil for the treatment of androgenetic alopecia and hair loss [44]. The significance of Minoxidil in cancer treatment was also discovered; in a xenograft model of ovarian cancer, it was identified to activate the Kir6.2/SUR2 channel, which inhibited tumor growth. In addition, Minoxidil causes severe DNA damage and mitochondrial malfunction by changing the oxidative and metabolic states of cancer cells. As a result, a caspase-3-independent pathway for cell death is activated. This proves that it has potential as an anticancer drug for gynecologic tumors [45].

Propranolol

In 1964, Propranolol was identified as a β -receptor antagonist with the potential to fight heart conditions, being a nonselective β 1- and β 2-adrenergic antagonist. Since then, it has been used in managing heart conditions [46]. In 2008, Propranolol demonstrated its clinical antiangiogenic therapeutic capabilities in 11 cases of infantile hemangioma (IH) after inducing apoptosis in capillary endothelial cells (ECs) [47]. IH is a benign vascular tumor that typically affects the limbs and face in newborns. The surgical procedure was the only therapeutic strategy, as any other medications were inefficient towards IH. However, Propranolol trials were found to be effective in several cases. In 2014, Propranolol was formulated as an oral treatment for IH by EMA [48,49,50].

Raloxifene

Raloxifene, a selective estrogen receptor modulator (SERM), was originally used for the treatment of osteoporosis in postmenopausal women, as it strengthens the bones, especially the spine. It slows down bone deterioration by imitating the effects of estrogen on bone. According to clinical research, it lowers the risk of vertebral fractures in postmenopausal women and enhances bone mineral density [51]. Furthermore, Raloxifene was repurposed to reduce the risk of breast cancer, as it plays a role as an estrogen antagonist in breast tissue, competing for the binding sites on estrogen receptors (ER), thereby inhibiting estrogen-dependent proliferation of breast cancer cells, which decreases breast cancer risk by 76% when compared to placebo strategies. In addition, Raloxifene was repositioned in the treatment of COVID-19, as it showed antiviral activity against SARS-CoV-2 *in vitro* in preclinical studies. The protective effects of Raloxifene may be attributed to its mechanistic interactions with the Spike protein and host pathway modulation, such as its ability to prevent Spike-mediated ADAM17 activation in pulmonary cells. Its potential has been further confirmed by clinical trials; Phase 2, as it was reported that Raloxifene treatment improved the virological results and symptoms in mild-to-moderate COVID-19 patients, demonstrating its potential for COVID-19 management [52].

Rituximab

Rituximab is a human-mouse chimeric monoclonal antibody that rapidly and specifically depletes B cells by targeting the B-cell CD20 antigen. Since its approval in the United States in 1997, Rituximab has been used in the treatment of low-grade or follicular, relapsed or refractory, CD20-positive B-cell non-Hodgkin's lymphoma (NHL). Rituximab was used off-label to treat hundreds of autoimmune diseases, and it was the only entity available for focused B-cell-targeting therapy in rheumatoid arthritis[53,54,55].

Sildenafil citrate

The repurposing of Sildenafil citrate, also known as Viagra, for erectile dysfunction was based on retrospective clinical experience. It was originally used as an antihypertensive medication, as it works as a selective inhibitor of phosphodiesterase type 5 (PDE5). Cyclic guanosine monophosphate (cGMP), an essential chemical that regulates smooth muscle relaxation and vasodilation in the corpus cavernosum of the penis, is prevented from degradation by Sildenafil via blocking PDE5. Nitric oxide (NO) is released during sexual intercourse, which raises cGMP levels. The erection then occurs more easily because of the increased blood flow to the penis. By encouraging vasodilation in the lungs, Sildenafil's action also works in the pulmonary capillaries, lowering blood pressure. Sildenafil was reformulated by Pfizer to treat erectile dysfunction and marketed as Viagra. In 2012, it held a dominant 47% market share in the erectile dysfunction drug industry, with \$2.05 billion in global sales [56].

Tamoxifen

Tamoxifen was first presented as a contraceptive, although it failed to stop ovulation. When the estrogen receptor (ER) was identified as a key factor in breast cancer, Tamoxifen was developed to be effective in blocking estrogen and suppressing the proliferation of ER+ breast cancers. Since then, Tamoxifen has become one of the most popular medications for breast cancer [57,58,59]. Being an estrogen agonist, it is used to maintain bone density, protecting the body from osteoporosis. It also has the ability to overexpress the tumor suppressor gene maspin (mammary serine protease inhibitor) [60].

Thalidomide

In 1995, Thalidomide was developed to work as a sedative during pregnancy; however, this turned out to be catastrophic since it was found to cause limb birth defects and developmental abnormalities. However, afterwards, it was declared FDA-approved as a cure for leprosy immunologic complications [61].

Tocilizumab

Tocilizumab was originally developed for the treatment of rheumatoid arthritis (RA). It is a monoclonal antibody that targets and inhibits the interleukin-6 (IL-6) receptor, thereby reducing inflammation and immune system hyperactivity, which play a

role as contributors to autoimmune disorders such as RA. Tocilizumab was first authorized to treat giant cell arthritis, juvenile idiopathic arthritis, and rheumatoid arthritis. Recently, it was used to treat severe COVID-19 cases that involve cytokine release syndrome (CRS), commonly referred to as a "cytokine storm." In severe COVID-19 patients, CRS is a potentially fatal inflammatory reaction brought on by an overabundance of immunological activation [62].

Zidovudine

In the 1960s, the National Cancer Institute was funded for the development of a new anti-cancer agent, Zidovudine, which was developed at the time, but unfortunately, it didn't show much success in the cancer-drug candidate selections; it exhibited only limited attention in human virology. Around 20 years later, when Human Immunodeficiency Virus Type 1 was first recognized, Zidovudine showed effectiveness against it *in vitro* because it inhibits reverse transcriptase, thus halting the change of viral RNA to DNA, and so it was declared to be the first FDA-approved medication against HIV-1 [63,64].

1.3. Drug repurposing and rare diseases

A one-size-fits-all approach does not work in medicine, especially with the rare diseases

Rare disorders collectively affect around 3.5–5.9% of the population (Figure 3). Despite the progress, challenges remain in creating and implementing therapies for rare diseases. Advances in genomics, omics technologies, and computational tools have improved early diagnosis for rare diseases. And scientific research is driving the development of disease-modifying treatments, including gene therapy, nutraceuticals, and repurposed drugs [65,66].

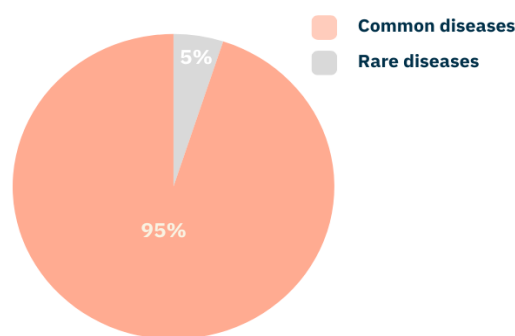


Fig. 3. Distribution between common and rare diseases

Time plays a vital role in managing life-threatening conditions and rare diseases, highlighting the importance of prompt access to treatments. Finding treatments for rare diseases can be difficult because of their low prevalence, which frequently results in a lack of funding and resources for research. Additionally, appropriate techniques for testing possible drugs might not be available. According to reports, the time it takes to find and develop new medications can range from 10 to 17 years, whereas repurposed medications are typically approved more quickly; some processes for repurposed drugs might take approximately 3 years. While the cost of developing novel drugs currently averages approximately \$12 billion, whereas drug repurposing (DR) typically costs about \$1 billion – thus, DR is making significant contributions to cost savings within the drug development process [67]. In addition, drug repurposing provides an incredibly high degree of success of about 30% compared to the 10% success rate observed for the traditional *de novo* drug discovery process (Figure 4)[68].

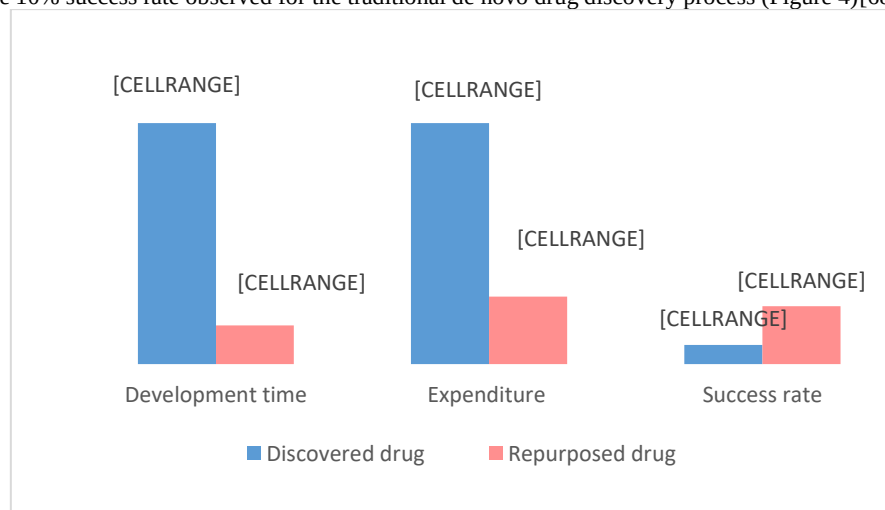


Fig. 4. Drug repurposing versus novel drugs

If a rare mutation has a certain pathway, researchers can repurpose an existing drug developed for a different condition sharing the same pathway for treatment. For many patients with very rare diseases, there are no available treatments. Drug repurposing (DR) can reveal untapped potential in existing medications, providing life-saving therapies where none were previously available. This approach often uncovers how seemingly unrelated diseases may share common, targetable disease networks (Figure 5) [69].

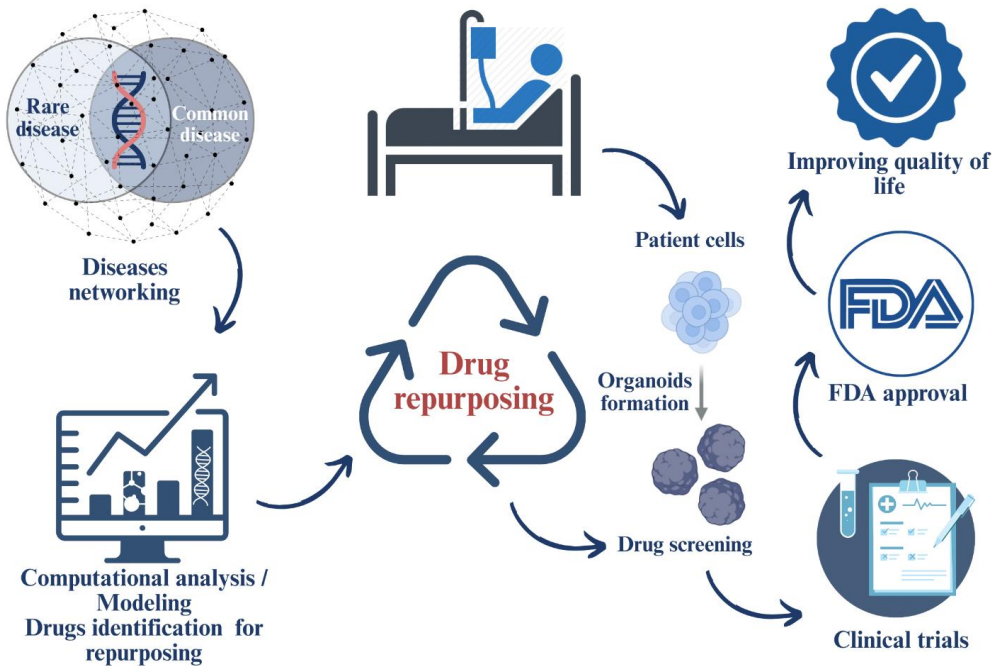


Fig. 5. Mapping drug repurposing strategies in rare diseases

The following examples highlight successful applications of drug repurposing in rare diseases (Table 1):

Everolimus

Everolimus is a repurposed drug that primarily received approval for renal cancer [70].

Tuberous sclerosis complex is a rare genetic disorder that has shown a response to the repurposed drug Everolimus (an inhibitor of the mammalian target of rapamycin (mTOR)), enabling the reduction of hamartomas and correcting the specific molecular defect that causes Tuberous sclerosis complex [71].

Sirolimus

Lymphangioleiomyomatosis (LAM) is a rare, progressive, and potentially life-threatening interstitial lung disorder [72]. Sirolimus was first represented as an immunosuppressant agent with further investigation in renal transplantation [73].

Sirolimus's efficacy in treating LAM has been validated by numerous clinical investigations. The first trial, called the Cincinnati Angiomyolipoma Sirolimus Trial, assessed sirolimus's use for angiomyolipomas (AMLs), and it was found that it significantly affected LAM. Numerous additional studies later supported this, showing that the medication could slow down the disease's progression [73,74].

Auranofin, & Ganetespib

Ewing sarcoma (EWS) is a rare and highly aggressive cancer arising from neuroectodermal tissue, primarily affecting the bones and less frequently involving soft tissue structures [75].

Auranofin, an inhibitor of thioredoxin reductase, and Ganetespib, an HSP90 inhibitor, were successfully identified *in silico* as potential anticancer agents and *in vitro* shown to be effective against a gene-specific panel of Ewing sarcoma (EWS) cell lines. Furthermore, when combined, they showed significantly potent effects *in vivo* compared to monotherapy with either drug. These *in vitro* and *in vivo* screenings highlight the promise of the combination of Auranofin & Ganetespib in finding novel therapeutic targets in this rare and aggressive malignancy, Ewing sarcoma (EWS) [76].

Lonafarnib

In 2020, Lonafarnib became the first and still the only drug approved by the FDA for the treatment of progeria. It was authorized specifically for reducing the risk of mortality in individuals affected by the syndrome [77,78].

Lonafarnib is a farnesyltransferase inhibitor that binds reversibly to the CAAX recognition site of the enzyme, thereby preventing the farnesylation of progerin and its intercalation into the nuclear membrane [79].

Before this, inhibition of the farnesylation process, essential for the oncogenic functions of the RAS family, prompted the development of farnesyltransferase inhibitors (FTIs) as anti-cancer agents [80].

Fluoxetine, Fluvoxamine, Sertraline, Paroxetine, Citalopram, and Escitalopram

SSRIs, or selective serotonin reuptake inhibitors, represent a group of antidepressant drugs that function by elevating serotonin concentrations in the central nervous system, thereby alleviating symptoms of depression and managing additional psychiatric conditions such as anxiety disorders, obsessive-compulsive disorder (OCD), and post-traumatic stress disorder (PTSD).

By reaching out to their mechanism for the inhibition of actin polymerization, suppression of lamellipodia formation, reduction of FAK, Akt, and mTOR phosphorylation, increased mitochondrial Ca^{2+} influx, and the release of pro-apoptotic factors such as cytochrome c and caspase enzymes, these drugs have been shown to inhibit glioblastoma (GBM) growth and enhance apoptosis [81].

Nelfinavir

The primary indication of Nelfinavir was for the treatment of HIV [82].

In vitro experiments have revealed that endoplasmic reticulum stress induced by nelfinavir amplifies TRAIL-mediated apoptosis in glioblastoma (GBM) cells. This occurs through the inhibition of the phosphatidylinositol-3-kinase (PI3K)-AKT mechanistic target of rapamycin (mTOR) signaling pathway [81,83,84].

Table 1. Representative of drug repurposing in the treatment of rare diseases

Rare Diseases category	Disease	Drug	Primary Indication	Mechanism of Action	Reference
Genetic & Metabolic Diseases	Friedreich Ataxia	PPAR γ agonists	Type II diabetes	Increases frataxin mRNA and protein.	[85]
Rare Autoimmune / Immune Disorders	Behçet's syndrome	Colchicine	Gout	It was reported that the daily dose of 1.5 mg colchicine produced a significant reduction in erythema nodosum and arthralgia. In another clinical trial, colchicine demonstrated efficacy comparable to cyclosporine in controlling symptoms, while offering a safer profile and a more cost-effective treatment option for Behçet's syndrome.	[86,87]
Rare Neurological Disorders	Rett and Rett-like syndromes	Bumetanide	Managing various edematous conditions	Bumetanide inhibits the NKCC1 chloride importer, helping to normalize the disrupted GABAergic shift characteristic of Rett syndrome. Maternal administration in RTT models restores the impaired GABA shift in offspring, indicating potential therapeutic benefit for Rett and Rett-like disorders.	[88,89]
Rare Pulmonary Diseases	Idiopathic pulmonary fibrosis (IPF)	The small-molecule adrenoreceptor-inhibitor carvedilol	Hypertension	Treatment with carvedilol suppressed fibroblast metabolic activity. It downregulated core fibrotic markers such as α -smooth muscle actin and collagen I. Proteomic findings indicated disruption of extracellular matrix signaling through altered collagen and integrin synthesis.	[90,91]
Rare Infectious Diseases	Chagas Disease	Tyrosine kinase inhibitor imatinib 21	Anti-cancer	Imatinib was screened for activity against <i>Trypanosoma cruzi</i> the causative parasite of	[92]

				chage disease and exhibited <i>in vitro</i> trypanocidal effects, with EC50 values of 24.8 μ M for intracellular forms and 30.0 μ M for extracellular forms (Y strain), showing moderate selectivity (SI = 1.5).	
Rare Endocrine Disorders	Cushing's Disease	Bexarotene	Cutaneous T-cell lymphoma	Bexarotene acts on Nur77 in pituitary adenoma cells, promoting the formation of the Nur77-RXR α complex. This reduces POMC expression, leading to decreased ACTH synthesis and inhibition of tumor growth. Its effect is stronger when combined with lapatinib.	[93]
Rare Dermatological Diseases	Pemphigoid Diseases	Doxycycline	Antibiotic	Although the exact mechanism of doxycycline is unclear, it has been reported to regulate the activation of metalloproteinase-9 (MMP-9) in certain organs, suggesting that doxycycline may represent therapeutic effects in bullous pemphigoid by modulating MMP-9 activity, since MMP-9 levels are elevated in bullous pemphigoid.	[94,95,96]
Ultra Rare Diseases	Fibrodysplasia Ossificans Progressiva	a. Saracatinib b. Rapamycin c. Palovarotene	a. Anti cancer b. Antibiotic c. Chronic obstructive pulmonary disease	a. Saracatinib inhibits the kinase activity of the mutant ALK2 receptor. b. Rapamycin suppresses mTOR signaling, reducing abnormal bone formation. c. Palovarotene blocks SMAD1/5/8 signaling, preventing ectopic ossification.	[97,98,99,100,101]

1.4. Computational drug repurposing (in silico drug repurposing)

The development of computational drug repositioning approaches (Figure 6) has been accelerated by the enormous growth of publicly available large-scale biological, biomedical, and electronic health-related data, as well as high-performance computing power, since drug repositioning is data-dependent for both known drugs and diseases [102]. Numerous attempts have been carried out by multiple scientists and researchers to computationally investigate the possibility of repositioning medications for the discovery of new indications, with varying degrees of success and efficacy. [4].

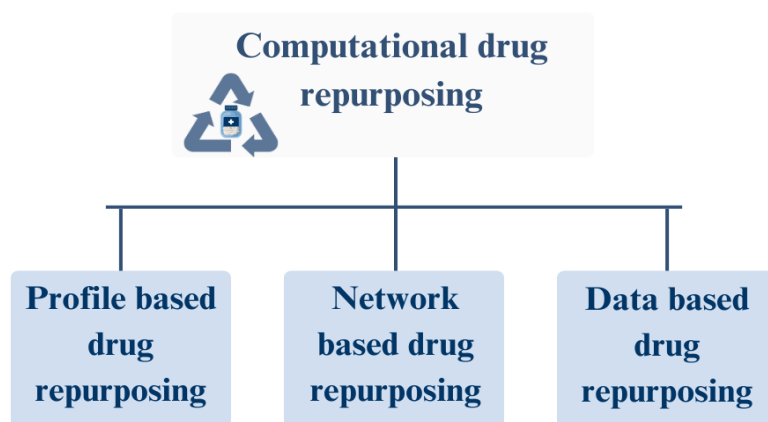


Fig. 6. Computational drug repurposing approaches include three approaches: Profile based drug repurposing, network-based drug repurposing and data-based drug repurposing

Computational drug repurposing provides fast results, reduced costs, and greater accuracy by screening compounds rapidly and predicting their activity through modeling such as quantitative structure-activity relationship (QSAR). In addition, it integrates a large amount of biological information, offers access to targets that may not be accessible, and optimizes the properties of compounds, making it a powerful tool in modern drug discovery [103].

Computational drug repurposing faces significant challenges, such as the inconsistent integration of data, the limitations of the systems used, and legal or clinical impediments that slow development. Future progress will be aided by improvements in AI, access to real-world data, personalized approaches to drug discovery, and collaboration among regulatory authorities, academia, and industry [104].

Computational drug repurposing techniques

Computational drug repurposing has developed rapidly in recent years, using artificial intelligence (AI), big data analytics and systems biology to uncover new therapeutic applications for existing drugs.

1. Artificial intelligence and machine learning approaches

AI and machine learning have become central to modern drug repurposing approaches [105]. These approaches utilize large-scale biomedical data to detect hidden drug-disease associations. Deep learning models, such as graph neural networks and autoencoders, have been particularly effective in handling complex biological data and chemical features to predict new drug uses [106].

2. Network-based approaches

Network-based methods simulate interactions in biological systems using protein-protein interaction (PPI) networks, gene regulatory networks and drug–target networks [107]. By examining the proximity of drug targets to disease-related genes or proteins within these networks, researchers can prioritize potential repositioning candidates [108].

3. Transcriptomics and gene expression analysis

This technique compares gene expression profiles of diseases with drug-induced gene signatures [109]. The goal is to identify drugs that reverse disease-associated gene expression patterns. Advances in transcriptomic platforms and analysis tools have made this approach more reliable and scalable [112].

4. Natural language processing (NLP) for literature mining

NLP techniques have been used to extract valuable insights from the large body of biomedical literature. By processing unstructured text data, NLP algorithms can identify previously unrecognized drug-disease associations, adverse drug reactions, and potential repurposing candidates. This approach leverages the wealth of existing scientific knowledge to inform repurposing strategies [108].

5. Deep learning for predictive modelling

Deep learning models have been applied to predict pharmacological properties of drugs and their potential repurposing opportunities [111]. By training on large datasets of drug characteristics and biological activities, these models can accurately predict drug efficacy and safety profiles in new therapeutic contexts [110].

2. Conclusion

Using already approved drugs for new medical purposes enriches the medical field by providing an efficient way to address treatment needs, especially in countries with limited healthcare resources, as the drug repurposing approach shortens timelines and reduces financial burdens. Drug repurposing is essential for rare diseases, offering faster and more accessible treatment options despite limited research resources and funding. This could be highly beneficial in cases of health crises, as was the case with COVID-19. This approach is also suitable for rare diseases, as it could be considered cost-friendly. Computational techniques have further strengthened repurposing efforts by enabling efficient analysis of complex biological data. As technology advances, the integration of bioinformatics and drug repurposing is expected to play an increasingly vital role in expanding treatment options and supporting global health initiatives.

3. Conflicts of interest

N.A.

4. Formatting of funding sources

N.A.

5. Acknowledgments

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