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ADVANCES AND DEVELOPMENTS IN DRUG REPURPOSING; STATE OF ART

Sarmad dheyaa noori[1*], Mais Mazin Al-Hamdani[2] and Amira B kassem[3,4]

[1]*Department of Pharmaceutical Chemistry, College of Pharmacy , Al-Ayen University*
[2]*Department of Pharmaceutics, College of Pharmacy , Al-Ayen University*
[3]*Department of Clinical Pharmacy and Pharmacy Practice, Faculty of Pharmacy, Damnhour University*
[4]*Department of Clinical Pharmacy, Collage of Pharmacy, Al-Ayen University*

Although the rapid progress in science and technology, developing new drugs from scratch has been expensive in recent decades. As a result, drug-repurposing, which implies seeking new utilizes for presently approved drugs instead of discovering new drug compounds, has emerged as a substitution tool to speed up the drug development procedure. Nowadays, drug repurposing accounts for 30% of newly approved drugs. With the explosive growth of pharmacological compounds' molecular, genomic, and phenotypic data, a novel area of drug repurposing called computational drug repurposing has emerged. This review provides an overview of recent progress in computational drug repurposing, including repositioning approaches, commonly used computational methods, validation techniques for repurposing studies, and the remaining encounters in computational repurposing. In this Review, we outline methods for drug repurposing (also known as drug repositioning), talk about difficulties encountered by the repurposing community, and suggest creative solutions to these issues. addressed to aid in maximising the benefits of medicinal repurposing.

Keywords: *Drug repurposing, nanosystem, anticancer, bacterial infection, fungal infection*

INTRODUCTION

Despite significant advancements in technology and a greater understanding of human diseases, the translation of these benefits into therapeutic breakthroughs has been slower than anticipated[1]. The global pharmaceutical industry faces numerous challenges, including high rates of attrition, extended timelines to introduce new drugs to the market for some therapeutic areas, and evolving regulatory requirements, all of which can contribute to increased costs[2]. Because of rising expenses and the longer time of new drug research, less than a dollar of profit is returned for every dollar invested in development. This could potentially makes the pharmaceutical industry a less appealing option for investors [3].

Drug repurposing, which is also referred to as drug repositioning, implies identifying novel medical applications for drugs that are already recognized. This includes approved, discontinued, and experimental drugs[4]. Although the technique is not new, it has acquired massive popularity during the last decade. Approximately one-third of recent drug approvals are a result of drug repurposing and repurposed drugs currently account for about 25% of the yearly profits generated by the pharmaceutical industry [5].

Because drug repurposing depends on pre-existing information, such as pharmacokinetic and manufacturing data, the required expenses can be greatly reduced. One of the key advantages of repurposed candidates is that, in many cases, they have previously established appropriate safety in preclinical simulations

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*Corresponding author: Sarmad dheyaa noori, E-mail: sarmaddheyaa@gmail.com

and, at the very least, early-stage human trials [6]. This makes them less likely to fail from a safety perspective in subsequent efficacy trials without drug-disease interactions being identified. In the case of authorized medicines, they have already conceded clinical trials and regulatory analysis, and they have experienced post-marketing investigation [7].

Drug repurposing strategies

Knowledge-based repurposing

One approach to drug repurposing involves creating models that use information related to drugs, such as their goals, chemical structures, and opposing effects, to make predictions about unknown targets, or disease mechanisms[8]. This approach encompasses three types of drug repurposing: target-based, pathway-based, and target mechanism-based[9].

Target-based drug-repurposing

Target-based drug repurposing involves using high-throughput and/or high-content screening (HTS/HCS) of drug compounds, followed by in silico screening from drug libraries, such as ligand-based screening or docking, to identify potential drugs for proteins or biomarkers of interest [10]. Unlike blinded search or screening methods that do not use biological or pharmacological information, target-based repurposing directly links targets with disease mechanisms, which improves the likelihood of drug discovery [11]. One advantage of this approach is the ability to screen almost all drug compounds with known chemical structure. However, target-based methods are limited in their ability to identify unknown mechanisms beyond the known targets[12].

Pathway-based drug-repurposing

It involves utilizing information on metabolic pathways, signaling pathways, and protein-interaction networks to forecast the similarity among a disease and a potential drug [13]. One example of this is using omics data obtained from humans or animals to reconstruct disease-specific pathways that can perform as novel targets for repurposed drugs[14].

Target mechanism-based drug-repurposing

It involves combining signaling pathway data, and protein interaction networks to identify mechanisms of action for drugs [15]. This approach is motivated by the need for precision medicine, which has become increasingly important. The benefit of these repurposing methods is that they aim to determine mechanisms that are correlated not only to diseases or drugs but also to specific drug treatments for those illnesses [16].

Phenotype-based repurposing

Phenotypic information has emerged as a new resource for drug repurposing. Recently systems approaches have increasingly utilized this type of information to identify genetic attributes correlated with human diseases [17]. Natural language processing techniques directed to electronic health records can also uncover extra adverse drug actions that were not detected throughout drug development. For instance, mining EHRs has led to the discovery that metformin can be repurposed for cancer treatment[18].

Drug repurposing in cancer prevention

Aspirin

Aspirin is a non-steroidal anti-inflammatory drug and broadly employed due to its analgesic, and antipyretic properties [19]. Despite its primary use, there is documented evidence that daily intake of low-dose aspirin has a protective effect against cardiovascular disease. This is because aspirin inhibits COX-1, which is implied in the synthesis of Thromboxane A2, a key factor in platelet aggregation, resulting in anti-platelet and anti-thrombotic effects[20]. In addition, several experimental studies have demonstrated a strong association among inflammation and cancer, which suggests that the anti-inflammatory aspects of aspirin contribute to its cancer protective effects. Inflammatory processes are considered a major driver of carcinogenesis for certain types of cancer, such as colorectal cancer and hepatocellular carcinoma [13]. Notably, a previous study found that use of aspirin decreased the incidence of colorectal, biliary, and breast cancers. This was achieved by systematically relating randomized trials with case-control studies[21]. Furthermore, a decrease in the risk of metastasis was observed. While less remarkable, similar effects have been documented for prostate and lung cancer as well[22].

The anti-cancer effect of aspirin is believed to be due to its inhibition of COX enzymes that promote carcinogenesis by synthesizing PGE2. These enzymes are responsible for the limiting stage in the synthesis of various prostaglandins, which exerts pro-inflammatory and immunosuppressive effects[23]. Tumor tissue from various types of cancer contains elevated levels of PGE2, which has been shown to facilitate malignant alteration. Therefore, aspirin's ability to inhibit COX enzymes and reduce PGE2 production is believed to be the mechanism behind its anti-neoplastic effect [24].

Metformin

It is a widely prescribed for the treatment of type 2 diabetes. However, diabetic patients have an elevated risk of acquiring various types of cancer. A meta-analysis of 20 studies in 2007 revealed that women with diabetes have a 20% higher risk of developing breast-cancer, as well as an increased risk of cancer-related death [25]. Additionally, other studies have linked type 2 diabetes to the progression of non-Hodgkin's lymphoma, bladder cancer, and endometrial cancer[26]. In general, improving glycemic control is expected to have a protective effect against the development of cancer.

Through extensive research on preclinical models, it has been uncovered that metformin modulates several molecular pathways, either directly or through downstream targets, following in a decrease in the growth and proliferation of tumor cells. Among the possible significant mechanisms that enable the anti-cancer effects of metformin is the inhibition of mTOR (mammalian target of rapamycin) in tumor cells[27]. Further, another clinical study proved the capability of metformin for treating breast cancer in non-diabetic patients[28].

Statins

By blocking the rate-limiting enzyme 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) and the mevalonate pathway, which is the first step in cholesterol manufacture, statins are a class of medications that are frequently recommended to treat lipid diseases [29]. Importantly, evidence suggests that inhibiting HMG-CoA may also have a protective effect against cancer. This is because the mevalonate pathway produces Geranylgeranyl pyrophosphate (GGPP) and farnesyl pyrophosphate (FPP), which are employed for prenylation of proteins, a procedure critical for addressing these proteins to the cell membrane. Interfering with these steps may disrupt cell cycle progression and cell proliferation, thereby facilitating anti-neoplastic effects [30].

It should be highlighted that the mechanism of action for statins' hypolipidemic effect is through the inhibition of HMG-CoA reductase. However, in bacterial cells, HMG-CoA reductase plays a crucial role in the biosynthesis of isoprene[31]. Therefore, it is doubtful that the antibacterial action of statins can be ascribed to the known mechanism of action. Other potential mechanisms, such as the cytotoxic properties of certain statins, notably atorvastatin and simvastatin, may be responsible for their antibacterial effects [32]. Investigates have established that statins can destroy cell growth and induce apoptosis, which may be related to their reported antibacterial activity. It is worth noting that in vitro studies have shown that statins, particularly simvastatin, exhibit antimicrobial impacts at concentrations higher than those used clinically. Therefore, it is unlikely that statins have a significant antimicrobial effect in patients, but this unexpected class effect warrants further investigation, including assessing of statins and their metabolites[33].

Drug repurposing in bacterial infection

Dexamethasone

Dexamethasone, a steroid medication, possesses strong anti-inflammatory and immunosuppressive properties and has been utilized to treat multiple systemic and localized skin ailments [34]. Its effective anti-inflammatory capabilities additionally act as an inhibitor of SEB-induced inflammatory cytokines, including TNF-α, IFN-γ, IL-1α, IL-2, and IL-6, safeguarding mice from hypothermia and shock[35].

Nicotinamide

Beyond its usage as a dietary supplement, nicotinamide (vitamin B3) lowers inflammatory cytokines including IL-1, IL-6, IL-8, and TNF- and is used to treat inflammatory skin conditions such atopic

dermatitis and acne vulgaris[36]. Mice with staphylococcal septic shock demonstrated enhanced survival rates when administered a combination of nicotinamide and nafcillin [37]. Despite its immune modulation activity, the precise molecular mechanism underlying the effects of nicotinamide remains uncertain. However, a separate investigation indicated that nicotinamide amplifies S. aureus elimination in vivo by regulating host factors. Host factors, including the phagocytic capacity of monocytes and macrophages, play a significant role in bacterial clearance. Monocytes and macrophages with higher levels of anti-staphylococcal peptide expression, such as lactoferrin (LTF) and cathelicidin, are better able to phagocytose and eliminate bacteria [38]. CCAAT/enhancer-binding protein ε (C/EBPε), a transcription factor specific to myeloid cells, regulates the expression of antimicrobial peptides (LTF and cathelicidin) in phagocytic cells. Nicotinamide enhances C/EBPε activity in neutrophils, resulting in up to a 1000-fold increase in the killing of S. aureus in vivo. Therefore, by modulating C/EBPε expression, the phagocytic ability of certain immune cells can be improved, leading to increased bactericidal activity. Additionally, nicotinamide lowers staphylococcal enterotoxin (SEB)-induced responses. It reduces SEB-induced T-cell proliferation and the release of inflammatory cytokines such as IL-2 and IFN-γ, protecting mice against SEB-induced toxicity. Consequently, the potent immunomodulatory activity of nicotinamide, which includes enhancing S. aureus killing and reducing SEB-induced inflammation, could have therapeutic potential in the treatment of staphylococcal infections[39].

Ibuprofen

Ibuprofen, a phenylpropionic acid derivative, has analgesic, antipyretic, and anti-inflammatory effects in both humans and animals [40]. Ibuprofen is commonly administered in the context of bacterial infections to alleviate the inflammation caused by the immune system response, rather than for its antibacterial properties [41]. Nevertheless, a previous study illustrated the antibacterial effects of ibuprofen [42]. In vitro studies were conducted to evaluate the impact of ibuprofen on bacterial growth. The results showed that it hindered the growth of Gram-positive bacteria, including *Bacillus subtilis* and *S. aureus*, with a Minimum Inhibitory Concentration (MIC) of 1.25-2.5 mg/mL. Ibuprofen also demonstrated comparable antibacterial activity against three Gram-negative human pathogens - *Escherichia coli*, and *Enterobacter sp*. - with an MIC range of 2.5-5 mg/mL[43]. The *in-vitro* antibacterial aspects of ibuprofen are pH-dependent, exhibiting greater potency in acidic conditions. *In-vivo* studies using murine infection models have established that ibuprofen is highly effective with good bioavailability. In one study, mice infected with *P. aeruginosa* PAO1 were administered an oral dose of 0.75 mg ibuprofen, resulting in a blood serum concentration of 124.22 ± 15.40 µg/mL after 1 hour. The study also assessed the in vivo antibacterial efficacy of ibuprofen in infected mice by evaluating the bacterial burdens in their lungs and spleens. Following treatment, a significant reduction in bacterial burdens was observed in the lungs and spleens of mice treated with ibuprofen, with a 1 log10 reduction in both organs compared to the control group ($P = 0.0314$ for lungs, $P = 0.0096$ for spleen). Moreover, when the effect of ibuprofen on the survival of infected mice was evaluated, a significantly higher survival rate (92%) was observed in mice treated with ibuprofen compared to the control group ($P = .0386$) after 72 hours [43]. Recent studies have revealed that ibuprofen exhibits antitubercular properties, selectively inhibiting the growth of replicating, nonreplicating, and drug-resistant clinical isolates of *Mycobacterium tuberculosis* (Mtb). It has also supported potent effects in reducing bacillary loads in the lung tissue of mice infected with Mtb [44]. In addition, ibuprofen has been shown to eliminate the bacillary burden in necrotizing pulmonary granulomas by inhibiting tumor necrosis factor, thereby providing protection against the disease [45]. Furthermore, ibuprofen has been found to enhance treatment efficacy and exhibit synergistic effects with pyrazinamide in murine infection models. Therefore, it could serve as a viable option or adjunct in future antituberculosis (TB) regimens. In terms of safety and tolerability, previous clinical trials have shown that ibuprofen is well-tolerated with minimal adverse events. The FDA-approved daily dose of ibuprofen is 3200 mg,

and persisted administration results in a plasma C_{max} of 90.4 µg/mL [46], which is well above to achieve antibacterial action. Clinical trials have assessed ibuprofen's pharmacokinetic profile, revealing a short half-life of 3 hours and a favorable safety profile compared to other NSAIDs like aspirin or paracetamol, which are associated with irreversible liver or renal damage. These findings add weight to the argument for repurposing ibuprofen as an antibacterial agent.

Drug repurposing in fungal infection

Proton Pump Inhibitors

Antifungal medications target the plasma membrane H+-ATPase, an extensively studied enzyme that is found in the membranes of several fungi, including *Candida albicans*, *Saccharomyces cerevisiae*, and *Aspergillus Niger* [47]. Proton pump inhibitors that inhibit these pumps can function as antifungal agents or can help to reverse acquired resistance to azoles. Compounds such as omeprazole, and lansoprazole can block this pump, resulting in a range of antifungal effects. Omeprazole, for instance, has been shown to possess antifungal activity against Saccharomyces.[48]; CAN-296 had fungicidal activity against *Candida spp* [49]; the novel benzimidazole Ag 2000 inhibited the hyphae formation of *Candida albicans in vitro* [50] and a conjugated styryl ketone had potent fungicidal activity against yeasts and molds, including *Candida spp*., and *Aspergillus Niger*[51]. More data, especially animal models, are needed to confirm the in vitro activity.

Antineoplastic Agents

A highly effective chemotherapy agent called cisplatin is used to treat different kinds of solid tumours. Its propensity to produce DNA adducts, which cross-link with nearby purine residues, is primarily what gives it its cytotoxic effects. The medication inhibited the growth of Candida albicans in vitro [35] and demonstrated activity at dosages as low as 40 g/ml [52]. Pretreating cells with amphotericin B or miconazole increased the activity of cisplatinum in Candida albicans. Additional in vitro and in vivo research are required to corroborate this positive relationship, which may be caused by synergistic interaction. For *Candida* and *Trichosporon*, the MICs of methotrexate, bleomycin, and doxorubicin range from 500 to 1,500 g/ml[53]. Bleomycin and doxorubicin seem to have the greatest anti-*Candida tropicalis* activity among these drugs. Bleomycin is harmful to yeasts in vitro, however an animal model found little evidence of antifungal action[54]. *In vitro* tests against several *Candida spp*. and *Trichosporon* were conducted using a number of antineoplastic medications, including methotrexate, cyclophosphamide, and 5-fluorouracil alone and in combination with amphotericin B, flucytosine, and miconazole. However, the ideal medication ratios for producing synergy varied. It was shown that effective combinations were active against numerous fungus species. Generally, a polyene administered in combination with methotrexate, doxorubicin, or 5-fluorouracil shown a synergistic interaction against yeasts. This may be because amphotericin B caused membrane perforation, which allowed the second medicine to enter the cell. Contrarily, it was discovered that medications like cyclophosphamide and bleomycin counteracted the antifungal effects of the polyene[53].

Table 1: Examples of recently approved repurposed drugs.

Drug	Old Use	Repurposed Use	Nanosystem Fabricated
Propranolol Hydrochloride	Beta-Blocker	Spermicide	Invasoemes
		Infantile Hemangiomas	Colloidal Silicon Dioxide
Levocetirizine Dihydrochloride	Antihistaminic	Alopecia	Cationic Ceramide/Phospholipid Composite
		Bacterial Skin Infection	Terpesomes
Spironolactone	Diuretic	Hirsutism	Hyaluronic Acid Enriched Cerosomes
Pitavastatin	Hyperlipidemia	Wound Dressing	Nanocomposite Alginate Hydrogel
Atorvastatin	Hyperlipidemia	Antifungal	Liposomes
Metformin	Diabetes	Colorectal Cancer	Cubosomes

Drug repurposing formulated as nanocarriers

Propranolol hydrochloride is known as a beta-blocker that is used primarily for hypertension, angina, myocardial infarction, arrhythmias, and sinus tachycardia[55] was recently repurposed as topical spermicide for vaginal drug delivery[56]. Further, another study on propranolol hydrochloride using colloidal silicon dioxide dispersed proved its efficacy for treating infantile hemangiomas [57]. In addition, levocetirizine dihydrochloride which is well known as antihistaminic used as cationic ceramide/phospholipid composite as nanocarriers for effective management of alopecia[58]. Moreover, levocetirizine hydrochloride was recently approved its efficacy against bacterial skin infection with Methicillin-Resistant Staphylococcus aureus by formulating the drug into terpene enriched vesicles [4]. Another study performed by Albash et al. proved the enhanced repurposed effect of spironolactone for reducing hair production and as a treatment for hirsutism using hyaluronic acid enriched cerosomes[59]. Further, another study performed in human subjects proved the efficacy of the repurposed effect of spironolactone against acne using nanocarrier called phytosome[60]. Another investigation proved the efficacy of 3-D nanocomposite-alginate-hydrogel loaded with pitavastatin nanovesicles as a functional wound dressing with controlled drug release aspect [61]. In addition, Nour et al. performed another research proved the repurposed antifungal effect of Atorvastatin liposomes in a 3D-printed polymer film: a repurposing approach for local treatment of oral candidiasis[40]. Regarding metformin it was formulate as cubosomes as repurposed medication for targeting colorectal cancer **(Table 1)**[62].

Challenges in drug repurposing

Repurposing medications for new therapeutic applications are not without their drawbacks and difficulties. The small number of medications that can be used for repurposing is one of the biggest obstacles, which is partly caused by the high rate of failure in therapeutic development and approval. Out of the thousands of drug candidate applications that were received between 2010 and 2018, the FDA on average only approved 41 medicines annually. The rigorous evaluation procedure that is necessary to guarantee the safety and efficacy of medication candidates is the cause of this low approval rate. Because there aren't many new pharmaceuticals accessible for repurposing, drug repurposing studies are difficult to do. This is because there aren't many unique drugs released each year. The successful repurposing of pharmaceuticals can also be hampered by issues with regulations, patents, and the low efficacy of repurposed medications[3].

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أوجه التقدم والتطورات في مجال إعادة استخدام الأدوية

سرمد ضياء نوري[١*] – ميس مازن الحمداني[٢] – أميرة قاسم[٣،٤]

[١]قسم الكيمياء الصيدلية ، كلية الصيدلة ، جامعة العين

[٢]قسم الصيدلانيات ، كلية الصيدلة ،جامعة العين

[٣]قسم الصيدلة الإكلينيكية والممارسة الصيدلية ، كلية الصيدلة ، جامعة دمنهور

[٤]قسم الصيدلة الإكلينيكية ، كلية الصيدلة ، جامعة العين

على الرغم من التقدم السريع في العلوم والتكنولوجيا، إلا أن تطوير الأدوية الجديدة من البداية أصبح مكلفًا ويستغرق وقتًا في العقود الأخيرة. ونتيجة لذلك، ظهرت إعادة استخدام الأدوية، والتي تتضمن البحث عن استخدامات جديدة للأدوية الموافق عليها بدلاً من اكتشاف مركبات دوائية جديدة، كأداة بديلة لتسريع عملية تطوير الدواء. وفي الوقت الحاضر، تمثل إعادة استخدام الأدوية ٣٠% من الأدوية الموافق عليها حديثًا. ومع النمو المتفجر للبيانات الجزيئية والجينومية والظاهرية للمركبات الدوائية، ظهر مجال جديد لإعادة استخدام الأدوية يسمى إعادة استخدام الأدوية الحسابية. توفر هذه المراجعة نظرة عامة على التقدم الحديث في إعادة استخدام الأدوية الحسابية، بما في ذلك استراتيجيات الإعادة التوجيه المتاحة، والطرق الحسابية الشائعة المستخدمة، وتقنيات التحقق من دراسات إعادة الاستخدام، والتحديات المتبقية في إعادة استخدام الأدوية الحسابية.