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Chapter

Trends in Molecular Aspects and Therapeutic Applications of Drug Repurposing for Infectious Diseases

Ankur Gupta, Angila Theengh, Swatantra Kumar, Vimal K. Maurya, Santosh Kumar, Bipin Puri and Shailendra K. Saxena

Abstract

The pharmaceutical industry has undergone a severe economic crunch in antibiotic discovery research due to evolving bacterial resistance along with enormous time and money that gets consumed in *de novo* drug design and discovery strategies. Nevertheless, drug repurposing has evolved as an economically safer and excellent alternative strategy to identify approved drugs for new therapeutic indications. Virtual high throughput screening (vHTS) and phenotype-based high throughput screening (HTS) of approved molecules play a crucial role in identifying, developing, and repurposing old drug molecules into anti-infective agents either alone or in synergistic combination with antibiotic therapy. This chapter briefly explains the process of drug repurposing/repositioning in comparison to *de novo* methods utilizing vHTS and HTS technologies along with 'omics- and poly-pharmacology-based drug repurposing strategies in the identification and development of anti-microbial agents. This chapter also gives an insightful survey of the intellectual property landscape on drug repurposing. Further, the challenges and applications of drug repurposing strategies in the discovery of anti-infective drugs are exemplified. The future perspectives of drug repurposing in the context of anti-infective agents are also discussed.

Keywords: drug repurposing, repositioning, poly-pharmacology, anti-infectives, HTS

1. Introduction

Antibiotic resistance is a major threat that may lead to approximately 10 million deaths per year by 2050 [1]. Nevertheless, pharmaceutical companies' entire economic model for antibiotic drug discovery has clashed with the low profitability index. An estimated cost of developing an antibiotic in 2017 was nearly US $1.5 billion, whereas the average revenue generated per year is nearly US $46 million, which cannot be justified in any way [2]. Therefore, in an attempt to accelerate the identification of potential and safe anti-infective drugs, reduce discovery research expenses,

and minimize drug development timeline, "drug repurposing" and/or "drug repositioning" has arisen as an excellent alternative approach because the developer already has the complete pharmacological and toxicological data of the drug candidate from preclinical and clinical trials. Drug repurposing and/or repositioning simply mean new treatment indication or pharmacological use of an old drug [3]. For example, Aspirin, the first-ever drug repurposed, was originally indicated as an analgesic but later repurposed for various pharmacological effects such as anti-platelet in cardiovascular events [4].

"Drug repurposing," "drug repositioning," and "drug rescuing" are the terms generally used interchangeably; however, these terms may slightly differ from each other. Drug repurposing means, "approved drug for one disease is identified potentially useful and repurposed in another disease" such as aspirin, whereas drug repositioning explains a situation when "an approved drug for one disease is used as a template and derivatized to a different form for use in another disease" [5, 6]. Nevertheless, drug rescuing is the term given to the concept where "the clinically failed or market abandoned drugs for one clinical indication is rescued or used for another clinical indication" such as thalidomide which was banned initially but later rescued to multiple myeloma [5]. However, the ultimate goal remains the same and that is "repurposing of old drugs for new diseases."

2. Need for drug repurposing

Nobel Laureate Sir James Whyte Black (1924–2010) had once said that "the most fruitful basis for the discovery of a new drug is to start with an old drug" [7]. However, the systematic screening approach introduced by Paul Ehrlich became the cornerstone of antibiotic search strategies for pharmaceutical industries and along with further advancement in *de novo* drug design methods, various potential novel classes of antibiotics were discovered. Nevertheless, the rate of discovery of a novel

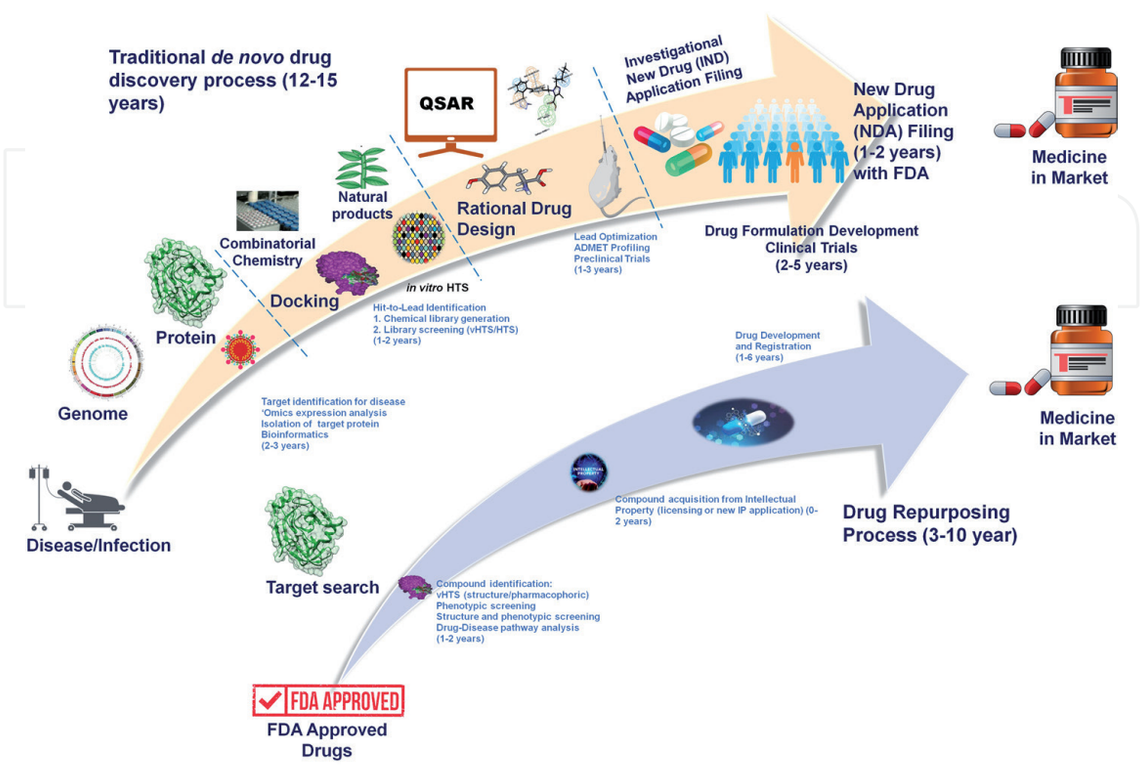

Figure 1.
Traditional de novo *drug discovery process versus drug repurposing process.*

class of drugs suddenly dropped by 1970 with the increasing rate of resistance [8]. Even with all the scientific tools of traditional methods of drug discovery such as 'omics (genomics, proteomics, and metabolomics), virtual high throughput screening (vHTS), phenotypic, and whole cell-based high throughput screening (HTS), no new class of antibiotics are getting discovered [8]. On the contrary, there is an overall increase in the expenses leading to a collapse in the economic model of antibiotic drug discovery research [2]. Therefore, a change in the financial models is required to translate scientific advances into clinically approved antibiotics [9]. Drug repurposing is the best possible way to escape from this dilemma and reposition the drug candidates from the approved pharmacopeia. Drug repurposing offers great advantages over traditional drug discovery methods such as no chemical optimization and reduced developmental risk because the drug candidates have often been through several stages of preclinical and clinical trials and therefore have well-known toxicological safety and pharmacokinetics profile. Even formulation stages and bulk manufacturing are also bypassed, enabling a shorter route to the market [3]. A comparison of traditional *de novo* drug discovery versus drug repurposing is summarized in **Figure 1**.

3. Intellectual property landscape in drug repurposing

The drugs may either be on-market (ONM) or off-market (OFM) drugs. Further, the ONM drugs may be on-patent (ONP) or off-patent (OFP) drugs. As per the latest version of the United States Food and Drug Administration-Orange Book (US FDA-OB), 1577 drugs are ONM drugs and 1543 drugs are OFM drugs. Out of 1577 ONM drugs, 1142 drugs lack patent/exclusivity claims and could be utilized for drug repositioning projects [10]. Nevertheless, obtaining patent protection for known drugs can be a challenging task. The repurposed drug can be patented in the United States if the drug constitutes patentable subject matter under 35 U.S.C. § 101. According to 35 U.S.C. §, 101 repurposed drugs may be patented provided its new indication or use has not been published before. Nevertheless, the eligibility of patentability of "therapeutic use" varies between jurisdictions from country to country [11]. While the patent based on "therapeutic use" is possible in the United States and some other countries, it is not permitted in India. Therefore, another approach to obtain a patent for previously known drugs in India is to draft claims for novel pharmaceutical formulations. On the contrary, if a drug to be repurposed is still under patent protection, then that drug can either be acquired or in-licensed from the patentee. Hence, patent protection of repurposed drugs for new indications is possible. However, initial experimentation should establish the usefulness of the drugs along with robust invention disclosures and detailed formulation applications may be directed to the patent office [12].

4. Strategies involved in drug repurposing

Drug repurposing in infectious diseases involves different strategies by integrating both vHTS and HTS methodologies to identify a drug molecule, a microbial target, and an immunopathological pathway to fight against an infectious pathogen. The various strategies involved are (i) computer-aided (structure-based [13] and ligand-based pharmacophoric [14]) repurposing, (ii) phenotype-based HTS aided repurposing [15], (iii) 'omics-based drug repurposing [16], (iv) drug-disease biological pathway analysis [17, 18], (v) poly-pharmacology-based drug repurposing [19, 20], and (vi) serendipity [21], which are summarized in **Figure 2**.

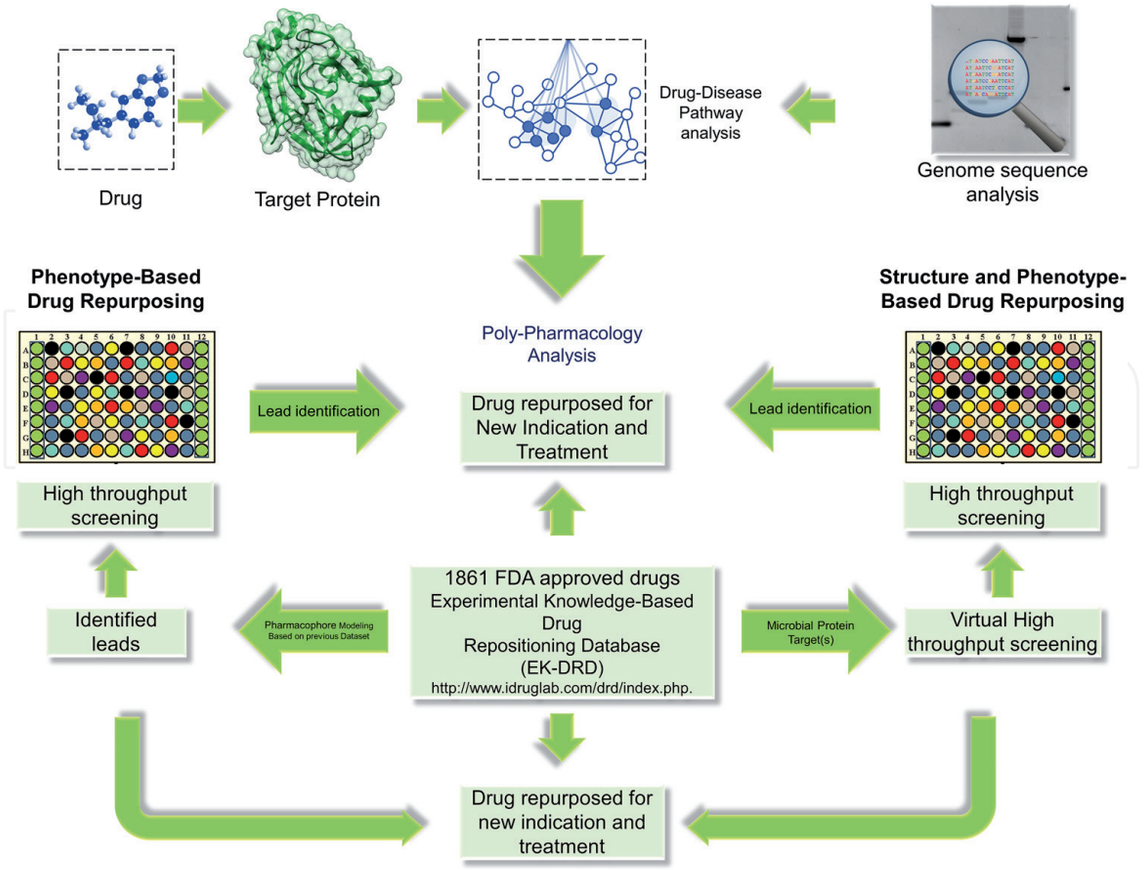

Figure 2.
Strategies involved in drug repurposing.

However, the plausible drugs for anti-microbial repurposing may fall into three different evaluating scenarios and two different approaches, namely, "on-target repurposing" and "off-target repurposing" [22] as shown in **Figure 3**.

4.1 Computer-aided drug repurposing

vHTS is an efficient approach to identify compounds for drug repurposing. Where vHTS is a generalized term for different screening filters, it is categorized under two broad classes of virtual screening for drug repurposing, that is, (i) structure-based drug repurposing and (ii) ligand-based pharmacophoric repurposing.

4.1.1 Structure-based drug repurposing

Protein data bank (PDB) is the largest compilation of structural data on microbial target proteins. Presently, there are 62,402 structural deposits related to bacterial target proteins and 9653 structural deposits related to viral target proteins in PDB.

Further, nearly 60% of these proteins are complexed with a biologically relevant ligand, which provides information about the shared binding sites and amino acids of the target site involved in intramolecular interactions with the ligand. These proteins are utilized for structure-based drug repurposing by virtual screening (docking studies) the drugs for repurposing in comparison to the ligand. The ligand in comparison could either be the one that is already complexed at the target site or any other approved drugs available as a particular modulator of the target site. The selection of screened drugs for repurposing is completely based on scoring and drug interactions. To complement the structures available in the PDB, another method used for structure-based screening is called homology modeling. Homology

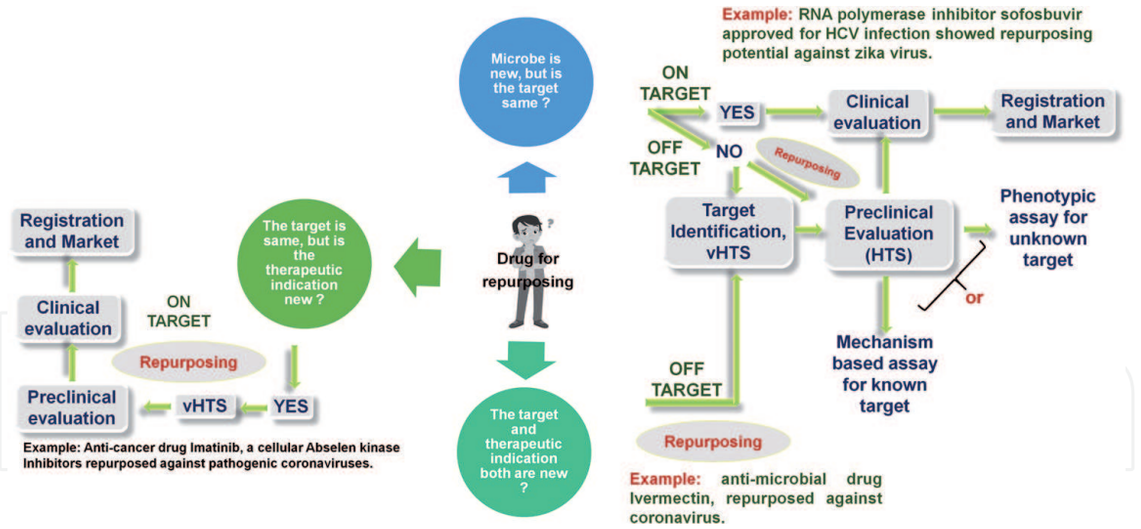

Figure 3.
Various scenarios and approaches in drug repurposing.

modeling can generate 3D structures of even those proteins whose structures are difficult to obtain through X-ray crystallography. Apart from these sources, there are other databases of high-quality 3D protein models, such as SWISS-MODEL Repository (SMR) to support structure-based drug repositioning pipelines [13].

4.1.2 Ligand-based drug repurposing

In the absence of structural information about the microbial target protein from source, structural databases, or homology modeling, the structure-based repositioning and discovery efforts are hampered. Nevertheless, there are other virtual screening methods such as ligand-based screening methods, which can be employed for drug repurposing. The process involves the generation of a ligand-based mathematical "QSAR (quantitative structure–activity relationship) model" and ligand-based 3-dimensional (3D) "pharmacophore fingerprint" using in-house or approved microbial target site inhibitors as the active set I. The drugs sought to be repurposed are arranged in set II and screened using the derivatized models for their optimum physicochemical descriptors and/or conformational search for active pharmacophore. The potential molecules through ligand-based screening approach will be shortlisted for phenotype-based HTS studies [14].

4.2 Phenotype-based HTS-aided repurposing

There are various unexplored targets and pathways within the complexity of the microbial intracellular mechanisms along with the identified targets. The drugs for repurposing may be screened for known off-target, on-target, and unknown targets using HTS (**Figure 3**). Mechanism-based biochemical assays may be carried out for known off-target and on-target screening of drugs employing specific proteins such as enzymes in the assay. However, the unknown off-target screening can be carried out through phenotype cell-based HTS assays, so that the multiple targets can be screened to conclude the efficacy of repurposed drug related to its pharmacodynamic status, heterogeneity, biomarker readout, membrane permeability, and cytotoxicity. Further, the phenotype-based assays may be carried out using two-dimension (2D) and three-dimension (3D) approaches. The 2D approach is a traditional cell-based HTS that is carried out on cultured cells propagated in 2D on plastic surfaces

optimized for cell culture. Anti-infective screening for drug repurposing traditionally utilizes a 2D cell-based HTS approach. However, this approach is not suitable for accessing the drug resistance status in antimicrobials. Thus, for drug repurposing or discovery, bioengineered 3D cell culture technology that closely resembles the in vivo cell environment is now being pursued [15].

4.3 'Omics-based drug repurposing

Omics technology comprises various approaches such as genomics, transcriptomic, proteomics, and metabolomics. The genomics and transcriptomic approaches analyze the gene pattern and mRNA sequence of a pathogen before and after exposure to a drug under consideration for repurposing. The study of the gene expression at the transcription level helps researchers to predict possible metabolic pathways of microorganisms, genomic mutation leading to drug resistance, and potential targets. Further, large-scale microbial gene expression studies may be carried out using advanced microchip technology. The proteomic approach evaluates the overall protein expression profile of the entire organism pre- and post-exposure to an antimicrobial agent under various environmental conditions. It helps identify drugs that may be repurposed for plausible new targets with the least chances of resistance and novel mechanism of action. In contrast, metabolomics involves the analyses of metabolites, and biological/molecular substrates present in a pathogen at a particular time interval. Further, exometabolomics, also known as "metabolic footprint" measures charged or polar molecules being consumed or released by an organism as a secondary metabolite. Sound knowledge of metabolomics can predict the alternative mechanism or pathway during drug resistance, and synergy in combination therapy. Hence, 'omics technologies have transformed the anti-infective drug discovery by generating an unparallel amount of data on potential antimicrobial targets and their resistance from the array of biological libraries. The unique signature (characteristics) of a disease and its co-relationship with a drug can be derivatized using 'omics technologies and drug databases, respectively, such as CARD (Comprehensive Antibiotic Research Database), ARDB (Antibiotic Resistance Genes Database), and NDARO (National Database of Antibiotic-Resistant Organisms) [16].

4.4 Drug-disease biological pathway analysis

Traditionally, computer-aided approaches were mainly aimed toward target and drug molecules involving structure-based drug design. However, it has also been employed toward the assessment of biological pathways, and mechanisms of drugs through network systems to formulate the correlation between drugs and disease pathways for possible drug repositioning. The scientific data over the drug-disease pathways network may be designed using various databases such as NCBI, MMDB, GEO, and PubChem. Using this approach, Yang et al. generated three network-based systems between cardiovascular diseases, diabetes mellitus, and neoplasms to establish the drug-disease biological pathway correlation and to predict possible drugs for repositioning. Similarly, Pan et al. studied 16 FDA-approved drugs for possible drug repurposing by using a drug-disease pathway-based approach. Their approach involved the analysis of the drug, protein, and corresponding gene target with affected gene expression level after drug treatment [17, 18].

4.5 Poly-pharmacology-based drug repurposing

The "single drug, single target" approach is an oversimplified disease mechanism which is in fact, a complex sub-network of the underlying distorted

physiological pathway within the interactome. In contrast, network pharmacology considers disease a casual mechanism within the "diseasome cluster" and treats by identifying the synergistic co-targets leading to reduced dose and side effects of the drug. Similarly, "polypharmacology" is the concept of designing or utilizing pharmaceutical agents that can synergistically act on multiple targets or disease pathways. Thus, the drugs which are poly targeting allow a broader impact not only in the early stages of drug discovery but in drug repositioning as well. Various polypharmacology- and network pharmacology-based databases have been published which are employed to develop polypharmacology-based drug repurposing predictions. Polypharmacology apart from the concept also incorporates the use of computational fingerprinting such as structure-based polypharmacology and ligand-based polypharmacology similar to SBDD and LBDD [19, 20].

4.6 Serendipity

"Serendipity," a term used by medical writers for almost 50 years, was originally coined in 1754 by Horace Walpole in an allusion to an ancient oriental legend of the "Three Princes of Serendip." Today serendipity means, "discoveries not purposely searched for" [21]. However, this term has become one of the methods for discoveries. A thorough survey (via social media platforms) based on medical questions and answers can form a database for the serendipity approach in drug repurposing. This approach can be best understood by various examples where patients taking medication "A" for a specific ailment but suffering from comorbidities have claimed to have found relief from the comorbid disease as well. For example, a patient taking hydrochlorothiazide prescribed for hypertension found relief in kidney stones. However, there is a logical scientific connection between the two conditions. Hydrochlorothiazide is an antihypertensive drug that functions through its diuretic properties (increased urine production and flow) leading to either dissolution or removal of small kidney stones. Similarly, a second example is of a 41-year-old woman with depression and psoriasis and was under treatment for depression with sertraline. She noticed that with sertraline her psoriatic lesions started disappearing. However, scientifically these two conditions are also correlated as psoriasis being an autoimmune disorder having a direct impact on psychosocial factors leading to depression and periodical inflammatory lesions. The main limitations of this method can be questioned in terms of its credibility as these databases are just an output of a questionnaire where other factors such as lifestyle change and environmental factors too might have played an important role. However, the conclusions may be evaluated using drug-disease pathway analysis and other drug repurposing strategies [22].

5. Challenges in drug repurposing

Traditional drug discovery is a time-consuming (10–17 years) process that bears failure risk and huge investment. In this regard, drug repurposing strategy has a lower rate of failure and is found to be safe in early preclinical and clinical trials, thus reducing the cost and time spent during formulation development, safety, and efficacy studies. However, the major challenges in drug repurposing could be (i) untoward side effects due to higher dose of the nonantibiotic drug repurposed for infectious diseases to show the required therapeutic effect and (ii) variation in the pharmacokinetic profile of the drug after off-target repurposing.

6. Therapeutic applications of drug repurposing in infectious diseases

Drug repurposing strategy recently identified that the anthelmintic drug niclosamide (NCL) is a strong inhibitor of the 3OC12 – HSL-dependent QS system in *Pseudomonas aeruginosa* by inhibiting the LasR-dependent signaling leading to reduced virulence, and attenuated *P. aeruginosa*. Pulmonary administration is an ideal route to treat respiratory infections but the major obstacle in pulmonary administration of NCL was the achievement of appropriate particle size and its poor dissolution properties in alveolar fluids due to hydrophobicity. Hence, therapeutic applications of nanotechnology were employed to formulate NCL nano dry powders using high-pressure homogenization and spray drying technologies. Thus, repurposed drugs based on their pharmacokinetic profile may be modified in the form of nano-suspensions enhancing the drug's potential for the treatment of infectious diseases [23]. Similarly, synergistic drug combination along with antibiotics is a useful therapeutic option for various repurposed nonantibiotic drugs showing less potential against infections leading to reduced chances of attaining antibiotic resistance [24, 25].

7. Repurposed drugs for infectious diseases

Few examples of directed repurposed drugs for bacterial, viral, and fungal diseases are summarized in **Table 1**. Drugs such as Auranofin, Celecoxib, Clomiphene, and Finasteride have been repurposed for several bacterial infections. Similarly, Remdesivir, Favipiravir, Lopinavir-Ritonavir, Ivermectin, Ribavirin, Interferon, and Hydroxychloroquine have been repurposed for COVID-19. Haloperidol, Aripiprazole, Alexidine dihydrochloride, Pentamidine, bifonazole, and Sulfonamide drugs have been repurposed for fungal infections.

8. Conclusion

The growing number of resistant infectious agents is a threat to the world. Various screening strategies such as vHTS, HTS (phenotypic cell-based 2D/3D screening), and therapeutic approaches (nanotechnology, synergistic combinations) for drug repurposing may be employed for rapid identification and formulation of new therapeutics against infections. These approaches are especially useful during emerging outbreaks and pandemics of infectious diseases such as MERS, SARS, SARS-CoV-2, and Ebola viruses because it is highly impractical to develop vaccines and therapeutic agents in a short period. Nevertheless, there is an important question that needs to be addressed by the scientist working toward a drug repurposing approach. What if the existing pharmacopoeia for repurposing will get exhausted one day?

9. Future perspectives

The boom in drug repurposing strategies may occupy the existing drugs from pharmacopoeia and the drug bank may get exhausted for further repurposing. Therefore, pharmaceutical companies with advanced biological and technological expertise should invest in biodiversity-oriented drug discovery programs to discover and develop early-stage new pharmacophoric compounds

Sr. No.	Drug repurposed	Clinical indication	Target pathogen and mechanism of action
Repurposed drugs for bacterial infections			
1.	Auranofin	Rheumatoid arthritis	*Staphylococcus aureus*: inhibition of DNA/protein synthesis, and downregulation of toxin production.
2.	Celecoxib	Inflammation	*S. aureus*, *Bacillus anthracis*, *B. subtilis*, and *Mycobacterium smegmatis*: inhibition of bacterial DNA, RNA, protein synthesis, and cell wall.
3.	Clomiphene	Fertility	*S. aureus*: inhibition of undecaprenyldiphosphate synthase involved in the synthesis of a teichoic acid wall.
4.	Finasteride	Prostate hyperplasia	*Candida albicans*: inhibition of filamentation.
5.	Clotrimazole and Miconazole	Fungal infection	*P. aeruginosa*: inhibition of the pqs activity through the possible inactivation of 2-alkyl-4-quinolones (AQ) production or reception.
Repurposed drugs for viral infections			
6.	Ivermectin	Anthelmintic	SARS-CoV-2: acts blocking the nuclear transport of viral proteins
7.	Nitazoxanide	Parasitic and viral infection	Influenza virus: inhibition of the pyruvate: ferredoxin/flavodoxinoxidoreductase cycle.
Repurposed drugs for fungal infections			
8.	Haloperidol	Antipsychotic agent	*C. albicans*: inhibition of filamentation, melanin production, and biofilm formation.
9.	Aripiprazole	Antipsychotic agent	Inhibition of biofilm formation and hyphal filamentation.

Table 1.
Directed repurposed drugs for infections [26–28].

and fill their anti-infective pipelines while still taking the advantage of drug repurposing. Further, the advancement in nanotechnology may lead us to design better therapeutic formulations of repurposed drugs targeting pulmonary infections such as multidrug-resistant tuberculosis. Drug repurposing raises several concerns in terms of quality and ethical integrity of preclinical and clinical research specially during emergency pandemic situations such as COVID-19 involving accelerated drug approval based on statistical exploration of small, scientific data with the real-world population. This issue may not only increase the chances of adverse events; also, if the drug is withdrawn, the pharmaceutical industry may lose public confidence over healthcare needs. According to patent regulations, there are no safeguards for Intellectual property (IP) protection of drug development through the repositioning method. IP protection for repositioned drugs is limited. If the current evidence is not sufficient and does not meet the standards of according to regulatory guidelines, regulatory agencies such as the FDA or EMA, further preclinical and/or clinical studies may be necessary.

Acknowledgements

The authors are grateful to the Director-General, Department of Health and Family Welfare, Government of Sikkim, India; Principal, Government Pharmacy College, Sikkim, India; and the Vice-Chancellor, King George's Medical University (KGMU), Lucknow, India for the encouragement for this work.

Conflict of interest

The authors declare no conflict of interest.

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