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REVIEW

Strategies of Pharmacological Repositioning for the Treatment of Medically Relevant Mycoses

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Abstract: Fungal infections represent a worldwide concern for public health, due to their prevalence and significant increase in cases each year. Among the most frequent mycoses are those caused by members of the genera *Candida, Cryptococcus, Aspergillus, Histoplasma, Pneumocystis, Mucor*, and *Sporothrix*, which have been treated for years with conventional antifungal drugs, such as flucytosine, azoles, polyenes, and echinocandins. However, these microorganisms have acquired the ability to evade the mechanisms of action of these drugs, thus hindering their treatment. Among the most common evasion mechanisms are alterations in sterol biosynthesis, modifications of drug transport through the cell wall and membrane, alterations of drug targets, phenotypic plasticity, horizontal gene transfer, and chromosomal aneuploidies. Taking into account these problems, some research groups have sought new therapeutic alternatives based on drug repositioning. Through repositioning, it is possible to use existing pharmacological compounds for which their mechanism of action is already established for other diseases, and thus exploit their potential antifungal activity. The advantage offered by these drugs is that they may be less prone to resistance. In this article, a comprehensive review was carried out to highlight the most relevant repositioning drugs to treat fungal infections. These include antibiotics, antivirals, anthelmintics, statins, and anti-inflammatory drugs.

Keywords: action mechanisms, antifungal resistance, clinical pathogens, repositioning, new treatments

Introduction

It is estimated that fungal diseases may eventually affect more than 1 billion people, and cause the death of 1.7 million people annually.[1,2] These infections often exemplify underserved emerging diseases, and although most deaths are preventable, delays in diagnosis and treatment can exacerbate symptoms.[2,3] Fungal infections are a serious global concern, as many species can spread and colonize host tissues, especially in individuals with weakened immune systems, as a consequence of health problems such as asthma, AIDS, cancer, organ transplantation, and corticosteroid therapies.[4–6]

Although the epidemiology of fungal diseases has changed in recent years, genera such as *Candida, Aspergillus, Cryptococcus, Histoplasma, Pneumocystis, Mucor*, and *Sporothrix* are still the main fungal pathogens responsible for cases of severe fungal diseases.[2,6] Nevertheless, approximately 70% of invasive fungal infections worldwide are caused by species of the genus *Candida*, which result in invasive candidiasis.[2]

The treatment of such infections often involves antifungal drugs, which target specific mechanisms of the fungal cell. There are four main classes of antifungal drugs employed to treat these infections: flucytosine, azoles, polyenes, and echinocandins.[7,8] Flucytosine functions as an antimetabolite, disrupting the synthesis of RNA and proteins. It is often used in combination with other antifungals, particularly in the treatment of *Cryptococcus* infections. The mechanism of action of azoles is to inhibit the synthesis of ergosterol, an essential component of the fungal cell membranes.[9,10] This class of drugs includes fluconazole, itraconazole, and voriconazole, which are effective against a broad spectrum of fungi. Polyenes are often used as a first-line treatment for severe systemic fungal infections. Unlike azoles, amphotericin B acts by binding to ergosterol in the fungal cell membrane, disrupting its integrity and causing cell death.[9] Echinocandins target the fungal cell wall by inhibiting the synthesis of β-1, 3-glucans. This class of antifungal drugs is useful against

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Candida species and *Aspergillus*.[9,10] The antifungal therapy depends on factors such as the causative organism, the infection site, and the patient's status health. Combining antifungal drugs or using other strategies may be an alternative for the treatment of opportunistic fungal infections.[10]

Despite the number of commercially available antifungal drugs, many fungal species have developed mechanisms of resistance, including alteration in drug targeting, alterations in sterol biosynthesis, overexpression of the antifungal drug target, reduction in intercellular concentration of the target enzyme, and modifications in cell wall and membrane drug transport efficiency.[11,12] In addition, other factors such as phenotypic plasticity, chromosomal aneuploidies, and horizontal gene transfer are also driving forces contributing to antifungal drug resistance.[13,14] Resistance mechanisms are recognized as an evolutionary process that has allowed fungi over time to maintain their viability in the presence of damaging chemical agents. Therefore, although new derivatives of the above-mentioned antifungals are constantly being developed, fungi have demonstrated a remarkable ability to adapt and maintain cell viability in the presence of these agents.[6,10] On the other hand, the pharmaceutical industry is no longer interested in developing and commercializing new antifungal drugs, due to the high costs and long testing processes they need to place new products out in the market.[3,8,15]

This problem has led to the search for new therapeutic alternatives, and drug repositioning has emerged as a promising strategy to counteract this phenomenon. Through repositioning, it is possible to take advantage of existing and well-established pharmacological compounds for the treatment of other diseases, and thus exploit their potential antifungal activity, offering an effective and perhaps less resistance-prone alternative.[16,17] This approach could accelerate the development process of new antifungal treatments by avoiding the initial phases of testing. In this article, we will conduct a comprehensive review related to drug repositioning for the treatment of clinically important mycoses, such as those caused by *Candida, Aspergillus, Cryptococcus, Pneumocystis, Mucor*, and *Sporothrix*.

Drug Repositioning for the Treatment of Clinically Important Mycoses

The management of pathogenic fungi has become increasingly challenging due to the scarcity of effective drugs available. In addition, conventional antifungal treatments can induce cytotoxicity in vital organs, such as the kidneys and liver, and added to this is the ability of many fungal species to generate resistance.[18] Most of the resistant species belong to the genera *Candida, Cryptococcus, Aspergillus, Mucor, Sporothrix*, and *Paracoccidioides*.[14,19,20]

Given the rapid evolution of antifungal drug resistance and the high prevalence of mycoses in clinical settings, there is a need to enhance the efficacy of current treatments and to develop new therapeutic strategies. The drug repositioning or repurposing strategy opens up new possibilities for the use of previously approved drugs that are already on the market for other medical indications. The availability of previously established pharmacokinetic, pharmacodynamic profiles and toxicity data facilitates more efficient and cost-effective development. Hence, their clinical application could be contemplated as a strategy to address the treatment of medically relevant fungi. In the following subsections, the description of the repositioning of different drugs for the treatment of the most common mycoses in clinical settings will be reviewed.

Antibiotics

Initially, the use of antibiotic drugs was restricted to the treatment of gram-negative and gram-positive bacteria, *Mycoplasma*, *Chlamydia*, *Rickettsia*, and spirochetes.[21] However, studies in vitro and animal models have shown that they may have broad-spectrum antifungal activity.[21] Antibacterial drugs that have been shown to have this activity include tetracyclines, aminoglycosides, macrolides, quinolone polypeptides, and rifampicin (Table 1).[21] Colistin belongs to the class of lipopeptide antibiotics and is used for the treatment of gram-negative bacteria, as this targets lipopolysaccharides found within membranes, causing the displacement of divalent Ca^{2+} and Mg^{2+} cations from the phosphate groups of membrane lipids.[22–25] Colistin is not considered an antifungal drug, however, several studies have indicated that it has antifungal activity against *Candida tropicalis*, and when used in synergy with isavuconazole it has activity against *Candida auris*.[26,27] Polymyxin B and colistin have shown antifungal activity against multidrug-resistant strains of *Candida* and *Cryptococcus*, but not *Aspergillus*, with minimum inhibitory concentrations (MICs) ranging from 16 to 128 $\mu g\ mL^{-1}$.[26] Colistin was reported to induce damage to the *Candida albicans* plasma membrane and when synergized with amphotericin B or itraconazole, the antifungal activity is improved, leading to the death of resistant *C. albicans* strains.[26]

Table 1 Most Studied Antibiotics and Antivirals for the Possible Treatment of Mycoses of Medical Relevance

Medication	Initial Use	Fungi that can be Affected	Synergy with Antifungal Drugs	MICs
Antibiotics				
Colistin	Treatment mainly for aerobic gram-negative enterobacteria representing life-threatening infections such as *P. aeruginosa, A. baumannii, K. pneumoniae, E. coli*, and others.	*C. tropicalis* *C. auris* *C. albicans* *C. glabrata* *C. parapsilosis* *C. krusei* *C. neoformans*	Isavuconazole Amphotericin B Itraconazole Echinocandins Fluconazole	0.25 μg mL^{-1} fluconazole combined with 2 μg
Polymyxin B	Used to treat infections caused by multidrug-resistant gram-negative bacteria such as *P. aeruginosa.*	*C. neoformans* *A. fumigatus* *C. albicans*	Fluconazole Ketoconazole Amphotericin B	8 μg mL^{-1}
Tetracycline analogues (minocycline, doxycycline, demeclocycline)	Broad-spectrum bacteriostatic that act on gram-positive and gram-negative bacteria, such as *Rickettsia, Chlamydia, Mycoplasma pneumoniae*, etc., as well as, some protozoario, such as, *Plasmodium*	*C. albicans* *A. fumigatus* *A. flavus* *C. neoformans*	Amphotericin B Itraconazole Voriconazole Posaconazole Fluconazole	10 μg mL^{-1}
Erythromycin	Effective mainly for respiratory and skin infections, as well as against bacteria, such as, *Chlamydia trachomatis.*	*C. albicans* *C. glabrata* *C. auris* *C. parapsilosis* *C. tropicalis* *C. krusei* *C. neoformans* *C. gattii*	Amphotericin B	0.1 to 0.025 mM
Clarithromycin and Azithromycin	Antibacterial treatment of both gram-positive and gram-negative infections, mainly respiratory tract infections, such as, *S. pneumoniae, S. pyogenes, H. influenzae, M. catarrhalis, and H. parainfluenzae*	*C. albicans* *C. tropicalis* *C. glabrata* *C. parapsilosis* *C. krusei* *A. fumigatus* *A. flavus*	Amphotericin B	No Found
Norfloxacin, Levofloxacin, Ciprofloxacin and Rifampicin	Treatment for gram-positive bacteria as *Staphylococcus, Streptococcus, Enterococcus, Bacillus* spp. and *Mycobacterium*, as well as, with gram-negative bacteria within the *Enterobacteriaceae*, such as, *N. gonorrhoeae, Neisseria meningitidis, Haemophilus influenza, Moraxella catarrhalis, P. aeruginosa*, etc. Use in the treatment of tuberculosis.	*C. albicans* *C. tropicalis* *C. glabrata* *C. parapsilosis* *C. krusei* *A. fumigatus* *A. flavus*	Amphotericin B	No found
Antivirals				
Lopinavir (LPV)	Protease inhibitor used as a treatment primarily for HIV, as well as, for use in MERS-CoV and SARS-CoV viral infections.	*C. albicans* *C. auris*	No found	128 μg mL^{-1}
Atazanavir (ATV)	Antiviral treatment against HIV type II, has also been effective in the treatment of HIV-1 and SARS-CoV-2.	*C. albicans* *C. auris*	Fluconazole Itraconazole	512 μg mL^{-1}

(*Continued*)

Table 1 (Continued).

Medication	Initial Use	Fungi that can be Affected	Synergy with Antifungal Drugs	MICs
Darunavir (DRV)	Widely used for the treatment of HIV-1.	*C. albicans* *Aspergillus candidus* *C. neoformans* *C. gattii*	Fluconazole Amphotericin B 5-flucytosine	64 μg mL^{-1}
Ritonavir (RTV)	Commonly used for the inhibition of HIV proteases, in addition to, its use for the treatment of SARS-CoV-2 and in some cases of Hepatitis C genotype 4.	*A. candidus*	No found	No found
Tenofovir (TFV) and Emtricitabine (FTC)	They are antiretroviral treatments mainly used for the HIV virus and are widely used for the treatment of Hepatitis B virus.	*A. candidus*	Voriconazole	No found
Raltegravir (RAL)	Used in the antiretroviral treatment of HIV and in synergy with other antiretroviral drugs, it has been used to treat Hepatitis C.	*Paracoccidioides*	No found	1 mg kg^{-1}
Ribavirin (RBV)	It has demonstrated efficacy in the treatment of Hepatitis C genotype 1, as well as, the Hepatitis E virus.	*C. albicans* *C. parapsilosis* *C. tropicalis* *Pneumocystis* *Mucormycetes*	Amphotericin B Fluconazole Itraconazole	0.37–3.02 μg mL^{-1}
Sofosbuvir (SFV), Galidesivir and Remdesivir (RDV)	Treatment for Hepatitis C and E virus, as well as yellow fever virus, and also used in broad spectrum antivirals for RNA viruses such as Ebola virus, as well as respiratory syncytial virus (RSV), SARS-CoV and MERS-CoV.	*Rhizopus oryzae*	No found	No found

Previous studies have demonstrated in vitro synergies between colistin and echinocandins for the treatment of several *Candida* species, such as *C. albicans, Candida glabrata, C. tropicalis, Candida parapsilosis*, and *Candida krusei*.[28] Recent studies indicated that colistin improves the efficacy of fluconazole. When 0.25 μg mL^{-1} fluconazole is combined with 2 μg colistin it reduces 2-fold the growth of *C. albicans*.[25] It is believed that the synergism of colistin with fluconazole can improve cell death. Fluconazole inhibits ergosterol biosynthesis, leading to ergosterol depletion in the membrane. This depletion alters membrane properties, making it more susceptible to colistin-mediated permeabilization, thus increasing intracellular azole concentrations, and leading to cell death.[25] Also, several studies have been conducted with the antibiotic polymyxin B, which can bind to anionic lipids in the fungal membrane, and it has been confirmed that when used alone at a MIC of 8 μg mL^{-1} or in synergy with fluconazole, it can destroy the cell membrane integrity of *C. neoformans* and *A. fumigatus*.[29,30] When this antibiotic is combined with ketoconazole and amphotericin B, it can also alter the *C. albicans* cell membrane permeability.[31]

Tetracycline analogs have been used in synergy with amphotericin B to see their antifungal effect. Microtiter assays showed that minocycline, at a concentration of 10 μg mL^{-1} acts synergistically with amphotericin B against resistant strains of *C. albicans*; however, other tetracyclines such as doxycycline and demeclocycline have no such effect at this concentration.[32] The use of minocycline and azoles such as itraconazole, voriconazole, and posaconazole were tested for the treatment of infections caused by *Aspergillus fumigatus* and *Aspergillus flavus*, and the results revealed that minocycline shows no significant antifungal activity. However, there was a significant synergy of this antibiotic when combined with itraconazole, voriconazole, and posaconazole against 61%, 50%, and 68% of clinical isolates of these species, respectively.[33] Although *Aspergillus* species typically have high MICs to azoles, combinations with minocycline

result in a 4- to 16-fold reduction in MICs.[33] When the in vivo effects of combinations of minocycline and the different azoles were analyzed on *Galleria mellonella* larvae infected with *A. fumigatus* strains, a significant increase in larval survival was observed for all isolates.[33] Minocycline in synergy with fluconazole has been shown to have an effect against resistant strains of *C. albicans*.[34] Furthermore, it is suggested that minocycline potentiates the action of fluconazole, penetrating biofilms and inducing intracellular calcium release.[34]

Erythromycin is a macrolide antibiotic known to fight bacterial infections. Recent findings established that it has an advantage because it does not increase toxicity in cell lines or live models, such as zebrafish.[35] It is well known that amphotericin B is the most commonly used antifungal drug and the one with the strongest antifungal activity. However, its administration is associated with high levels of toxicity in different organs.[36,37] With this in mind, several studies have tried to identify whether erythromycin can improve the activity of amphotericin B, using lower therapeutic doses that can help decrease the toxicity.[35] When the effect of erythromycin was tested against *C. albicans, C. glabrata, C. auris, C. parapsilosis, C. tropicalis*, and *C. krusei*, the checkerboard assays indicated that there is a synergistic effect of this antibiotic with amphotericin B. These results confirmed that erythromycin enhances the antifungal activity of amphotericin B on the mentioned *Candida* species.[35] Furthermore, the strongest synergistic effect occurred at erythromycin concentrations ranging from 0.1 to 0.025 mM, which contributed to a decrease in the concentration of amphotericin B that can vary between 0.03 and 0.12 μg mL^{-1}, being somewhat lower than that commonly used. Under these conditions, *C. albicans* and *C. glabrata* growth was inhibited in percentages higher than 90%.[35] Cryptococcosis is a mycosis that is also usually treated with amphotericin B. When the effectiveness of erythromycin in synergy with amphotericin B was tested against *C. neoformans* and *Cryptococcus gattii*, inhibition in the growth of both species was observed.[35]

Murines, invertebrates, and zebrafish have been used to determine the antifungal activity of some antibacterial agents. These models are useful for determining the degree of inflammation in different organs when using combination therapies compared to monotherapies with antifungals.[38] For *Candida* spp, a murine model of candidiasis showed that when there is a combination of sulbactam and colistin with caspofungin, there is a lower fungal burden in the kidneys, compared to that observed in treatment with caspofungin alone.[38] In addition, inflammation in this organ is reduced by 25%.[21,28,38] The β-lactams have also been used for treatment against *Candida* spp and *Aspergillus* spp.[39] In the case of quinolones, when combined with fluconazole and amphotericin B, a significant effect against invasive candidiasis was observed.[21] Other antibacterials, such as clarithromycin, azithromycin, norfloxacin, levofloxacin, ciprofloxacin, and rifampicin, have been used as possible antifungal therapy against *C. albicans, C. tropicalis, C. glabrata, C. parapsilosis, C. krusei, A. fumigatus*, and *A. flavus*.[31,40–42]

The strategy of repositioning drugs, specifically antibiotics, for the treatment of mycoses such as histoplasmosis, mucormycosis, pneumocystosis, and sporotrichosis has not been addressed in recent studies. The lack of information reflects a regrettable inattention to these mycoses over time, despite their clinical importance. It would be relevant to conduct a systematic exploration of the repositioning of antibiotics that have already demonstrated efficacy in other mycoses, such as candidiasis, aspergillosis, and cryptococcosis, to identify potentially effective treatments against the aforementioned mycoses.

Antivirals

Research related to antiviral drugs for the treatment of medically relevant mycoses represents an emerging frontier in the area of antifungal therapy. Initially, antiviral drugs were designed to combat viral infections; however, in the search for innovative approaches and broader therapeutic strategies, the use of these drugs for the treatment of pathogenic fungi is being explored (Table 1).[8,43] Different mycoses such as candidiasis, histoplasmosis, cryptococcosis, mucormycosis, sporotrichosis, and aspergillosis tend to be more prevalent in people who are immunocompromised, or those undergoing viral infection.[44] The compromised immunity creates an environment prone to the development of these mycoses, often generating additional challenges in clinical management.[44] Several antiretrovirals have been used for the treatment of oral candidiasis, among which are the first-generation HIV protease inhibitors (HIV-PIs). These drugs inhibit the activity of HIV-1 protease, an enzyme responsible for cleaving viral polyproteins during the maturation process.[45–47] Previous work suggests that HIV-PIs can affect important virulence factors of *C. albicans*, such as biofilm formation, adhesion, morphogenesis, and protease secretion.[48–50] Lopinavir, another important HIV protease inhibitor, was shown to have the

ability to bind to the *C. albicans* Sap2 catalytic site, resulting in fungal growth inhibition. Microscopic analysis revealed striking changes in fungal morphology, arresting dimorphism, causing defects in ergosterol synthesis, and decreasing the secretion of hydrolytic enzymes.[50] In a murine model of candidiasis, administration of lopinavir stopped the infection, and reduced fungal burden in the kidneys.[50] Second-generation PIs, such as atazanavir and darunavir showed antifungal activity against planktonic cells of *C. albicans* at a concentration of 512 μg mL^{-1}; while lopinavir inhibited the *C. auris* growth at an MIC of 128 μg mL^{-1}.[51] In addition. Both drugs reduced the biomass and cell viability of biofilms of these species.[51,52]

Different antiretrovirals used for HIV treatment, such as darunavir/ritonavir and tenofovir/emtricitabine have been used to treat cases of lung abscesses caused by *Aspergillus candidus*. When voriconazole is used in synergy with tenofovir/emtricitabine, the results are favorable and often improve the patient's life quality.[53] Darunavir can reduce proteolytic activity and capsule production in different *C. neoformans* strains.[54] Another important finding is that this antiretroviral, at concentrations of 64 μg mL^{-1}, can significantly decrease *C. neoformans* and *C. gattii* biofilm formation, reducing both metabolic activity and biomass.[54] Synergism between darunavir and fluconazole was observed in *C. gattii*, while synergism between darunavir-amphotericin B, and darunavir-fluconazole was observed in nine clinical isolates of *C. neoformans*.[55–57] For the case of the synergy between darunavir and 5-flucytosine for the treatment of cryptococcosis, the results showed that this retroviral does not interfere with the activity of antifungals in vitro, on the contrary, it is thought to enhance their action.[56] Antifungals alter the membrane sterols concentration, causing changes in porosity and structure. Thus, when the antiretroviral enters the fungal cell it reaches higher MICs than the antifungal. The advantage of this process is that the MIC values of cytotoxic drugs, such as amphotericin B are reduced.[57]

The antiviral drug raltegravir, also used to treat HIV, has antifungal activity against species of the genus *Paracoccidioides*. Infection assays with murine models showed that there is a reduction of the fungal load when this drug is administered. In addition, the lungs' function is less compromised. For in vivo assays, the drug has been administered at a concentration of 1 mg kg^{-1}.[43]

Most of the antivirals used to treat mycoses are those used for HIV, however, others such as ribavirin, galidesivir, sofosbuvir, and remdesivir, which are purine nucleoside analogs, exhibit broad-spectrum activity against many RNA and DNA viruses, such as hepatitis C and SARS-CoV-2.[58,59] Ribavirin was identified as a possible disrupting agent of the *C. albicans* vacuole, which plays an important role in yeast pathogenicity. In addition to having activity against this species, fungicidal activity has also been demonstrated against *C. parapsilosis* and *C. tropicalis*, with MICs ranging from 0.37–3.02 μg mL^{-1}.[8,26,60] Ribavirin in synergy with amphotericin B, fluconazole, or itraconazole was also shown to be effective against *C. albicans*.[26] Previous reports indicate that ribavirin may have action against some species of *Pneumocystis* and *Mucor*.[58,59] Antivirals, such as sofosbuvir, galidesivir, and remdesivir, have shown activity against the main causative agent of mucormycosis *Rhizopus oryzae*.[59]

The repositioning of existing antivirals could be an efficient way to treat some fungal infections since information is available regarding their safety profiles and efficacy. However, it is imperative to dissect the mechanisms of action of these antivirals in the fungal context. A detailed understanding of these mechanisms is essential to optimize their application and ensure clinical efficacy.

Anthelmintics

The utilization of anthelmintic drugs introduces an innovative perspective in the field of medical mycology. Traditionally, anthelmintics were designed to combat parasitic infections; however, these pharmacological agents have attracted great interest in their potential efficacy against some mycoses.[61,62] This idea allows the exploration of specific properties of these drugs to widen the spectrum of available therapeutic options.[61] The most common diseases caused by protozoa are malaria, trypanosomiasis, leishmaniasis, toxoplasmosis, and cryptosporidiosis. For the control of these, there are a large number of drugs that can be optimized for the treatment of other diseases, as will be presented below.[61]

In recent years, trials have been conducted to evaluate the impact of some anthelmintics on fungal genera, including *Sporothrix, Mucor, Histoplasma, Candida*, and *Cryptococcus*.[62–66] Miltefosine is a phospholipid analog that exhibits antiparasitic activity against cutaneous and visceral leishmaniasis and *Trypanosoma cruzi*.[63,67] The action mechanism is based on changes in the lipid composition of the protozoan membranes, which leads to an alteration in their structure, affecting intracellular signaling processes that are important for cell survival and growth.[68] The activity of this drug has

already been evaluated against yeast isolates of *Sporothrix brasiliensis* that exhibit low sensitivity to itraconazole and amphotericin B in vivo, and miltefosine was found to exhibit fungicidal activity, with MIC values of 1 to 2 μg mL^{-1}.[69] Exposure to miltefosine results in defects in plasma membrane integrity. In addition, transmission electron microscopy analyses determined that there is a decrease in cytoplasmic density, changes in cell wall thickness, and accumulation of electron-dense material in the cell wall.[69] Other effects observed were an increase in cell wall melanin in yeast treated with the drug compared to untreated cells. Cytotoxicity assays in the cell line LLC-MK2 showed that miltefosine has similar cytotoxicity values to amphotericin B; however, this drug turns out to be more selective against *S. brasiliensis*.[69] Previous work indicates that miltefosine also exhibits activity against the filamentous form of *S. brasiliensis* isolates, however, there is a broader spectrum of MIC, ranging from 0.5–4 μg mL^{-1}.[63,70]

Synergistic effects of the combination of miltefosine with some azoles have been described in several fungal species; however, when this interaction was tested using isolates of *S. brasiliensis* no synergistic effect between itraconazole and this drug was detected.[69,71] For the case of sporotrichosis the use of miltefosine could be useful to treat this disease. In addition, the MICs used were lower than those used to treat leishmaniasis.[69,72]

This antiparasitic drug has also been used for the treatment of other mycoses caused by *C. albicans, C. glabrata, C. krusei, C. auris, C. neoformans, C. gattii, A. fumigatus, Paracoccidioides* spp, and *Rhizopus* spp.[73–75] In *H. capsulatum*, the in vitro activity of miltefosine was determined, and the results showed that this drug can inhibit its development. MICs were lower when yeast-like morphology was analyzed and compared with the filamentous morphology, being these results similar to those observed in *S. brasiliensis*.[63] Considering the similarities in the clinical manifestations of leishmaniasis, histoplasmosis, and sporotrichosis, it is thought that miltefosine could potentially be used for the treatment of both mycoses.[76,77] However, these experiments need to be extrapolated to in vivo models to validate its use as a therapeutic alternative in these species.

In the case of *C. neoformans*, miltefosine was also shown to be effective in treating the infection in a murine model of cryptococcosis; however, at higher concentrations than those mentioned above.[73,78] Some causative agents of mucormycosis, such as *R. oryzae, Rhizopus microsporus, Rhizopus stolonifer*, and *Mucor velutinosus* showed growth changes when interacting with miltefosine.[66] The effects caused by this drug on fungal cells are related to modifications of cell wall components, changes in cell morphology, and oxidative stress. It is hypothesized that this drug can interact with fungal lipids (ergosterol and glucosylceramide) and cause cell death.[65,66,79]

Taking into account these findings, it has been proposed that the mechanism of action of miltefosine in fungi is related to its penetration into the plasma membrane, through its lipid component that allows it to interact with the hydrophobic chains. This drug can form micelle-like structures with proteins that favor more dynamic conformations. Proteins that have higher hydrophobicity can cause the hydrophilic groups of miltefosine to penetrate the membrane and cause a rupture (Figure 1). Fungal and mammalian cells show structural and molecular similarities, which could suggest that the inhibitory mechanism of miltefosine is similar.[80,81]

Like miltefosine, other anthelmintics, such as buparvaquone, iodoquinol, oxyclozanide, chloroquine, mebendazole, albendazole, flubendazole, and triclabendazole, have also been tested for the treatment of some mycoses.[62,82–88] Buparvaquone is an antiprotozoal used to treat the infection known as theileriosis, caused by *Theileria* species, and is administered by intramuscular injection.[89] Through bioinformatic analysis, this drug was selected because it was identified as a potential inhibitor of *S. brasiliensis* growth at low concentrations.[87] Subsequently, its activity was analyzed using the *G. mellonella* model, in addition to evaluating its mechanism of action in yeast cells.[88] The drug was administered in a single dose of 10 mg kg^{-1} to *G. mellonella* larvae to rule out cytotoxic effects and then the survival profiles were analyzed, where the activity of buparvaquone was compared against itraconazole, a drug that is commonly used to treat sporotrichosis.[88] The larva survival of the group treated with 40 mg kg^{-1} itraconazole was similar to that of the untreated infected group, only 25% of the population survived at the end of the experiment. Treatment with the antiparasitic at a lower dose than itraconazole (5 mg kg^{-1}) was able to contain the *S. brasiliensis* infection, keeping more than 80% of the larval population alive for one week after infection. After the time of experimentation, the fungal load in the larval tissue was analyzed and a decrease was observed with buparvaquone.[88] In vitro assays showed that this drug is more active than itraconazole with a MIC of 0.02 μg mL^{-1}, indicating that this antiparasitic can inhibit fungal growth at concentrations that are 4 times lower than that of common drugs, such as itraconazole.[88] In addition to the effects

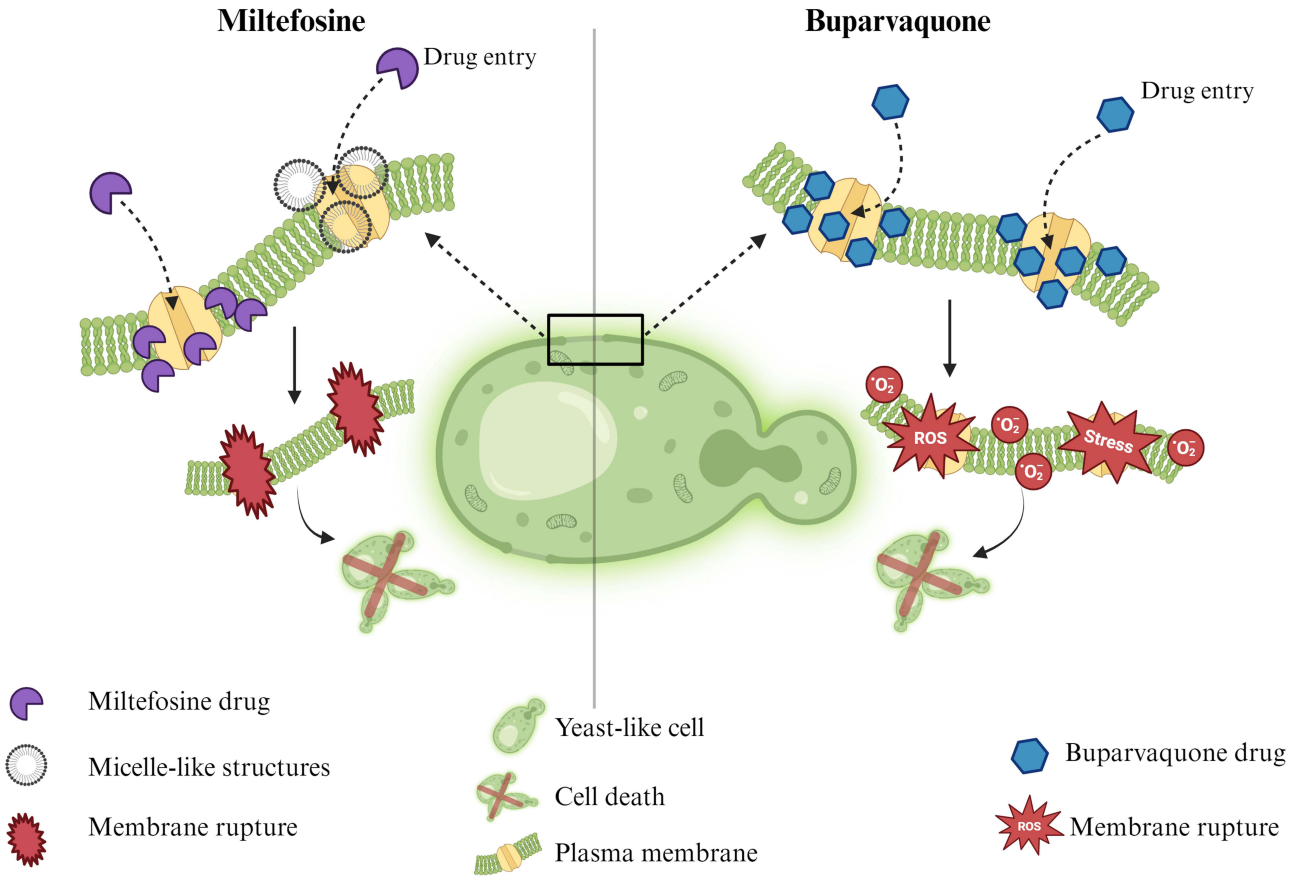

Figure 1 Action mechanisms of two of the most studied anthelmintic drugs for the treatment of different mycoses. Miltefosine can penetrate the plasma membrane of species such as *Candida albicans, Candida glabrata, Candida krusei, Candida auris, Cryptococcus neoformans, Cryptococcus gattii, Aspergillus fumigatus, Sporothrix brasiliensis, Histoplasma capsulatum, Rhizopus oryzae, Rhizopus microsporus, Rhizopus stolonifer,* and *Mucor velutinosus*. Once it penetrates the membrane, this drug can form micelle-like structures, causing changes in the membrane hydrophobicity and subsequent rupture, leading to cell death. On the other hand, buparvaquone, which has been most studied in *S. brasiliensis*, is thought to alter the redox environment of the plasma membrane, increasing the release of reactive oxygen species, and leading to membrane defects and cell death. Created with BioRender.com.

observed on growth, buparvaquone also induces morphophysiological alterations in *S. brasiliensis* yeasts, causing lesions in the cell wall and plasma membrane.[88] Taking into account the results obtained in the aforementioned study, it was suggested that buparvaquone alters mitochondrial activity in fungal cells. These changes could affect the intracellular redox environment, increasing cytosolic reactive oxygen species, and leading to plasma membrane damage in yeasts treated with the drug (Figure 1).[90,91] Buparvaquone may exert antifungal activity through a different mechanism than the antifungal drugs normally used to treat these mycoses, which could be useful for treating infections of species that have acquired resistance to commonly used antifungals.[88,92]

Iodoquinol is a quinoline derivative used as an antiparasitic drug, which has been shown to have activity against *Sporothrix* spp at low concentrations of 1 µM and almost complete growth inhibition. In addition to exhibiting antifungal activity against this genus, iodoquinol has also been reported to inhibit the in vitro growth of *Candida* species.[87,93] In general, this drug also induces changes in cell morphology, and affects membrane integrity, leading to defects in fungal survival.[87] Another anthelmintic used to treat candidiasis is oxyclozanide, which is widely used as a veterinary drug against *Fasciola hepatica*. This drug is capable of inhibiting *C. albicans* growth by 99% at a concentration of 100 µM. However, in vivo studies are needed to obtain information about its pharmacokinetics in humans.[86,94] Chloroquine, a drug used to treat malaria, can affect fungal morphogenesis and ergosterol synthesis of *C. albicans* antifungal drug-resistant strains.[84] This drug has also been used for the cryptococcosis treatment.[82]

Benzimidazoles, such as mebendazole, albendazole, flubendazole and triclabendazole, stand out as broad-spectrum anthelmintic drugs. Studies evidenced the efficacy of benzimidazoles in inhibiting the *C. neoformans* and *C. gattii*

growth, especially in the case of mebendazole and flubendazole.[95,96] Viability assays determined that flubendazole causes cellular decrease up to 9 h after treatment.[62] Interactions with current commonly used antifungals, such as amphotericin B, fluconazole, itraconazole, voriconazole, and 5-flucytosine with anthelmintics such as flubendazole, mebendazole, and benomyl were also explored against *C. neoformans* and *Cryptococcus deuterogattii*. In these assays, all combinations were found to produce indifferent results, where no synergistic or antagonistic interactions were observed.[62] Using mebendazole, it was found that this drug can penetrate the blood-brain barrier in animal models, for the treatment of cryptococcosis.

The repositioning of anthelmintics for the treatment of mycoses stands out as a strategy of great importance in the search for effective therapeutic alternatives. Among the various drugs studied for this purpose, such as those mentioned above, anthelmintics have been the subject of a more exhaustive examination, showing considerable scientific interest in their potential application against fungal infections, such as sporotrichosis and histoplasmosis, which are poorly studied mycoses. These studies have shown the versatility of these drugs, and have allowed us to put forward hypotheses that help to understand their action mechanisms in fungal cells.

Statins

The use of statins in the treatment of mycoses represents a novel and constantly explored prospect in the field of drug repositioning. Initially known for their efficacy in cholesterol regulation, statins have revealed additional properties, including potential antifungal effects (Table 2).[21,97] Studies have suggested that these drugs, by interfering with the synthesis of essential lipids for the fungal cell membrane, may exhibit antifungal activity against various fungal pathogens.[98] In addition, statins have also demonstrated the ability to modulate the host immune response, suggesting

Table 2 Summary of Statins and Anti-Inflammatory Drugs with Antifungal Activity

Medication	Fungi can be Affected	Synergy with Antifungal Drugs	Effect	Concentration Used for Treatment
		Statins		
Atorvastatin	*C. albicans* *C. glabrata* *C. tropicalis* *C. gattii* *S. schenckii* *S. brasiliensis* *S. globosa* *S. mexicana*	Fluconazole Itraconazole Ketoconazole Amphotericin B	Reduction of ergosterol content in the cell membrane	100 μM
Fluvastatin	*C. albicans* *C. glabrata* *C. dubliniensis*	Itraconazole Ketoconazole Fluconazole	Fungistatic and fungicidal effect	1–8 μg mL^{-1}
Rosuvastatin	*C. albicans* *C. glabrata* *C. dubliniensis*	Ketoconazole Fluconazole	Not reported	1–8 μg mL^{-1}
Pravastatin and Simvastatin	*S. schenckii* *S. brasiliensis* *S. globosa* *S. mexicana* *C. neoformans* *A. fumigatus* *Candida spp*	Not reported	Inhibitory activity against biofilms	No found

(*Continued*)

Table 2 (Continued).

Medication	Fungi can be Affected	Synergy with Antifungal Drugs	Effect	Concentration Used for Treatment
Anti-inflammatory drugs				
Ibuprofen	*S. schenckii* *S. brasiliensis*	Amphotericin B Itraconazole Terbinafine	Ability to inhibit growth Defects in hyphal-to-yeast dimorphism Alteration in plasma membrane	256 μg mL^{-1}
	C. albicans *C. neoformans* *C. gattii*	Not reported	Changes in plasma membrane integrity and an increase in ROS	10 mg mL^{-1}
Diclofenac and Aspirin	*Candida* spp, *Sporothrix* spp, *Cryptococcus* spp and *Aspergillus* spp	Not reported	Not reported	No found

a dual potential by affecting both the pathogen and the immune system response.[99] According to their hydrophobicity, they can be divided into hydrophilic statins, including pravastatin and rosuvastatin, and lipophilic statins, including atorvastatin, cerivastatin, fluvastatin, lovastatin, pitavastatin, and simvastatin.[100] Fluvastatin, rosuvastatin, atorvastatin, and simvastatin are drugs used to reduce cholesterol synthesis by inhibiting the enzyme hydroxy-methyl-glutaryl-CoA (HMG-CoA) reductase.[101]

Of the mentioned statins, some of these have been confirmed to exert a broad antifungal effect on medically relevant genera, such as *Candida, Aspergillus, Cryptococcus, Mucor*, and *Sporothrix*.[57,100,102,103] Atorvastatin is one of the commonly used statins for the treatment of candidiasis, sporotrichosis, and cryptococcosis. In vitro analyses revealed that this drug causes a strong inhibition of the growth of *C. albicans, C. glabrata*, and *C. tropicalis* at a concentration of 100 μM.[104] This statin has been used as an adjuvant to control infections caused by *C. gattii*.[103] Interaction assays of atorvastatin with fluconazole showed a reduction of ergosterol content in the cell membrane and an alteration of *C. gattii* capsule properties.[103] In a murine model of cryptococcosis infection, mice treated with this statin in synergy with fluconazole showed higher survival rates, improved clinical condition, and reduced fungal burden in the lungs and brain.[103] Thus, this statin could be an important drug for the treatment of cryptococcosis.

Fluvastatin and rosuvastatin also show activity against reference strains and clinical isolates of *C. albicans*, with MICs ranging from 1–8 μg mL^{-1}, and the activity of these drugs is also moderately promising against *C. glabrata* and *C. dubliniensis*.[105] Fluvastatin causes a fungicidal effect against *C. albicans*, but in C. dubliniensis the effect is fungistatic, with fungicidal potential only at high concentrations.[105] Most of the species that are included in the *Candida* genus can evade the mechanisms of action of conventional antifungal drugs; however, when trials were done with atorvastatin, fluvastatin, and rosuvastatin it was found that those strains that were resistant became susceptible when treated with these statins.[105] It was also analyzed whether these statins could interact synergistically with some azoles, such as itraconazole, ketoconazole, amphotericin B, and fluconazole, and it was found that in the case of atorvastatin, it can create a synergy with all the antifungals evaluated, rosuvastatin only shows favorable results when interacting with ketoconazole and fluconazole, and fluvastatin shows synergistic interaction with itraconazole, ketoconazole and fluconazole.[105]

Although it was determined that these statins do not inhibit *C. albicans* virulence factors, it was found that there was a reduction in the number of hyphae, compared with untreated cells. In addition, there was no change in fungal dimorphism. These therapeutic effects were also analyzed in a murine model of infection. In the case of fluvastatin, this was ineffective in vivo, this statin stimulated invasiveness, allowing the spread of this pathogen to extrahepatic sites.[105–107]

Statins have also been evaluated as a possible treatment against sporotrichosis caused by *S. schenckii, S. brasiliensis, Sporothrix globosa*, and *Sporothrix mexicana*. The assays were conducted using filamentous cells and yeasts because each morphology has different susceptibility profiles to antifungal drugs.[69] When the statins simvastatin, atorvastatin, and pravastatin were tested on the growth of both morphologies, an antifungal effect of the three drugs was found on both

morphologies of all four species.[57] The MIC used to inhibit yeasts was 4-fold lower than that observed for filamentous cells, which could be related to the cell wall organization in both morphologies and the presence of melanin.[57,108] Of the three drugs, pravastatin had the highest MIC, which may be related to the different chemical characteristics of statins.[57] Simvastatin produces inhibitory activity against biofilms of *Sporothrix* spp, which demonstrates the antifungal action of this drug.

Based on the results of several trials, it is proposed that statins cause mitochondrial dysfunction, changes in lipid structure, and plasma membrane dynamics in fungal cells. HMG-CoA reductase is an enzyme that catalyzes the conversion of HMG-CoA to mevalonic acid, which is a precursor of cholesterol. Therefore, at the cellular level, these drugs can inhibit the conversion of HMG-CoA to mevalonate, resulting in a reduction in the production of cholesterol by the cells. Extrapolating this process to fungal cells, it is thought that the same may occur with the biosynthesis of ergosterol, which behaves as the main fungal membrane sterol. Changes in ergosterol synthesis lead to cell death and membrane changes.[57,106,109,110] The antifungal activity of simvastatin has also been described in *Candida* spp, *C. neoformans*, and *A. fumigatus*.[107,111]

The repositioning of statins for the treatment of mycoses is not only an innovative strategy but also presents a comprehensive and promising approach in the fight against these fungal infections. The ability of statins to interfere with important fungal cellular mechanisms, combined with their role in modulating the immune response, suggests significant therapeutic potential. In addition, repositioning statins offers economic and time advantages by using already approved compounds. Although research will continue to explore the precise details of their clinical efficacy and safety, the potential of statins in the treatment of mycoses represents a promising horizon for the treatment of mycoses.

Anti-Inflammatory Drugs

Anti-inflammatory drugs, initially designed to modulate immune responses and reduce inflammation, show the potential to address some mycoses by influencing complex interactions between the immune system and fungal pathogens (Table 2). Furthermore, by modulating the inflammatory response, anti-inflammatories could influence the microenvironment surrounding fungi, altering conditions conducive to their proliferation.[57,112] Anti-inflammatory drugs act by inhibiting cyclooxygenases COX-1 and COX-2 to reduce the production of prostaglandins, which are lipid molecules that play an important role in fungal colonization. Anti-inflammatory drugs specifically block the biosynthesis of these prostaglandins by inhibiting one or both COX isoenzymes, contributing to a variety of physiological and pathological functions.[112–114]

Ibuprofen, a non-steroidal anti-inflammatory drug widely known for its antipyretic and analgesic properties, exemplifies a compound approved for clinical use that could play a prominent role as an antifungal agent.[88,115] In recent decades, several studies have shown that this drug can inhibit fungal growth and enhance the activity of some antifungal agents against some pathogenic fungi. The in vitro activity of ibuprofen alone or in synergy with antifungals, such as amphotericin B, itraconazole, and terbinafine was tested against *S. schenckii* and *S. brasiliensis*. Ibuprofen, as a single agent, can inhibit the growth of both species with an MIC of 256 µg mL-*1*.[88,116] When this anti-inflammatory is used in synergy with itraconazole, terbinafine, or amphotericin B the MIC of the antifungals is reduced. Transmission electron microscopy analyses after exposing *Sporothrix* species to ibuprofen and amphotericin B revealed defects in hyphal-to-yeast dimorphism. However, when ibuprofen alone is used as a treatment, it does not interfere with the cell dimorphism process.[116] In addition, changes in plasma membrane integrity and an increase in reactive oxygen species were observed.[88,116] Nevertheless, in vivo assays in animal models exploring the combination therapy of ibuprofen with antifungals are needed to confirm in vitro observations. Moreover, this drug has been reported to have action against *C. albicans* and non-*albicans* species. At a concentration of 10 mg mL^{-1}, ibuprofen can kill *C. albicans* cells, cause changes in ion exchange, mainly potassium, and induce ultrastructural alterations in the membrane.[115] In *C. neoformans* and *C. gattii*, ibuprofen also exerts antimicrobial action, and when used in synergy with itraconazole and amphotericin B the effect on fungal cells is enhanced. Treatment of cryptococcal cells with ibuprofen triggered cell death through reactive oxygen species, membrane damage, and induced cellular stress through activation of the high osmolarity glycerol pathway.[117] Other drugs, such as diclofenac and aspirin have also been studied for the treatment of mycoses such as candidiasis, sporotrichosis, cryptococcosis, and aspergillosis.[113,116,117]

Other Medications

In addition to the medications already mentioned, there are alternative drugs with antifungal activity that can be used. Antipsychotics, like haloperidol, trifluperidol, and sertraline have been already reported to possess activity against *C. albicans* and *C. neoformans*.[8,118] Chlorpromazine and trifluoperazine are confirmed to have activity against filamentous fungi, such as *Aspergillus* species.[8,16] Anticancer medications also represent a source of potential repurposing drugs. Tamoxifen has a potential activity against *C. albicans* and *C. neoformans* within macrophages.[8,119] Finally, antifolates also have been reported to be effective against yeast development by reducing the quantity of ergosterol.[8]

Advantages and Challenges of Drug Repositioning

Drug repositioning stands out as a novel strategy in the treatment of mycoses, offering several significant benefits. In contrast to the traditional drug development process, repositioning allows one to take advantage of already existing compounds, considerably accelerating the time needed to bring new treatments to market.[120,121] This methodology also takes advantage of extensive prior information on the safety and pharmacokinetics of the repurposed drugs, which simplifies clinical trials and decreases the risk of unexpected side effects. Furthermore, by repurposing already approved drugs, the costs associated with research and development are significantly reduced, resulting in a more efficient and economically viable therapeutic option (Figure 2).[121–123]

Despite its advantages, drug repurposing has some drawbacks in the treatment of mycoses. Reuse of existing drugs may limit the identification of new mechanisms of action, compromising the ability to address specific aspects of mycoses or develop more targeted therapies.[124,125] In addition, continuous exposure of microorganisms to the same drug

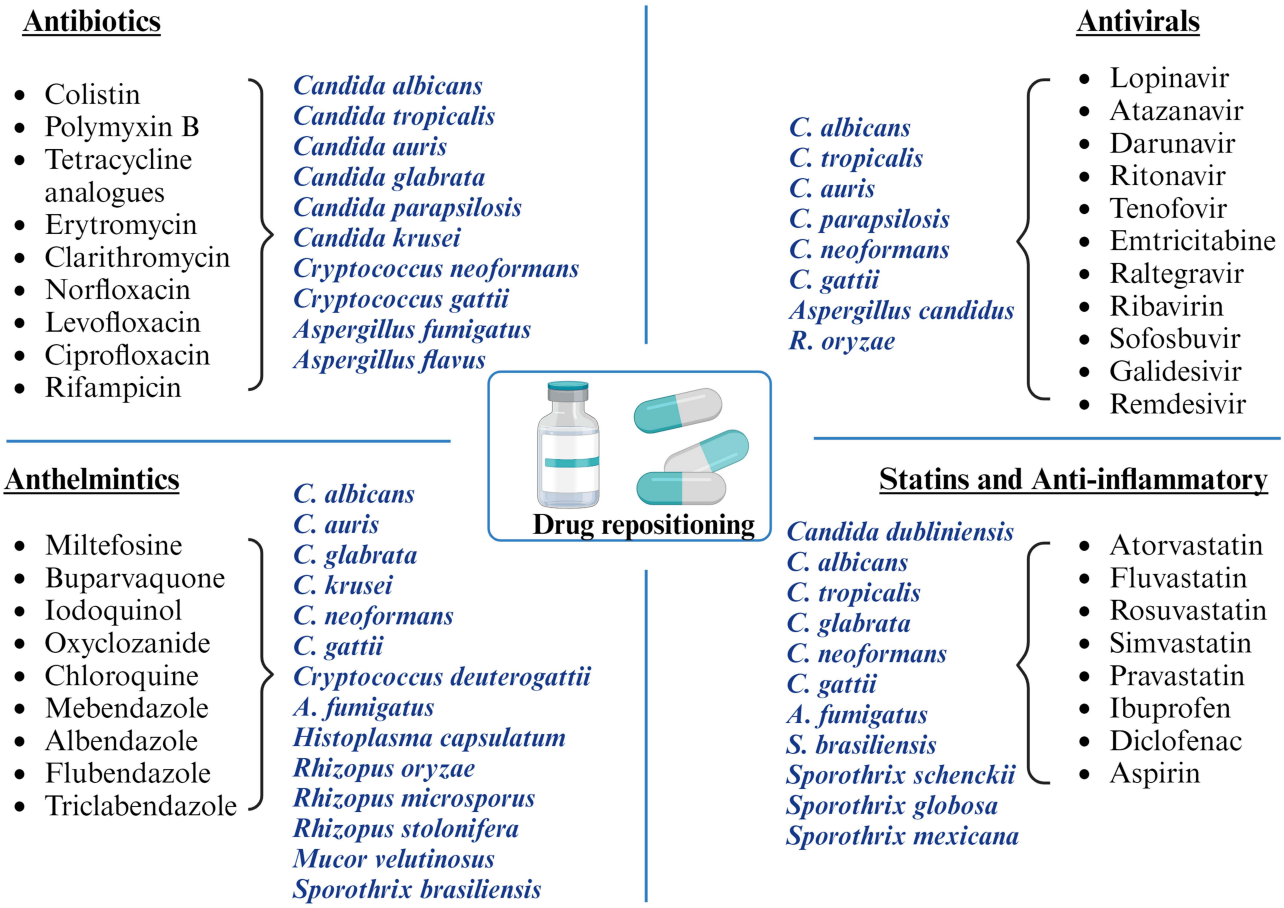

Figure 2 Drug repositioning. Summary of the most studied antibacterials, antivirals, anthelmintics, statins, and anti-inflammatory drugs for the treatment of medically important fungal species. Created with BioRender.com.

could contribute to the development of resistance, especially if the drug has been widely used in other indications.[125] Intellectual property and patent issues may complicate the process, as patent rights may still be in place for the original use of the drug, generating legal conflicts.[121] Complexities may also arise in adapting the formulation or delivery of some drugs to treat certain mycoses, requiring clinical adjustments and additional studies.[126] Regulatory approval can be challenging, as regulatory agencies may be cautious in evaluating drugs for new indications, especially without sufficient clinical evidence to support efficacy and safety in the new setting. Careful evaluation of these disadvantages is essential to ensure appropriate selection of strategies in the treatment of mycoses.[121,123,127]

Future research will focus on validating and optimizing these strategies, determining appropriate doses, identifying potential synergistic combinations, and addressing potential resistance. Successful clinical application of these repositioned therapies will depend on a deeper understanding of specific mechanisms of action in fungal settings and the ability to overcome inherent challenges, such as clinical adaptation and resistance. Ultimately, drug repositioning offers a promising outlook for improving therapeutic options against mycoses, responding to the urgent need for more effective and advanced treatments in the field of antifungal therapy.[17,128,129]

Conclusions

Drug repositioning for the treatment of mycoses, addressing pathologies such as aspergillosis, cryptococcosis, candidiasis, histoplasmosis, sporotrichosis, and mucormycosis, is a promising and necessary field. Reuse of existing drugs, such as antibacterials, antiparasitics, antivirals, statins, and anti-inflammatories, offers a valuable alternative to face the increasing resistance to conventional antifungal drugs. Although potential candidates have been identified, as mentioned above, in vivo assays with animal models are needed to fully understand the mechanisms of action of these compounds on fungal cells. In addition, standardization of protocols is required to help define appropriate doses of drugs to address mycoses, considering the diversity of strains and clinical isolates. The variability in the response of different pathogens, as mentioned throughout the paper, along with the development of resistance mechanisms, underscores the need to establish precise guidelines. These protocols would not only facilitate a more effective treatment delivery but would also be critical to addressing the increasing complexity of fungal infections and countering the challenges posed by evolving resistance mechanisms.

Ultimately, it is necessary to support these investigations with computational tools, to strengthen the understanding of the possible action sites of different drugs. The integration of computational approaches would allow a more accurate prediction, enriching and complementing the results of experimental trials. It is also important to mention that although repositioning is a good alternative, the search for therapeutic targets for the development of new antifungal drugs should keep going.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare no conflicts of interest in this work.

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