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Using Fungi to Combat Drug-Resistant *Candida*: Methods to Increase the Possibility and Reduce the Cost and Time for Finding New Antifungal Compounds

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ABSTRACT

The most common fungal infections in humans are caused by five species of *Candida* including *C. albicans*, *C. glabrata*, *C. tropicalis*, *C. parapsilosis*, and *C. krusei*. Although they generally cause non-severe, mild infection, *Candida* species cause life-threatening bloodstream infection (candidemia) and infection of internal organs (invasive candidiasis) in patients with compromised immunity or treated with invasive medical devices. The recent evolution of multidrug resistance among *Candida* species, the limited choice of antifungal medicines, and the reluctance of drug manufacturers to discover novel medicines are projecting *Candida* infection as a major global health threat. We stress here the importance of exploring fungi from less studied and extreme habitats and varying the culture conditions to increase the chance of finding novel anti-Candida drugs. We also bring into focus a crowd sourcing model involving students, faculty and research labs to reduce the time and cost of discovering such novel drugs.

1 | Introduction

Candida (Ascomycota, Saccharomycetales, Saccharomycetaceae), a unicellular yeast also exhibiting pseudohyphal and hyphal growth, is a commensal microbe of the mouth, digestive and vaginal tracts. Although a commensal, species of *Candida* can shift their lifestyle to pathogenic mode and cause less serious superficial mucocutaneous candidiasis or life-threatening invasive systemic candidiasis. Invasive infection happens when immunity is reduced due to chemotherapy or organ transplantation, and in people affected with HIV/AIDS, diabetes or kidney failure. Patients without an immunodeficiency disorder undergoing blood transfusion or total parenteral nutrition [1] or being treated with medications such as IL-17 inhibitors for autoimmune diseases [2] could develop invasive candidiasis [1]. *Candida* species cause nosocomial infections through medical implements such as central venous catheters, cardiovascular devices, and urinary catheters [3]. In such cases, it invades the bloodstream and spreads to different parts of the body causing invasive candidiasis. Candidiasis is controlled by treatment with antifungal antibiotics including polyenes, azoles, echinocandins, and 5-Flucytosine which kill the pathogen by inhibiting ergosterol, nucleic acid or cell wall biosynthesis [4]. In the last two decades, species of *Candida* including *C. albicans*, *C. auris* (*Candidozyma auris*), *C. glabrata* (*Nakaseomyces glabratus*), and *C. parapsilosis* have developed multidrug resistance to antifungals including azoles, echinocandins and polyenes thus gaining importance as an antimicrobial resistance (AMR) pathogen [5, 6]. The burden of Candidaemia has increased globally in the past few years [7] and is responsible for causing considerable morbidity and mortality worldwide [8].

2 | The Need for New Antifungal Drugs to Manage Drug-Resistant *Candida*

The emergence of drug-resistant *Candida* pathogens and the limited number of antifungal chemicals available make candidiasis a global health threat. Development of an antibiotic to manage drug-resistant *Candida* is fraught with difficulties. Apart from evolving cellular mechanisms like the development of drug efflux pumps, over expression of targeted enzymes and reducing the binding affinity of a protein to the drug and developing an extra copy of a chromosome harboring a drug-resistant gene (Figure 1), *Candida* cells within a genetically homogeneous population have different levels of resistance to an antifungal drug due to phenotypic variation. Such 'hetero-resistant phenotypes' could survive long enough till mutations affording resistance to that drug develop [9]. Since both humans and fungi possess many common metabolic pathways due to their eukaryotic nature, specific targets for antibiotic action are limited thus adding to the difficulties of finding new effective metabolites. Apart from this, a *Candida* sp. naturally resistant to one drug could acquire resistance to another drug [5] thus reducing the treatment options drastically. Originally thought to be strictly asexual, it is now known that several *Candida* species reproduce sexually thus bringing in to focus its potential role in the evolution of new virulence factors and drug resistance mechanisms [10]. Parasexual recombination is also responsible for the spread of drug resistance in *Candida* [11]. Furthermore, the emergence of fluconazole-resistant *C. parapsilosis* and multidrug resistance among *C. tropicalis* in various parts of the world is an increasing health concern [8, 12]. Indeed, *C. auris* and *C. albicans* were listed as two of the four critical group pathogens in the World Health Organization's first-ever fungal priority pathogens list emphasizing the need for new treatment options. The WHO's Fungal Priority Pathogens List has placed *C. auris* and *C. albicans* under the critical priority group [13] and insists on the discovery of novel drugs as one of the priority areas to manage drug-resistant candidiasis. Although chemical modifications of existing antibiotics to develop new drugs are easier, the discovery of new chemicals exhibiting new modes of action is essential. This is because such a drug could be used to manage AMR pathogens, and being hitherto unexposed to the drug, the pathogen is likely to take a relatively longer time to evolve resistance against it. Currently, various methods including AI and molecular methods are being tried to identify novel compounds and potential drug targets for managing AMR pathogens [14, 15]. Here, we stress the need to explore fungi from less explored habitats (LEH) using conventional culture methods to unravel such novel antibiotics to manage drug-resistant *Candida* and also recommend a crowdsourcing method to reduce the cost and time for achieving this.

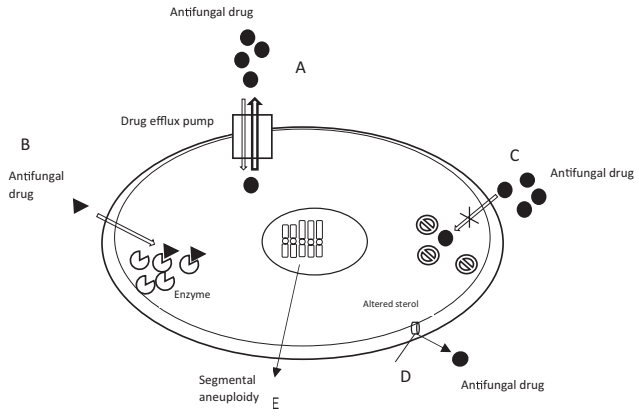

FIGURE 1 | Mechanisms of resistance to antifungal drugs in *Candida albicans*. (A) Increased production of efflux pumps increases drug efflux thus reducing the concentration of the drug inside the cell. (B) Increased expression of the protein targeted by the drug such that despite the presence of the drug several drug-free molecules are available. (C) Mutations resulting in proteins with reduced affinity for drug binding. (D) Alteration of sterol molecules of the cell membrane to decrease the binding of the drug to the membrane. (E) Aneuploidy resulting in an extra copy of the chromosome with the drug resistance gene.

3 | Fungi of LEH as a Source of Novel Antifungal Drugs

As a consequence of their long evolutionary history, unique lifestyle and adaptations to occupy a diverse variety of ecological niches, the fungi have developed the ability to synthesize an extraordinary number of secondary metabolites thus making them an attractive choice for discovering novel antibiotics. Indeed, a few reports of fungi of LEH producing anti-Candida metabolites support this (Table 1). The fact that in 2023 alone, a total of 553 natural products (219 polyketides, 145 terpenoids, 35 steroids, 106 alkaloids, and 48 peptides) of fungal origin have been reported substantiates this [25]. A survey of literature over a period of 46 years (from 1969 to 2015) on natural products exhibiting anti *C. albicans* activity shows that most of these are of plant origin with only a few from fungi underscoring the need to explore fungi more assiduously [26]. However, the discovery of novel natural products is fraught with the major drawback of the repeated discovery of the same molecules [27]. One reason for this could be that almost all the currently used antibiotics have been obtained from bacteria and fungi of only one ecological niche, viz. the soil [28]; this necessitates exploration of microbes of other habitats for novel antibiotics. Natural products of fungi are usually genus or species specific since horizontal gene transfer in fungi is rare compared to bacteria [29]. This underscores the need to isolate rare fungi for increasing the chances of isolating novel natural antifungal products. Generally, extreme habitats select microbes adapted to the harsh conditions they provide thus ending upharboring many unique species. Interactions among these species could result in the formation of novel metabolites. Considering the above, and the fact that fungi of LEH (endophytes, extremophilic, and extremotolerant) have not been studied assiduously for antifungal chemicals reinforces the need to explore these fungi.

4 | Fungal Endophytes

These are fungi which infect and thrive within living plant tissues without causing any disease. They are a constant constituent of a plant endobiome, conferring many fitness advantages to their host plants and are prolific producers of novel biologically active secondary metabolites [30]. Endophytic fungi possess higher metabolic potential than their soil or litter-dwelling counterparts due to selection pressures posed by the host plants'

TABLE 1 | Some novel anti-*Candida* compounds from different less-studied sources.

Source	Compound(s)	References
Endophytic fungus *Xylaria* sp. YM 311647 of *Aadirachta indica*	Sesquiterpenes	[16]
Endophytic fungus *Drechmeria* sp., of *Panax notoginseng*	Indole diterpenoids	[17]
Fungi from hypersaline soil	Unidentified	[18]
Scedosporium apiospermum FKJ-0499 isolated as a deep sea fungus	Tyroscherin	[19]
Aspergillus restrictus isolated from deep sea	Penicillenols	[20]
Endophytic *Alternaria tenuissima* OE7 of *Ocimum tenuiflorum*	2-Nitro-2-Methylpropanol, 1,2-Pentanediol and 3-Butenyl methyl sulfoxide, (Z)-2-Pentene, Sulfide, sec-butyl ethyl and 2-hydroxy-N,3,3-trimethylbutanamide	[21]
Aspergillus sp. isolated from soil	Waikialoid	[22]
Mycotoxin	Deoxynivalenol	[23]
Cocultures *of Penicillium fuscum* and *P. camembertii/clavigerum*	Berkeleylactones	[24]

chemical defenses [31] and hence could be a store house of novel molecules and natural product-based scaffolds [32, 33]. There are only a few reports on fungal endophytes exhibiting anti-candidal activity [16, 17]. Although endophytes of terrestrial flowering plants have been explored for bioactive compounds inhibiting pathogenic bacteria [34], those harbored by marine seaweeds and lichens have not been studied for this potential; we have shown that several fungal endophytes of sea grasses and seaweeds produce metabolites which inhibit the malarial parasite *Plasmodium falciparum* [35] as well as bacteria, fungi and algae [36]. However, their potential to manage *Candida* has not been addressed. Chitin, being the specific cell wall chemical of fungi, is a choice drug target which will not interfere with human metabolism [37]. Drugs interfering with chitin synthesis such as chitinase inhibitors would weaken the cell wall structure of the fungi enabling efficient entry of antifungal molecules into the cell. Endophytes produce a variety of chitin-modifying enzymes and thus could be a fit model for understanding the various mechanisms of chitin synthesis regulation to be used for obtaining novel antichitin drugs [38].

5 | Fungi of Extreme Habitats

Extreme ecosystems select microbes adapted to survive in such harsh environments. Although the density and diversity of microbes could be lesser in extreme habitats when compared with normal habitats, the evolution of strict extremophiles (those that live only in extreme habitats) leads to the presence of unique microbial diversity in such habitats. Owing to their high phenotypic plasticity, fungi survive in extreme habitats exhibiting desiccation [39], high and low temperatures [40], acidic and alkaline pH [41], salinity [42], or radiation [43] and even under simulated Mars conditions [44]. Since extreme habitats support unique microbes, interactions among them could result in the production of novel metabolites thus making them a rich source of antibiotics [45, 46]. Indeed, a few of these microbes produce antibacterial and antifungal compounds only under extreme growth conditions [47]. Many common fungi such as *Aspergillus niger* and *A. terreus* surviving as endosymbionts of marine sponges produce metabolites which inhibit pathogenic *S. aureus* (NCIM 5021), and *P. aeruginosa* and *E. coli* [48]. Panchal et al. [18] showed that halotolerant fungi from solar salterns inhibited human pathogenic *C. albicans*, *C. dubliniensis*, *C. glabrata*, *C. lusitaniae*, *C. tropicalis*, and two clinical isolates of *C. auris*. Of the 154 fungal endosymbionts isolated from 32 marine sponge species, we observed that 53 and 44 produced metabolites which inhibited the growth of *C. albicans* and *C. tropicalis* respectively (T. S. Suryanarayanan, J. P. Ravishankar, N. Thirunavukkarasu, M. B. Govinda Rajulu, unpublished). *Scedosporium apiospermum* FKJ-0499, a fungus isolated from a deep-sea sediment produces a new compound N-demethyl tyroscherin which inhibits a clinical isolate of *Candida auris* [19]. A deep-sea fungus *Aspergillus restrictus* inhibits hyphal growth and biofilm formation of *C. albicans* [20]. Apart from fungi of extreme habitats, less-studied fungi such as endolichenic, resinicolous, and endolithic fungi as well as those associated with marine sponges and corals, tropical peat, and rumen should be studied for the production of novel antifungal chemicals [49, 50].

6 | Biofilm Formation

Apart from the SNPs and aneuploidy-mediated methods (by which target protein production is increased, drug binding site is modified, or intracellular drug accumulation is decreased) to develop drug resistance [51], *Candida* species form biofilm to escape drug action. Individual *Candida* cells (planktonic cells) adhere to the surface of human body tissues and on medical devices, proliferate and produce extracellular matrix to form biofilm. The biofilm, apart from protecting the pathogen from host defense, is drug impermeable and increases the cells' resistance to antifungal therapy nearly 1000-fold [52]. When growing as a biofilm, *Candida* exhibits intrinsic, reversible,

multidrug resistance and also develops some extremely drug-tolerant "persister cells" which multiply and form new biofilms [52]. Furthermore, melanin pigment could be deposited on biofilm which increases pathogen virulence by evading immune response and antifungal chemicals. Apart from enzyme-mediated synthesis of melanin, *C. auris* also forms this pigment by non-enzymatic oxidation of L-DOPA [53]. Hence, chemicals inhibiting melanin formation could be useful in reducing the virulence of *Candida*. It is known that natural product antifungals exhibit higher antibiofilm activity compared to synthetic antifungals [54]. Plants are the main sources for deriving such metabolites [55]. Recently, fungi from extreme habitats are being investigated for these compounds [56]. Metabolites of an endophytic *Alternaria tenuissima* inhibit biofilm formation and hyphal development of *C. albicans* [21]. Metabolites of a soil isolate of *Aspergillus* [22] and the mycotoxin deoxynivalenol [23] produced by *Fusarium* spp. inhibit biofilm formation by *C. albicans*. Though endophytic fungi of seagrasses produce metabolites inhibiting biofilm development by Gram-positive and negative bacteria [57], very few of these fungi have been tested for their activity against *Candida*. These observations again stress the importance of studying fungi for managing Candidasis.

7 | Improving the Chances of Finding Novel Anti-Candida Compounds

7.1 | Culture Conditions

Antibiotic production is a method adopted by microbes to overcome competition exerted by co-occurring microbes in an environment. It is thus natural that many genes coding for antibiotic production are not expressed under conventional axenic culture conditions. Altering the culture conditions such as the carbon source, nitrogen source, pH, reduced nutrition status, and presence of metal ions could be tried to induce its production. Co-cultivation (fungal–fungal, fungal–bacterial, or fungal–host combination) recaptures natural conditions and stimulates/increases the production of metabolites including antibiotics that are not formed in axenic cultures [58–61]. Co-culturing of *Penicillium fuscum* and *P. camembertii* yields several new 16-membered-ring macrolides called Berkeley lactones which inhibit methicillin-resistant *Staphylococcus aureus* (MRSA), *C. albicans*, and *C. glabrata*, *Bacillus anthracis*, and *Streptococcus pyogenes* [24]. It is suggested that co-culturing drug-resistant *Candida* with actinomycetes or *Aspergillus niger* which are hyper secondary metabolite-producing microbes, could result in the production of novel antibiotics inhibiting the yeast [50]. To increase the chances of discovering novel antibiotics, communities of drug-resistant *Candida* and fungi from extreme environments could be incubated together which could result in the production of inhibitor metabolites. This could be more profitable than the routine search in a natural environment for novel antibiotics since it creates a habitat filtering mechanism as the interaction is more focused due to the use of specific *Candida* in the combat. For this, we propose a modified Rossi-Cholodny buried slide technique. A mixture of spores or mycelial bits of a fungus that co-occurs with *Candida* in hospital wastes is mixed with agar medium and allowed to set in a sterile beaker. Slots are made in this medium and sterile microscope slides coated with agar and inoculated with drug-resistant *Candida* are inserted in the slots and incubated in a moist chamber. The slides are removed periodically and plated on agar medium to detect inhibition of *Candida*.

Extreme habitats support, in addition to the obligate residents (which are adapted to survive only in the extreme condition), stress-tolerant microbes capable of growth even in normal environments. Because of their heightened ecological fitness, these facultative forms are adapted to tolerate different strengths of stress. Although many of these fungi may be common residents of normal environments, their conspecifics from a stressed environment could exhibit different traits due to phenotypic plasticity [62]. Stress-tolerant microbes should be subjected to various degrees of stress to unravel their secondary metabolite spectrum since the production/activity of their metabolites and enzymes could vary with the degree of external stress [63–66].

7.2 | Activating Silent Gene Clusters

Many of the fungal gene clusters regulating the production of secondary metabolites are inactive under culture conditions. Such silent genes could be activated to produce novel secondary metabolites by altering the various culture conditions and by the use of epigenetic modifiers. Epigenetic modifiers activate latent biosynthetic pathways to yield cryptic natural products. In fungi, more than 500 secondary metabolites were induced or enhanced by epigenetic modifiers. Some of them exhibited significant biological activities such as cytotoxic, antimicrobial, anti-inflammatory, and antioxidant activity [67]. Since epigenetic modifiers trigger novel metabolite production [68], select fungi such as endophytic xylaraiceae which support a high diversity of secondary metabolite gene clusters [69] and fungi that occur with *Candida* in hospital equipment/waste could be treated with these chemicals to obtain novel anti-Candida metabolites.

Apart from the above methods, heterologous expression and directional modification could reveal more novel bioactive metabolites from fungi [70]. This gains importance since many fungi in nature are uncultivable making their metabolites unavailable for use. Creating heterologous expression plat forms would increase the chances of finding novel metabolites and possibly anti-candidal molecules from uncultivable fungi and silent gene clusters of fungi from various habitats [71].

7.3 | Reducing the Cost and Time for Finding Novel Anti-Candidal Compounds

Development of a new antibiotic takes 10–15 years and costs more than 1 billion US$. Even if marketed, there are restrictions on its clinical use to reduce the chances of development of resistance against it. Considering the time taken and poor returns, pharma companies have stopped investing in finding new antibiotics. Recognizing the impending need for novel antibiotics, various methods including advance purchase contracts, not-for-profit research, and tax incentives [72] and incentives from government and non-government organizations [73] have been proposed to encourage the search for novel antibiotics. Taking some aspects of Phage Hunters

Integrating Research and Education (PHIRE) funded by the Howard Hughes Medical Institute, we proposed a four-phase crowdsourcing model which at once motivates undergraduate students to conduct scientific research and reduces the time and cost for building a national repository of microbial genetic resources [74]. This model could be used for obtaining novel antibiotics from microbes including fungi [50]. In *Phase I*, students in colleges/universities located near LEHs are trained to isolate fungi from those unique habitats. After a few months, each institution would have isolated a number of fungi from different LEHs. This is followed by training the students to do simple agar plate assays for screening these fungi for their production of anticandidal metabolites. *Phase II* involves national and voluntary funding agencies for funding further research as well as institutes/industries with expertise to identify novel genes present in these fungi. In *Phase III*, the institutions transfer the fungal cultures positive traits to national centers and private labs participating in the program to enable the purification and identification of the anti-Candida compound(s) and to carryout the mandatory steps involved in processing it for coming up with a marketable novel compound. In *Phase IV*, a portal for the collection of all the fungi identified by this model from various LEHs is created to provide all information such that it aids in providing information to improve such research and policy development for progress. An elaborate record of the exercise right from the beginning is maintained so that all the stakeholders are recognized for compensation when a successful antibiotic is marketed.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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