International Journal of Applied Pharmaceutics

ISSN- 0975-7058 Vol 16, Issue 3, 2024

Review Article

REVITALIZING THERAPEUTICS: DRUG REPURPOSING AS A COST-EFFECTIVE STRATEGY FOR DRUG DEVELOPMENT

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Received: 09 Oct 2023, Revised and Accepted: 01 Feb 2024

ABSTRACT

The process of developing new drugs is known for being drawn-out, expensive, risky, and having a high attrition rate. Drug repurposing has grown in favor recently as a practical way to speed up the development of new medicines while reducing the costs and time constraints associated with traditional drug research. The description of this study's pharmacological repurposing highlights its promise as a practical method to fill gaps in the market and revitalize treatment options. This review provides a full analysis of the ground-breaking tactic of repurposing medications, supported by numerous cases that demonstrate its revolutionary potential. We examine instances of repurposed drugs, such as thalidomide, sildenafil, and metformin, that have performed astoundingly well in a range of therapeutic settings despite being used outside of their original scope.

Overall, the paper's main goal-to study pharmacological repurposing as a potentially successful strategy for revitalizing treatments-is, succinctly summarized in this abstract. It highlights the potential benefits of this approach and how it might be used in the pharmaceutical industry's ongoing quest for more inexpensive and effective medicine development.

Keywords: Drug repurposing, Oncology, Anthelmintics, COVID-19, M. Tuberculosis and Sildenafil

DOI: https://dx.doi.org/10.22159/ijap.2024v16i3.49581 Journal homepage: https://innovareacademics.in/journals/index.php/ijap

INTRODUCTION

Despite improvements in technology and our understanding of human disease, we have seen far slower than anticipated progress in developing new therapeutics [1, 2]. It has been calculated that less than a dollar of value is generated for every dollar spent on research and development (R and D) on average [3]. Due to the increasing cost and length of time needed for new medication development, this may make the pharmaceutical business a less desirable alternative for investors.

Finding new medical uses for already approved, abandoned, shelved, and experimental drugs is a process known as drug repurposing, also known as drug repositioning, drug reprofiling, indication expansion, or indication shift. Although this tactic is not new, it has gained significant traction in the last ten years: around one-third of recent approvals are related to drug repurposing, and repurposed medications today account for about 25% of the pharmaceutical industry's yearly income [4]. The earliest stages of clinical trials can be omitted because the drug's efficacy, safety, and toxicity are already known, which reduces their cost and duration. A new drug must be developed for around 15 y before it can be sold, although repurposed drugs can be developed faster and for less money [5].

Existing compounds are those that have undergone successful Phase I or Phase II clinical studies and have a demonstrated safety and tolerability profile. As a result, a prospective repurposing medicine will have a well-established safety and toxicity profile and will have gathered data in preparation for regulatory approval [6]. The current review provides an overview of methods currently employed for repurposing and discusses case studies that demonstrate the effectiveness and utility of drug repurposing as evidenced by the significantly shorter development time for new drugs as a result of the availability of all pertinent clinical and toxicological data. This article discusses various repurposing strategies and the accompanying difficulties [7].

As we delve further into this review, we will cover successful case studies, various tactics employed in drug repurposing, as well as the difficulties that come with this method. By shedding light on the drug repurposing industry, we hope to shed light on its enormous potential to treat a variety of ailments, ultimately enhancing patient outcomes and altering the pharmaceutical industry.

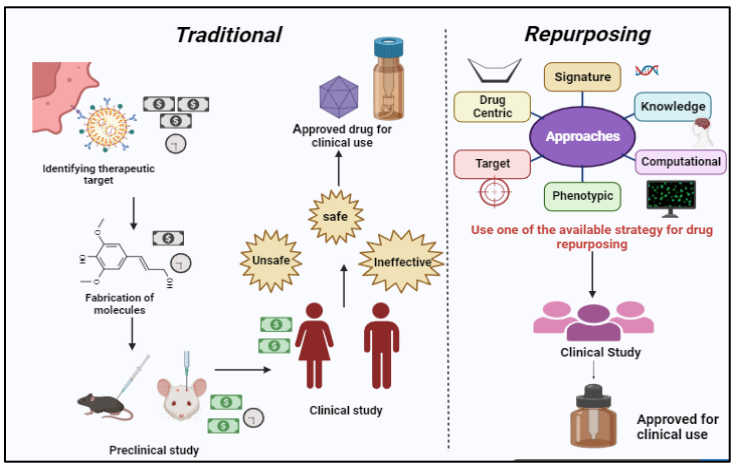

Fig. 1: Illustration of traditional method and drug repurposing

Significance of drug repurposing in healthcare

A new medicine must adhere to strict guidelines in order to be sold. Due to the various physicochemical features of the chemical entities and the difficulty of scaling up the manufacturing, it takes a considerable investment to identify a medicine and subsequently develop it [8–10]. A key strategy in drug development is drug repurposing. According to some statistics, between 2007 and 2009, the US Food and Drug Administration (FDA) authorized around 30–40% of novel pharmaceuticals and biologics that can be classified as repurposed or repositioned products [11].

Many experts believe that repurposing medications can be more efficient than standard drug development techniques in terms of speed, cost, safety, and effectiveness. This is mostly due to the fact that since the initial stages of development that establish medicine safety have already been completed, researchers can skip them [12]. However, it could be challenging to pinpoint exactly how much time, risk, and money are saved due to some contradicting information [13].

The preclinical, pharmacokinetic, pharmacodynamic, and toxicity characteristics of the drug are all known, which lowers the risk of compound development and is one of the key benefits of a drug repurposing procedure. As a result, the medicine can be used in Phase II and III clinical studies quickly, resulting in lower development costs [14], a higher return on investment, and a shorter development period [15]. From the standpoint of intellectual property (IP) and patent protection, drug repurposing is also intriguing because, assuming the new use is not specifically stated and supported by the original patents, patent protection for a new use of an existing drug whose composition of matter patents are still in force may be obtained [16].

One effective example of repurposing is the phosphodiesterase type 5 (PDE5) inhibitor sildenafil. The FDA granted sildenafil approval for its use in treating erectile dysfunction despite the fact that it was initially created to treat hypertension. Later, it was modified to treat the uncommon condition pulmonary hypertension [17].

Challenges in drug repurposing

Despite recent growth in popularity, there are fewer applications than anticipated due to several challenges to effective deployment.

- **Lack of comprehensive database**: The lack of centralized, comprehensive databases with thorough information on pharmacological characteristics, target interactions, and illness connections is one of the main obstacles to medication repurposing. Researchers frequently encounter difficulties locating trustworthy, current data, which makes it difficult for them to discover prospective targets for efforts at repurposing [18].

- **Intellectual property and patent issues:** Repurposing existing drops for new indications is significantly hampered by the complex web of intellectual property rights. The scope of prospective possibilities for repurposing can be constrained by existing patents, which can prevent the research of specific chemicals [19].

- **Clinical trial design and biomarker identification:** The selection of suitable dosages, patient demographics, and endpoints is necessary for the design of efficient clinical trials for repurposed medications. Finding trustworthy biomarkers to predict therapy effectiveness or illness response is also important but frequently difficult, which has an impact on the approval of repurposed treatments [20].

- **Regulatory challenges:** Regulatory organizations want solid proof of a drug's efficacy and safety. It can be challenging to meet these requirements, especially when repurposed medications are approved. Meeting these requirements can be challenging, especially when repurposed drugs don't follow conventional development pathways. This calls for creative solutions and cooperative efforts from researchers and regulators [21].

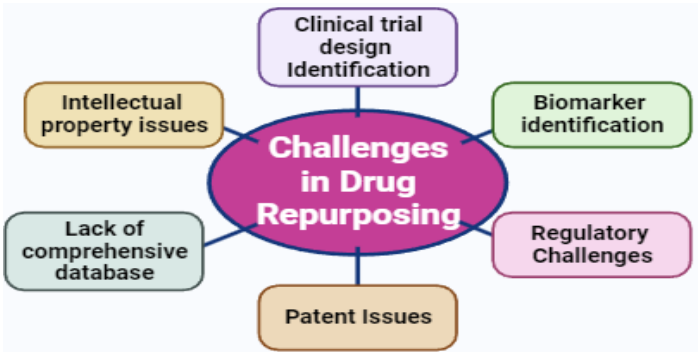

Fig. 2: Challenges in drug repurposing

Strategies for accelerating drug repurposing

- ***In silico* models**-Using bioinformatics or *in silico* models, we can find the intricate connections between medications, targets, and disorders that are necessary for repurposing [22].

- **Target docking**–Finding polypharmacological drugs that act on several targets and can treat multifactorial disorders like cancer and neurological diseases requires the use of high-throughput screening tools [23].

- **Artificial intelligence** (AI)-AI makes data more accessible. Finding drug interactions, side effects, mechanisms of action, and gene regulators by extensive literature data mining helps speed up drug development [24].

Infectious diseases: repurposing for rapid response

Anthelmintics for drug repurposing

A class of substances known as anthelmintics exhibit anti-infective activity against helminths that colonize the human intestine [25]. Anthelmintics come in a number of chemical forms and work by altering the metabolism of the parasite (worm) or paralyzing it so that the parasite can be killed by the immune system of the host. It has been shown that several anthelmintics have the ability to block important oncogenic pathways, including Wnt/b-catenin and STAT3 [25]; therefore, their application for cancer treatment has been considered.

The updated knowledge regarding anthelmintics with anti-cancer activity and their potential use as anti-cancer medicines (i.e., repositioned pharmaceuticals) is summarized in this paragraph.

The anti-tumor properties of albendazole have been proven *in vitro* against hepatocellular carcinoma (HCC) and colorectal carcinoma (CRC), as well as *in vivo* against a xenograft model of peritoneal carcinomatosis. Additionally, the drug has demonstrated antiproliferative effects on tumor cells, including those resistant to other microtubule-targeting medications (such as leukemia and ovarian cancer cells) [26].

Table 1: list of anthelmintic that have been repositioned in oncology and have shown to have anti-cancer effects

Drug name	New indication	Comments	Reference
Ivermectin	Colon and Lung Cancer	Block the T-cell factor (TCF) family transcriptional factor's main signaling pathway, which is influenced by the wingless-related integration site (wnt) gene.	[26]
Levamisole	Hepatocellular carcinoma	Boost the tumor necrosis factor levelDeath receptor 4 (DR4)-independent apoptosis rate by limiting the phosphorylation of c-Jun N-terminal kinase (JNK)-related apoptosis-inducing ligand (TRAIL)	[25]
Mebendazole	Colorectal cancer	Mebendazole inhibits a number of processes that help tumors grow, including angiogenesis, the polymerization of tubulin, pro-survival pathways, and matrix metalloproteinases.	[27]
Praziquantel	Anticancer	When combined with paclitaxel, praziquantel inhibits cell growth and induces death in a variety of cancer cells, including CRC DLD-1.	[25]

Drug repurposing for *mycobactrium tuberculosis*

The bacterium *mycobacterium tuberculosis*, which causes tuberculosis (TB), is now regarded as the world's most common cause of bacterial infection-related death [28]. According to recent estimates, 10 million individuals worldwide contract M. TB each year, infecting more than 30% of the world's population [28]. Fortunately, the finding of novel therapeutic options against extensively drug-resistant (XDR-TB) strains of tuberculosis, which are causing infections that are incurable, is currently seen as a very promising strategy through pharmacological repurposing of antibiotics [29]. Although there are a number of experimental and *in silico* methods to uncover drugs with repurposing potential, knowledge-based strategies, molecular docking, and phenotypic screening are the most frequently employed [30].

Metformin, a medication for type 2 diabetes, has been scientifically shown to have anti-tuberculosis effects (table 2). Particularly, metformin enhances phagosome-lysosome fusion and increases ROS concentration during the oxidative burst, preventing bacterial colonization, reducing lung damage and chronic inflammation, enhancing the immune response against tuberculosis, and enhancing the activity of conventional anti-tuberculosis medication [31-33].

Table 2: List of drugs repurposed against M. tuberculosis

Repurposed drugs	Primary mechanism of action	Reference
Transition metals (Cu2+and Co2+)	Interfering with urease	[36]
Eltrombopag	Inhibition of Zmp1 and PDF	[37]
Metformin	phagosome–lysosome fusion	[31-33]
Simvastatin	HMG-CoA inhibition	[38]
Doxycycline	Matrix metalloprotease inhibition	[39, 40]
Gefitinib	EGFR inhibition	[41]

Similar to the way statins are used to treat hypercholesterolemia and atherosclerotic cardiovascular disease, they are also a very promising source of antimicrobial substances that are effective against M. tuberculosis [34]. Simvastatin, for instance, can lessen the amount of germs present inside cells when taken with other antitubercular drugs [35, 34]. This drug's mechanism of action appears to include inhibiting the 3-hydroxy-3-methylglutaryl-coenzyme enzyme.

Drug repurposing for dengue

The most common virus spread by mosquitoes in the world today is dengue. Four antigenically different serotypes of the dengue virus (DENV), notably DENV1-4, are the cause of this viral illness that is spread by mosquitoes. There is still a need for an efficient antiviral treatment for Dengue Virus infection, and several replicative cycle inhibitors are now being investigated. The repurposing of licensed medications used for other diseases to find novel inhibitors of this pathogen represents an appealing approach for a swift therapeutic intervention [42], given the rapid spread of DENV and the typical timescale necessary for bringing a new drug to market. The repositioning of well-known medications for the prevention of DENV replication will be described in detail in the following paragraphs through a number of exemplary examples.

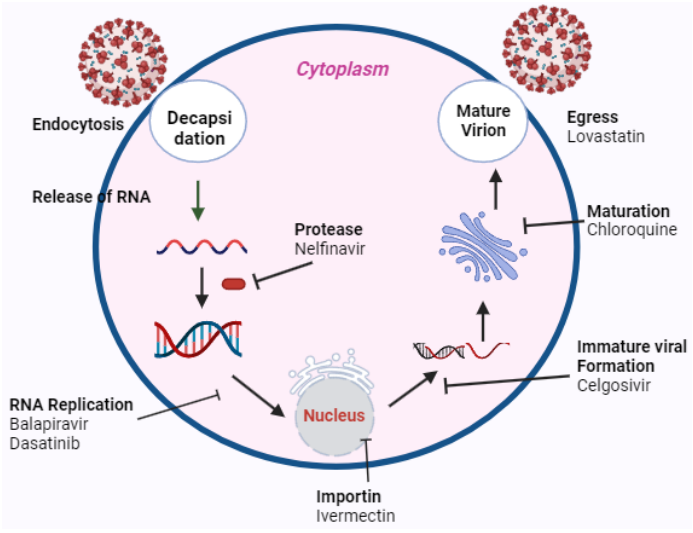

Fig. 2: Life cycle of dengue and steps inhibited by repurposed drug

A powerful protease inhibitor, nelfinavir (AG1343) is effective against human immunodeficiency virus type 1 (HIV-1) (24). An effort to reposition peptidomimetics against Nelfinavir and other viral protease inhibitors, such as Lopinavir and Ritonavir, were chosen as treatments for dengue virus infection using computer-aided drug design and molecular modeling [43]. Positive interactions between Nelfinavir and DENV NS2B-NS3 protease were found using molecular docking calculations and molecular dynamics simulations [42].

Similar to this, the antimalarial drug chloroquine has also been used to treat rheumatoid arthritis, systemic lupus erythematosus, and amebic liver abscesses by systemic therapy [44]. In the DENV scenario, chloroquine was utilized in a number of medication repositioning trials. Plaque test and qRT-PCR results demonstrated that it can prevent Dengue Virus Type 2 multiplication in Vero cells at a dose of 5 g/ml (the cytotoxic level is 500 g/ml) [45].

Table 3: List of repurposed drugs against dengue virus

Drug	Original indication	Activity against dengue virus	Reference
Nelfinavir	Antivirals	NS2B-NS3 protease inhibition	[42, 43]
Balapiravir	Antivirals	RNA-dependent RNA polymerase inhibition	[46, 47]
Chloroquine	Antimalarics	Inhibits low-pH dependent entry steps	[45]
Amodiaquine	Antimalarics	Inhibits low-pH dependent entry steps	[48]
Celgosivir	Antidiabetics	Accumulation of NS1 in ER	[49, 50]
Montelukast	Antihistamines	Reduction of vascular leakage DENV-induced	[51]
Dasatinib	Anticancers	Src Fyn kinases inhibition	[52]

Drug repurposing for breast cancer

Globally, physical examinations, breast scans, and tissue biopsies are used to diagnose breast cancer, one of the most prevalent cancers in women. 2018 saw a total of 2.089 million new instances of breast cancer, of which 627,000 cases resulted in death [53]. About 15% of all female cancer deaths worldwide were caused by this [53].

In India, there were 87,090 reported fatalities and 162,468 new cases of breast cancer in 2018, according to NICPR. According to one of the most current studies on the risk of breast cancer in India, 1 in 28 women will have breast cancer throughout their lifetime. In India, the incidence/mortality ratio is 0.48, which is more than in other nations [68].

The therapy options are quite expensive and have negative side effects. Repositioning older, off-patent, non-cancer medications with clinical approval and known targets into newer indications is analogous to employing older weaponry in a more recent conflict. Over the past ten years, various drugs have been repositioned for the treatment of breast cancer, including alkylating substances, anthracyclins, antimetabolites, CDK4/6 inhibitors, aromatase inhibitors, mTOR inhibitors, and mitotic inhibitors [54].

The PI3K/AKT/mTOR signaling pathway is inhibited by the mTOR kinase inhibitor everolimus. Everolimus was initially licensed for the treatment of pancreatic cancer in 2011, renal transplant immunosuppression, and renal cancer in 2009. Following the successful conclusion of a phase III clinical trial known as "Breast Cancer Trial of Oral Everolimus-2 (BOLERO-2)" that included everolimus in combination with exemestane, everolimus was approved by the US FDA in 2012 for the treatment of HR+, HER2-advanced metastatic cancers that are resistant to letrozole or anastrazole [55, 56].

A N,N',N''-triethylenephosphoramide (TEPA) derivative called thiotepa was introduced in 1953 as an immunosuppressive medication for transplantation in hematological illnesses [57]. The medication was subsequently advised for solid tumors in 1959 [58] and breast cancer (0.3 to 0.4 mg/kg IV repeated every 1 to 4 w) in 1963.

Drug repurposing for COVID-19

The use of repurposed medications has been used to treat a number of epidemic diseases, and the coronavirus disease 2019 (COVID-19) pandemic is one such instance [59]. A new coronavirus known as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is the source of COVID-19 [59]. A key phase in the infection process is the interaction of the viral spike protein with the human ACE2 and TMPRSS2 enzymes, according to the evidence for the mechanism of infection, which was also derived from earlier investigations on coronaviruses. The peptidase domain of the human ACE2 enzyme interacts to the receptor-binding domain of the spike protein [60].

Remdesivir is thought to be a promising drug candidate for repurposing against COVID-19 based on the existing understanding of its use in SARS-CoV2 infection. A nucleoside analog called Remdesivir (GS-5734) was initially created by Gilead Sciences Inc, a biopharmaceutical company with headquarters in the United States, to combat Ebola viruses. Despite the medication's ineffectiveness against the Ebola virus, preliminary findings from non vitro and *in vivo* preclinical research, as well as case reports, point to its effectiveness against the SARS-CoV2 virus [61-63].

Favipiravir is a prodrug that is produced by T-1105's pyrazine moiety being chemically modified. Because there is currently no proven cure for COVID-19 and there is a strong focus on repurposing existing medications because to the lengthy time it would take to develop new ones, favipiravir is swiftly becoming the medicine of choice. One new repurposing medication for the treatment of novel viruses is favipiravir [67].

The primary proteases of the coronavirus and HIV are aspartic and cysteine, respectively, in the lopinavir-ritonavir combination. It has been found that the non-specific protease inhibition of protease inhibitors used in HIV therapy makes them effective against SARS-CoV. The SARS-CoV2 and HIV-1 proteases have comparable binding energies to lopinavir [64]. Significant virus clearance has been accomplished in SARS-CoV2 patients with lopinavir-ritonavir treatment [65,66]. A 47-year-old patient quickly improved with extra lopinavir and ritonavir tablet therapy after failing to respond to methylprednisolone and interferon therapy.

CONCLUSION

The identification of new indications for currently existing pharmaceuticals (drug repositioning) could improve and boost the actual number of new medicines that reach the market because the traditional drug-discovery technique is frequently a lengthy, difficult, and expensive procedure. Thanks to the faster drug discovery route on which this technique is based, drug repositioning strives to meet the need for new medications for a given disease, notably for developing diseases or for those yet without treatment. For usage as antitubercular medicines, certain substances have previously received approval or are in the final phases of clinical testing. The most effective medications target the activation or inhibition of host genes that enable bacterial colonization, which may also prevent the selection of new strains that are resistant to antibiotics.

FUNDING

Nil

AUTHORS CONTRIBUTIONS

All authors contributed equally

CONFLICT OF INTERESTS

The authors declare that there are no conflicts of interest in this review article.

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