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Drug Reprofiling: A Prospective Approach to Battle Chronic Ailments

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Abstract

The concept of drug "reprofiling" has garnered attention in the recent past post the outbreak of coronavirus disease 2019 when traditional drug discovery seemed to fail. Even though repurposing is called pharma-friendly in terms of monetary relief, clinical trials play an integral role in repurposed nontarget /combination moieties. Nevertheless, when a drug exhibits no returns to the market, an exhaustive study on mechanism of action (MOA) can help for reprofiling of drugs for new indications. However, several papers have claimed that scarcity of resources and data access, and staffing issues, tends to pull down reprofiling of drugs. In contrast to this notion, a total of 155 patented articles to date give a strong base for drug repurposing. In the present review, a scientific prospection of reprofiled antifungal and antiviral agents for the past decade was made using the PubMed database wherein a total of 410 and 768 publications have resulted respectively. The authors have attempted to focus their attention to repurposing antifungal drugs for chronic ailments and infectious diseases by understanding their MOA.

For example, antifungal azoles, which work by blocking ergosterol synthesis, can be repurposed as they inhibit histone deacetylase as well significantly decrease the production of cytokines and modulate the inflammatory pathways used by cancer cells. Hence, we believe that the mentioned Food and Drug Administration-approved drug candidates can be utilized to treat nontarget diseases, notably rare/neglected diseases as well as chronic illnesses and the more recent viral infections that are spreading globally.

Keywords
- antibiotic
- FDA-approved
- tumors

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Introduction

The Discovery of a new chemical moiety utilizing the traditional drug discovery method, spanned several years with the expenditure of billions of dollars for the development of a single drug moiety. Even after the drug was launched, pharma companies were unable to meet the minimum level of expectations.[1] Hence pharmaceutical companies worldwide failed to face an immediate global emergency. The birth of repositioning was a heightened finding, with many successful stories clinically beginning from the drug Thalidomide[2,3] to Remdesivir, the first drug to hit the market for treating severe acute respiratory syndrome coronavirus 2. The U.S. Food and Drug Administration (FDA) approved an Emergency Use Authorization for the emergency use of Remdesivir for the treatment of hospitalized COVID-19 patients in light of these preliminary findings. Hence coronavirus disease 2019 (COVID-19) pandemic has boosted repurposed drug sales.[4] Although drug repurposing systems are said to be economical, trials are a requisite owing to the fact that testing of the drug is required in untried combinations with different agents, to ascertain the absence of toxicities. But, the long-run expensive process of drug discovery can be shortened. There exists a plethora of drugs in the market with no high profit due to therapeutic ineffectiveness. Such drugs can be made more efficient by carrying out an exhaustive study of their mechanism of action/therapeutic pathways to treat nontarget diseases, notably rare/neglected diseases. Due to a dearth of medications, there are over 5,000 rare diseases that cannot be treated, and where repurposing can play a significant role. While some consider repurposing to be a considerable improvement over traditional drug development, there remain certain obstacles, including a paucity of multicollaborators, academic experts, funding, subject matter expertise, and staff that is dedicated to outlicensing.

The prominence of drug repurposing in the pharmaceutical sector is, however, strongly supported by the increasing number of patents that are being published online. We have hereby attempted to the best of our abilities to collect patent-related information on repurposed drugs and have represented the same in a tabular as well as graphical form.

This review article focuses mainly on repurposing antifungal and antiviral agents to address the drug-resistant issue as the main pitfall that makes translational research to maximize return on investment in the asset.[5–16]

Methodology

After a thorough systematic literature survey based on all the available studies, the search for patent-related data on drug repurposing was performed. Search engines such as PubMed, SCOPUS, BASE, and Google Scholar were employed to carry out an efficient literature review. Various jurisdictions' patent Web sites were utilized for the excavation of patent portfolios. The patent portfolios on drug repurposing were extracted from the database by incorporating the following keywords a) Title: (drug AND repurposing) / [Abstract: (drug AND repurposing) / Claims: (drug AND repurposing)] and the Filters: Publication Date (*Aug 1, 2002 - Aug 08, 2022*).[17]

For the purpose of scientific prospection of the repurposed antiviral and antifungal medications from 2012 to 2022, the PubMed database was employed by using two phrases i) "Drug repurposing anti-viral drugs" and ii) Drug repurposing anti-fungal drugs [Title/Abstract].

Results and Discussion

A total of 155 patents relating to drug repurposing were recorded and a few are mentioned in the supplementary file (►**Table 1**).

It is evident from ►**Fig. 1** that the total number of patent applications filed has increased significantly since 2008, owing to the applicability of repurposing, but interestingly, this is followed by a zigzag pattern post-2014. However, after 2017, a steadily increasing slope is observed that is still evident to date. With regard to issued patents specifically, a downward slope was seen from 2019 to 2022. Country-wide sharing of these patents (►**Fig. 2**) shows that the United States ranked 1 with 59 patents followed by World Intellectual Property and Organization with 55.

The process of classifying patents according to their technical properties is known as patent classification. Earlier, this was only employed for document sorting. Through their technical classification, patents can be found in the most precise and best way possible. There are many different classifications in use across the globe, which may be related to each nation's unique or independent patent laws. Therefore, all the nations joined together and created a uniform code to consolidate patents. Cooperative Patent Categorization (CPC) and International Patent Classification (IPC) were mostly used to categorize these International Patent Classification. Furthermore, the IPC that was governed by the United State Patent and Trade Mark Office and European Patent Office, and CPC went into effect in Q4 of 2010.[18,19]

The maximum number of repurposing-related patents belongs to the A61K45/06 class. The patents for mixes of active compounds without chemical characterization, such as antiphlogistics and cardiac, are included in this class. This was followed by A61P35/00, a special class dedicated for antineoplastic agents. The patents A61P25/00 and A61K31/496 class featured noncondensed piperazines with additional heterocyclic rings, such as rifampin and thiothixene, which were used to treat nervous disorders.

A summary of the repurposed effect of the existing antifungal and antiviral drugs to outline the identified gap and to focus on novelty is represented pictorially in ►**Figs. 3** and **4**.

Repurposing Existing Antifungal and Antiviral Drugs

A scientific prospection of the repurposed antiviral and antifungal medications from 2012 to 2022 was made and the results are represented in ►**Fig. 5**. A total of 768 publications on drug repurposing of antiviral drugs resulted. In the same period, antifungal drugs were repurposed for many applications and the results were summarized in 410

Table 1 Existing drugs and their proposed repurposed activity based on their MOA

Sl.no	Antifungal classification	MOA	Examples of antifungal drugs	Primary therapeutic effect	Targeting receptor	Repurposed therapeutic effect	References
1.	• Polyenes	• Sequester the ergosterol found in fungal membranes to thereby disrupt the structure of the cell membranes. Cell wall inhibitor • blocking the synthesis of 2,3-oxidosqualene • Prevent conversion of ergosterol to lanosterol	Amphotericin B	Antifungal agent	• CD14 which is a receptor that activates the TLR signaling pathway after binding to LPS • AmB can bind to TLR, which initiates the release of cytokines and chemokine • The recruitment of the adaptor protein occurs when AmB binds to the TLRs, which causes polymerization of the receptors • This signaling causes NF-kB to translocate into the nucleus, which triggers the production of genes essential for macrophage activation	Immunomodulatory	27–29,31–35
2.	Azoles	Inhibit the production of ergosterol by inhibiting lanosterol 14-demethylase	Fluconazole, voriconazole, and posaconazole	Antifungal agents	• Remove the acetyl group from histones and other cellular proteins • Act as an HDAC inhibitor • Hinder cancer cells from survival, invasion, angiogenesis, and metastasis of cancer cells • Inhibit the production of cytokines and control inflammatory pathways in cancer cells	Anticancer agent	18,35–40
3.	Pyrimidine analogue	Blocks pyrimidine metabolism and DNA synthesis	5-fluorocytosine	Antifungal agent	• Interferes with nucleic acid synthesis. • DNA synthesis is ceased and inhibited • Disrupts the activity of enzymes necessary for the production of nucleic acids, such as DNA polymerases and ribonucleotide reductase	1. Antimalarial agents 2.Amebiasis (dysentery caused by amoeba)	27,29,30

Table 1 (*Continued*)

Sl.no	Antifungal classification	MOA	Examples of antifungal drugs	Primary therapeutic effect	Targeting receptor	Repurposed therapeutic effect	References
4.	Allylamines	Inhibiting the ergosterol synthesis by interfering with squalene epoxidase.	Terbinafine	Antifungal agent			41–45
5.	Echinocandins	Block the synthesis of cell walls by inhibiting (1–3)-D glucan synthase	Caspofungin, anidulafungin, and Micafungin	Antifungal agent	The lipophilic tail is inserted into the bacterial cell membrane through a mechanism that results in a rapid membrane depolarization and a potassium ion efflux. After then, DNA, RNA, and protein production are stopped, which causes bacterial cell death	As a powerful antibiotic having bactericidal activity against the majority of gram-positive organisms	25

Abbreviations: CPC, Cooperative Patent Categorization; HDAC, histone deacetylase; LPS, lipopolysaccharide; MOA, mechanism of action; NF-kB, nuclear factor kappa B; TLR, toll-like receptor.

publications. Starting with 2012, there were only six publications related to the repurposing of antiviral and antifungal drugs. However, the numbers have drastically increased since 2015. The number of publications with regard to the repurposing of antifungal drugs has exceeded 50 and it reached a maximum of 75 in the year 2021. The year 2022 has already witnessed the publication of 56 manuscripts and the number is likely to cross 100 by the end of the year. But the trend is quite interesting in the case of antiviral drugs. The total number of manuscripts on repurposing from 2012 to 2019 is only 117. After 2019, there is a rise in publications with the number being 252 in 2020, 292 in 2021, and 107 in 2022.

Based on the review of literature, here are some scientific hypotheses of drug repurposing, in terms of their modes of action, to a point of effective therapeutic indications.

- Despite the fact that colorectal cancer (CRC) is one of the most commonly diagnosed cancer worldwide, effective therapy is still challenging to attain. According to Shi et al, oxiconazole (OXI), a broad-spectrum antifungal drug, has some antitumor properties when applied to CRC. OXI-induced growth reduction of CRC cells is characterized by autophagy arrest and subsequent apoptosis as key processes. By deactivating the Akt/mTOR pathway and preventing RAB7A-mediated autophagosome-lysosome fusion, OXI initiates autophagy by lowering the protein levels of peroxiredoxin-2 (PRDX2), an antioxidant enzyme for reactive oxygen species (ROS) detoxication. This results in an extreme accumulation of autophagosomes and subsequently suppresses the growth of CRC cells. Overexpressing PRDX2 or interfering with autophagy consistently makes it harder for CRC cells to stop their proliferation as a result of OXI. Additionally, OXI combined oxaliplatin, a cornerstone medication for the treatment of CRC, achieves a better antitumor effect. Together, our results offer unique mechanistic insights into the mechanisms behind OXI-induced autophagy stoppage and the growth inhibitory effect on CRC cells, and they point to a potentially effective therapeutic role for OXI in the management of CRC.[17]
- The highest death rate among carcinomas is present in pancreatic ductal adenocarcinoma (PDAC). Elevated autophagy is necessary for the pathogenesis of PDAC, and hydroxychloroquine has shown promise in preventing it. However, due to its imprecise application and unexpected toxicity, current realization is hampered. A quick and convenient strategy is to look for novel autophagy-modulating therapeutics among already-approved medications. Weng et al undertook a comparative analysis of the treatment responses of different antimalarial/fungal/parasitic/viral medicines in this study utilizing a patient-derived organoid model, and econazole (ECON), an antifungal drug, emerged as the top contender. This action was confirmed by additional testing in cell-line and xenograft models of PDAC and was a direct result of impaired autophagy.

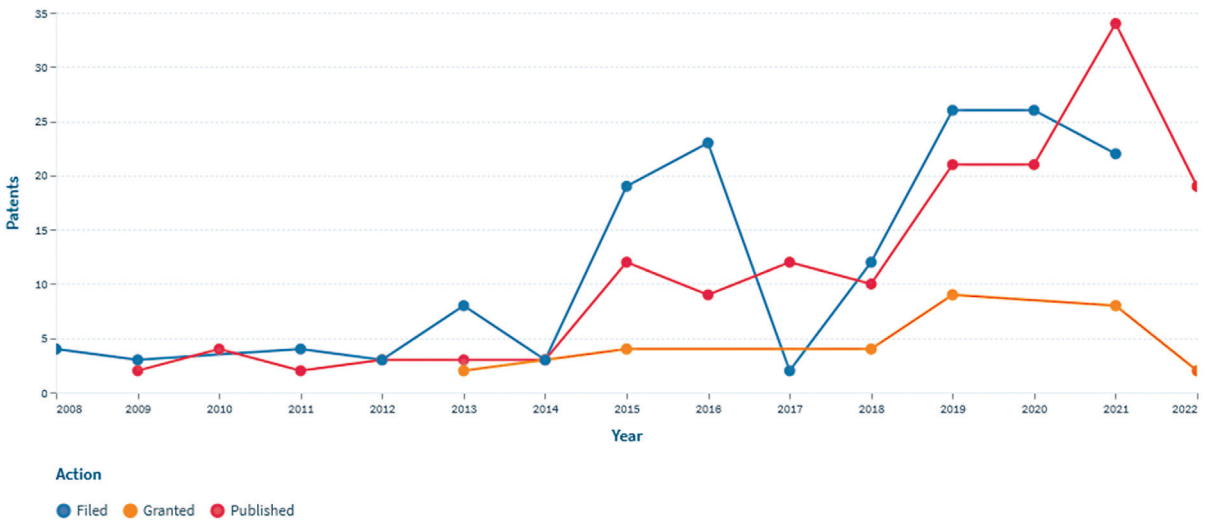

Fig. 1 Patents documents by published, granted, and filed with respect to year.

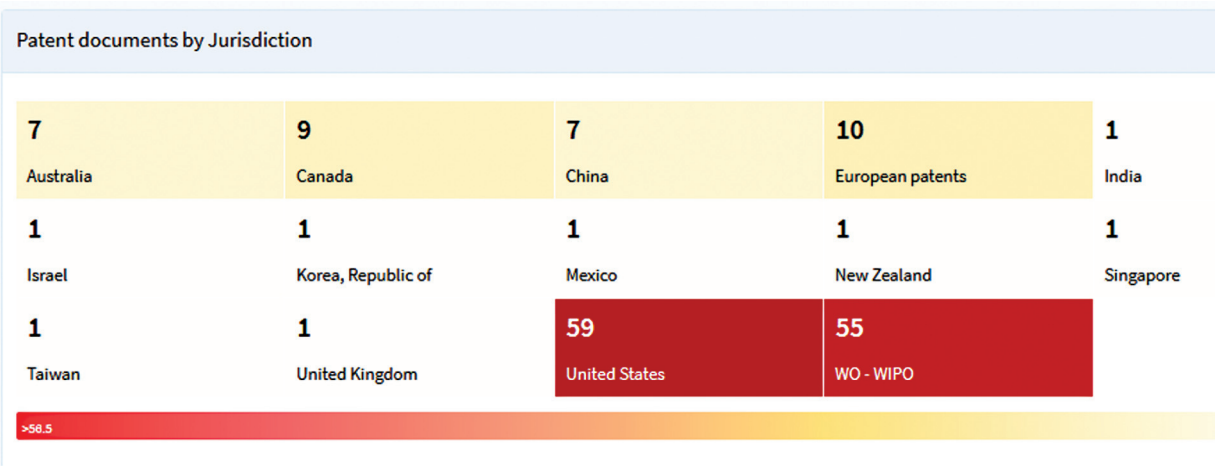

Fig. 2 Patent documents by jurisdiction (heat map).

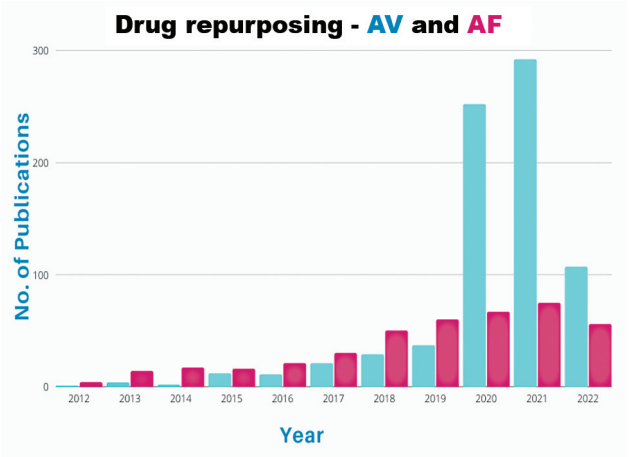

Fig. 3 Published data on repurposing of antiviral (AV) and anti-fungal (AF) drugs.

More specifically, ECON inhibited lysosome biogenesis while increasing autophagy start. This autophagic stimulation, according to RNA sequencing research, was predominantly caused by altered expression of activation transcription factor 3 (ATF3). In PDAC cells, increased nuclear import of ATF3 and its transcriptional suppression of inhibitor of differentiation-1 (ID-1) resulted in the inactivation of the Akt/mTOR pathway, which in turn caused autophagosome accumulation. The level of the autophagosome rise was enough to trigger ER stress-mediated apoptosis. Additionally, trametinib and ECON's synergistic effects on PDAC. ECON is an autophagy inhibitor. The therapeutic effectiveness of ECON in the treatment of PDAC is directly demonstrated in this study's preclinical and experimental data, and it is also revealed how ECON slows PDAC growth.[20]

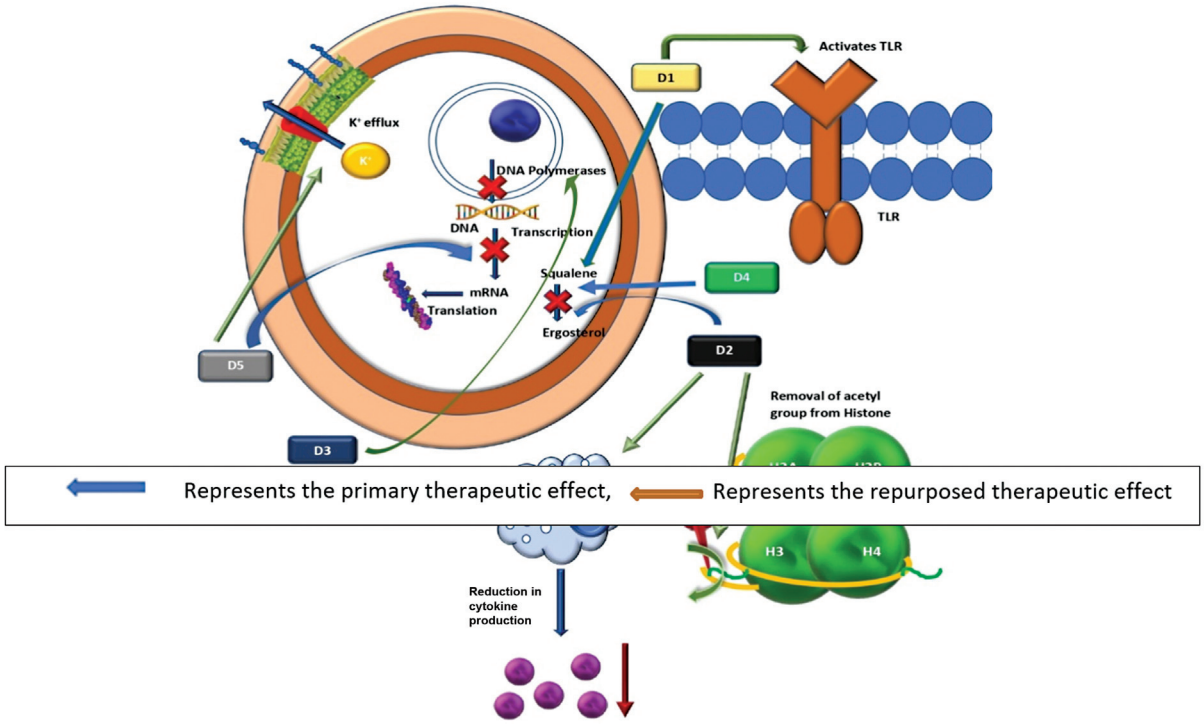

Fig. 4 Pictorial representation of existing drugs and their proposed repurposed activity on multiple targets. D1: polyenes, D2: azoles, D3: pyrimidines, D4: allyl amines, D5: echinocandins. TLR, toll-like receptor.

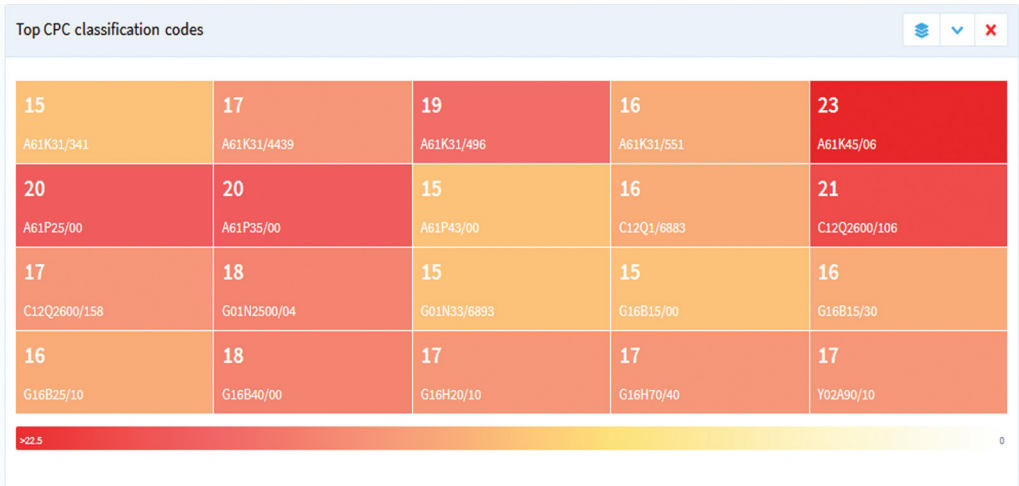

Fig. 5 Top Cooperative Patent Categorization (CPC) classification codes with heat map.

- Imatinib and a nontoxic dose of ketoconazole (10 M) were used to overcome drug resistance. These drugs also reduced P-gp overexpression and its efflux function, boosting the intracellular accumulation of doxorubicin, and caused higher levels of cell death in chronic myeloid leukemia (CML) cells. Imatinib resistance in CML cells is significantly influenced by P-gp. By concentrating on P-gp-related pathways, ketoconazole was able to overcome the imatinib resistance of CML cells. Patients who are resistant to imatinib would probably benefit from the repurposing of ketoconazole for CML treatment.[21,22]
- Disulfiram (Antabuse) has been repurposed as an antibacterial drug, and Custodio et al examined the preclinical and clinical research. As an anti-methicillin-resistant Staphylococcus aureus agent, carbapenamase inhibitor, antifungal drug for candidiasis, and treatment for parasitic diseases caused by protozoa (such as giardiasis, leishmaniasis, and malaria) and helminthes (such as schistosomiasis, trichuriasis), preclinical research on the alcohol sobriety aid has been covered.[23]
- Disulfiram has also been shown to be effective as a COVID-19 infection treatment, an HIV latency reversal

medication, and a post-Lyme disease syndrome therapy method. In many tropical locations of the world, leishmaniasis continues to be a severe public health issue. Leishmaniasis has the second-highest fatality rate among neglected tropical illnesses, right behind malaria. There are toxic side effects to every therapy currently on the market, and resistance is rising quickly. Drug discovery pipelines using both in-silico and in-vitro techniques were established to identify current medications with antileishmanial activity and anticipate the mechanism of action. Lansoprazole and Posaconazole were shown to be the two most promising active molecules after first screening. Several sites were used to identify potential Lansoprazole and Posaconazole medication targets for Leishmania. Posaconazole and Lansoprazole are two new antileishmanial medications that have previously received FDA approval for use in various conditions, and they both put forth plausible mechanisms of action for their antileishmanial effectiveness.[24]

- Due to their high mortality rates and multidrug resistance (MDR), *Klebsiella pneumoniae* poses a hazard to healthcare globally. DeSarno et al investigated the possibility of treating resistant *K. pneumoniae* strains by combining zidovudine (AZT) and an already-approved antibiotic.
- The NDM-1 or KPC-3 carbapenemase was produced by the pneumoniae strains used. By assessing larval mortality and bacterial load, the efficacy of AZT and meropenem combinations was contrasted with that of monotherapies against infections *in Galleria mellonella* larvae. Checkerboard and time-kill assays were used to determine the impact of the same combinations in vitro. Meropenem-resistant pneumoniae strains were responsive to AZT but resistant to meropenem. In *G. mellonella* infections, therapy with either AZT and meropenem or meropenem alone had only a modest therapeutic effect. As opposed to monotherapies, combination therapy using meropenem and AZT had significantly higher efficacy. This was associated with suppression but not the eradication of bacterial growth within the larvae. Checkerboard tests revealed an indifferent rather than a synergistic relationship between AZT and meropenem. In conclusion, AZT and meropenem combination therapy is a viable treatment for MDR *K. pneumoniae* strains that produce carbapenemase.[25]
- PI3K/Akt/mTOR pathway is a crucial target in the fight against cancer. De novo drug development takes years, though, and is frequently slowed down by decreased activity and/or unanticipated toxicity in clinical trials. Testing medications that have previously received approval for use in other conditions is one method of accelerating the discovery of new cancer medicines. The FDA-approved HIV-1 protease inhibitor nelfinavir, which is consumed orally to treat HIV/AIDS, has been shown by researchers to lessen endogenous. However, nelfinavir is profoundly effective in cancer cell lines that have been chosen to show signs of resistance to current therapy. Each of the 60 cell lines in the NCI panel has shown dose-dependent cytotoxicity at plasma concentrations that can hinder the growth of tumors in vivo. Arun Rajan and the National Cancer Institute (NCI), United States, have started a clinical trial [registered number-NCT01445106] for the same with the goals of correlating the pharmacokinetics of nelfinavir with the baseline activity of CYP3A4. The studies were performed by measuring midazolam clearance and preliminary examining the biological and clinical impacts using several correlative studies that included blood and tissue analysis across all research subjects.[26]

With reference to ►**Fig. 4** representing the mechanism of action of the existing antifungal drugs, it is evident that they work by either inhibiting the transcription of RNA / synthesis of DNA at the nucleic acid level. At the cellular level, they inhibit the synthesis of ergosterol thereby damaging the fungal cell membrane. Background research on the antifungal and potent antiviral compounds identified specifically has a significant dual effect on other receptors. Consequently, these medications can be repurposed to treat chronic illnesses as well as more recent viral infections that are spreading globally. This review article goals are to assist the researcher in transitioning forward with cutting-edge discoveries. According to our knowledge, antifungal and antiviral medications can also operate as life-saving treatments, but the discovery still leaves several medications with room for improvement, such as demonstrating their effectiveness in wet laboratory testing. For example, Azoles are a class of antifungal drugs that have a modus operandi of blocking ergosterol synthesis, thereby inhibiting the fungal cell wall synthesis. They can be repurposed as an anticancer agent as they inhibit HDAC as well as cancer cell survival, invasion, angiogenesis, and metastasis. They also reduce the production of cytokines and control the inflammatory pathways of cancer cells. Although a drug is reprofiled for newer indications, quantifying the effective dose, designing of the dosage forms, investigation of its therapeutic effectiveness, and identifying the appropriate route of administration still prove to be a challenge.

Conclusion

To recapitulate, data on repurposing of a drug using its mechanism of action and SAR as well as the already online published information of the drug can be done at the academic level. Drug reprofiling should be utilized to find therapies for nontarget diseases, notably rare/neglected diseases lest they become a global pandemic. This article strives to serve as a repository for researchers in the field of drug reprofiling. Through the extensive review of literature, it is evident that surplus information on patents relating to drug reprofiling is available. Through this article we want to

debunk the myth that no much information is available in the field of repurposing. However, to translate these findings from bench to bedside, a collaboration with academia subject experts as well as pharma companies is a prerequisite.

Statement of Institutional Review Board Approval and/or Statement of Conforming to the Declaration of Helsinki
Not Applicable.

Authors' Contributions
P.B. was involved in hypothesis of the subject and article writing, preparing the final draft Natasha. N.A. was involved in article writing, hypothesis of the subject, and article correction. S.S.M. contributed to hypothesis of the subject and article correction. N.R.N. and B.G. helped in article writing. All authors have read and approved the manuscript.

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None declared.

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