Review

Current Perspectives of Antifungal Therapy: A Special Focus on *Candida auris*

Ganeshkumar Arumugam *, Manickam Muthuselvam, Patrícia Michelle Nagai de Lima, Rajaram Rajendran, Juliana Campos Junqueira *

Posted Date: 23 May 2024

doi: 10.20944/preprints202405.1513.v1

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Current Perspectives of Antifungal Therapy: A Special Focus on *Candida Auris*

Ganeshkumar Arumugam [1,2,*], Muthuselvam Manickam [3], Patricia Michelle Nagai de Lima [1], Rajaram Rajendren [4] and Juliana Campos Junqueira [1,*]

[1] Department of Biosciences and Oral Diagnosis, Institute of Science and Technology, São Paulo State University/UNESP, São José dos Campos, São Paulo-CEP: 12245-000, Brazil.
[2] Department of Materials Physics, Saveetha School of Engineering, Saveetha Institute of Medical and Technical Sciences (SIMTS), Thandalam, Chennai, 602105, Tamil nadu, India.
[3] Department of Biotechnology, Bharathidasan University, Tiruchirappalli 620024, Tamil Nadu, India.
[4] Department of Marine Science, Bharathidasan University, Tiruchirappalli 620024, Tamil Nadu, India.
* Correspondence: Authors: Ganeshkumar Arumugam (ganeshbiotek@gmail.com) and Juliana Campos Junqueira (juliana.junqueira@unesp.br)

Abstract: *Candida auris* is considered an emerging *Candida* species that has rapidly spread all over the world. The evidence of its origin and emerging resistance is still unclear. The severe infection by this species causes significant mortality and morbidity among the elderly and immune compressed individuals. Development of drug resistance is the major factor associated with therapeutic failure of existing antifungal agents. Previous studies addressed the antifungal resistance profile and drug discovery for *C. auris*. However, comprehensive coverage of these information in a single investigation yet to be available. In this review, we have mainly focused on recent development in therapeutic strategy against *C. auris*. Based on the available information, several differential approaches were discussed, including existing antifungal drugs, chemical compounds, essential oils, natural products, antifungal peptides, immunotherapy, antimicrobial photodynamic therapy, drug repurposing, and drug delivery systems. Among them, chemical medications, natural products, and antifungal peptides are the prime contributors. However, a limited number of resources are available to prove the efficiency of these potential therapies in clinical usage. Hence, we hope that the data gathered in this review can encourage in vivo studies and clinical trials.

Keywords: *Candida auris*; antifungal therapy; antifungal natural products; antifungal peptides; antifungal essential oil

1. Introduction

1.1. Candidiasis, Outbreak, and Epidemiology

Candidiasis is an infection caused by opportunistic pathogens of *Candida* genus, with manifestations varying from mucocutaneous lesions to life threading bloodstream infections. *Candida albicans* is the most common *Candida* species found in various human anatomical sites, including oropharyngeal, esophageal, gastrointestinal, and genital mucosa. Other non albicans species and *Candida* related species are also simultaneously reported in human body, such as *Nakaseomyces glabratus* (formerly *Candida glabrata*), *Pichia kudriavzevii* (formerly *Candida krusei*), *Candida parapsilosis*, *Candida tropicalis*, etc. Recently, an emerging pathogen named *Candida auris* has been isolated from different clinical samples like urine, stool, vaginal and rectal swabs. Like other *Candida* species, patients with comorbidities or weakened immune system, previously exposure to antifungals and subjected to long-stay in healthcare settings, are at risk for *C. auris* infection [1,2].

C. auris is recognised as an emerging fungal pathogen because of its wide distribution, multidrug-resistant (MDR) behaviour, high transmissibility, strong association with nosocomial infections and high mortality rates. *C. auris* expresses numerous virulence traits as well as tolerance to common antifungals. This leads to development of therapeutic failure when tried to treat with most common class of antifungals that includes azoles, polyene and echinocandins. In 2009, the first

 doi:10.20944/preprints202405.1513.v1

isolate of *C. auris* was reported from Japanese female patient with ear discharge. In the same year, twelve isolates were obtained from otitis media patients in South Korea. During time frame between 2009 to 2011, twelve isolates of *C. auris* had identified in India in patients with bloodstream infection. The first outbreak was noted during 2016 and 2017 in Europe and USA respectively. Subsequently, *C. auris* was reported in more than 47 countries according to Centre for Disease Control (CDC) [3,4], and nowadays it is recognised as a threat to world community by World Health Organisation (WHO). Based on susceptibility profiles, outbreak potential and clinical manifestations, the *C. auris* isolates were broadly classified into five clades (Figure 1). Recently, an unpublished data indicated a sixth clade of *C. auris* isolated from the samples collect in Singapore. These uncommon Clade VI isolates were entirely different from all others isolates in relation to antifungal resistance genes, mating type locus, and chromosomal rearrangements. Although *C. auris* isolates have widely investigated, the real rate of prevalence remains uncertain because of availability of proper dataset [5].

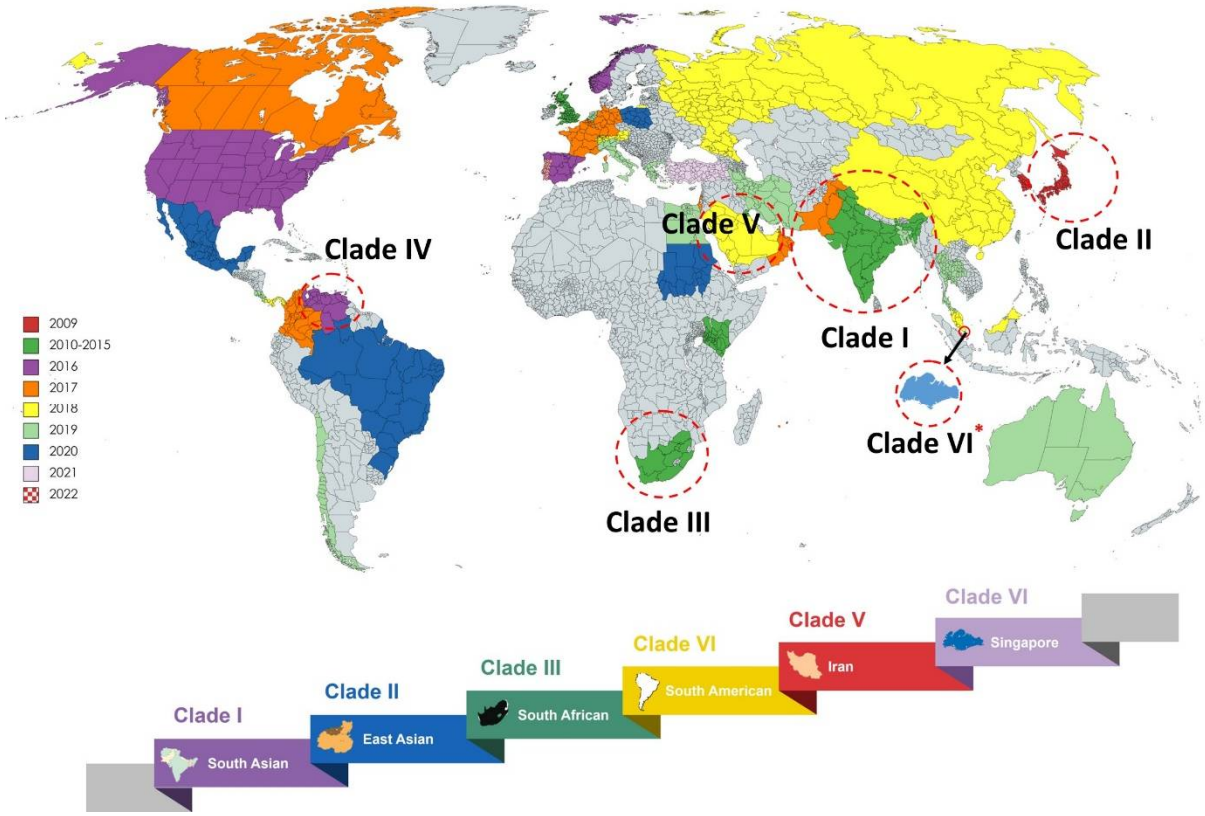

Figure 1. An updated illustration of distribution pattern of *C. auris* in different geographical location around the world. The data presented here are based on the information retained from recent publication A colour scheme was used to represent the year of *C. auris* reported. Over 40 countries reported positive for *C. auris* between 2009 and 2022. By 2022, five clades were reported worldwide; however, recently unpublished data reported the existence of a sixth clade, suspected to have originated in Singapore [5]..

Furthermore, the origin of *C. auris* has not yet been elucidated; and some authors speculates that global warming may be a possible reason for its spread [6]. *C. auris* cells remain viable for several month on environmental surfaces and medical equipment and prefer to colonize the skin of patients rather than other mucosal surfaces, leading to high probability of person-to-person transmission [7]. Since they freely live on the biotic and abiotic surfaces and tolerate antifungal and decontamination agents, the eradication of these fungal cells became extremely complicated [8–11]. All these factors make *C. auris* a global threat for the immunocompromised patients in healthcare settings.

1.2. Drug Resistance: Molecular Bases

Clinical breakpoints of existing antifungals for *C. auris* yet to be established; however, CDC has recommended clinical breakpoints established from closely related other *Candida* species. The general

 doi:10.20944/preprints202405.1513.v1

guideline defined to correlate the antifungal resistance of *C. auris* are ≥32, ≥2, ≥4, ≥2 and ≥4 for fluconazole, Amphotericin B (Amp B), anidulafungin, caspofungin and micafungin respectively (CDC, 2020). Most clinical isolates of *C. auris* are multidrug resistance or pan-resistant, especially for resistance to fluconazole followed by Amp B and voriconazole[12]. Wide administration of fluconazole for the *Candida* prophylaxis and the use of azole derivatives in various purposes, such as agriculture area, might be the prime factor for azole resistance. Thus, echinocandins are the only choice for *C. auris* infection treatment, although some studies already reported echinocandin-resistant strains [13].

Prevalence of drug-resistant *C. auris* strains were analysed in several studies worldwide. Isolates from India, Pakistan, South Africa, and Venezuela presented 93% of resistance for fluconazole, 35% for Amp B, and 7% for echinocandins [2]. A resistance rate of 90% for fluconazole was observed for isolates from India and United States, whereas all the isolates from UK showed resistance to fluconazole (100%). Amp B was the second most common antifungal related to *C. auris* resistance, with 20-30% of resistant isolates in India [14], 30% in US [15], 62.5% in Saudi Arabia [16], 23.2% in Kuwait [17] and 33.3% in Oman [18].

Besides prevalence analysis, some studies investigated the molecular bases of drug resistance in *C. auris* isolates. Different mechanisms of azole resistance have been discussed, including mutation in target genes (*ERG11*) [19], overexpression of genes encoding drug transporters and increased copy number of the TAC1B gene [20]. Mutation in TAC1B gene was the second most observed mutation in *C. auris* after ERG11. The mutations like F126L, Y132F, and K143R were frequently noted in ERG11 gene of fluconazole resistant isolates, whereas A640V, A657V, and F862_N866del mutation were observed in TAC1B gene of fluconazole resistant isolates [20,21].

Mechanisms of resistance to echinocandins are mainly associated with FKS1 gene involved in biosynthesis of glucan and maintain the integrity of cell wall. As like *C. albicans* and *C. glabrata*, FKS1 is the target of echinocandins and mutations like amino acid substitution and deletion in hot spots of FKS1 results in therapeutic loss [22,23]. The most frequently observed FKS1 mutations are S639F, S639P, and S639Y in hot spot 1; however, less common mutations in hot spot 1 were also reported (F635el, F635L/Y, S639T, D642Y) [24–26].

Regarding Amp B, the exact resistance mechanisms were not yet elucidated. The elevated MIC levels observed in Amp B-resistant *C. auris* isolates were associated with mutation in ERG6 gene [24]. Due to loss of sterol methyltransferase activity, these isolates accumulate more cholestatype sterols [21]. Similarly, in vitro studies evidenced that Amp B-resistant strains bearing nonsense mutations in genes like ERG11 and ERG3 [19].

2. Therapeutic Options

2.1. Current Approved/Considered Antifungal Therapy

The antifungal pipeline for *C. auris* infections includes different promising antifungal candidates, such as Rezafungin, Ibrexafungerp, Fosmanogepix and T-2307 (Figure 2). Rezafungin is a potential antifungal derived from anidulafungin that exhibited strong *in vitro* activity against *C. auris*, including strains resistant to other echinocandins. It boasts a long half-life allowing for once-weekly dosing schedule. In clinical trials, rezafungin has demonstrated a favourable safety profile with minimal side effects. On March 31, 2023, Rezzayo™ (rezafungin for injection) was approved in the US for use in adults with candidemia and invasive candidiasis. Nevertheless, it is still crucial to confirm its efficiency through realtime clinical data. Considering the cost, its more expensive than other antifungals, which could pose an access barrier in most of the clinical setting.

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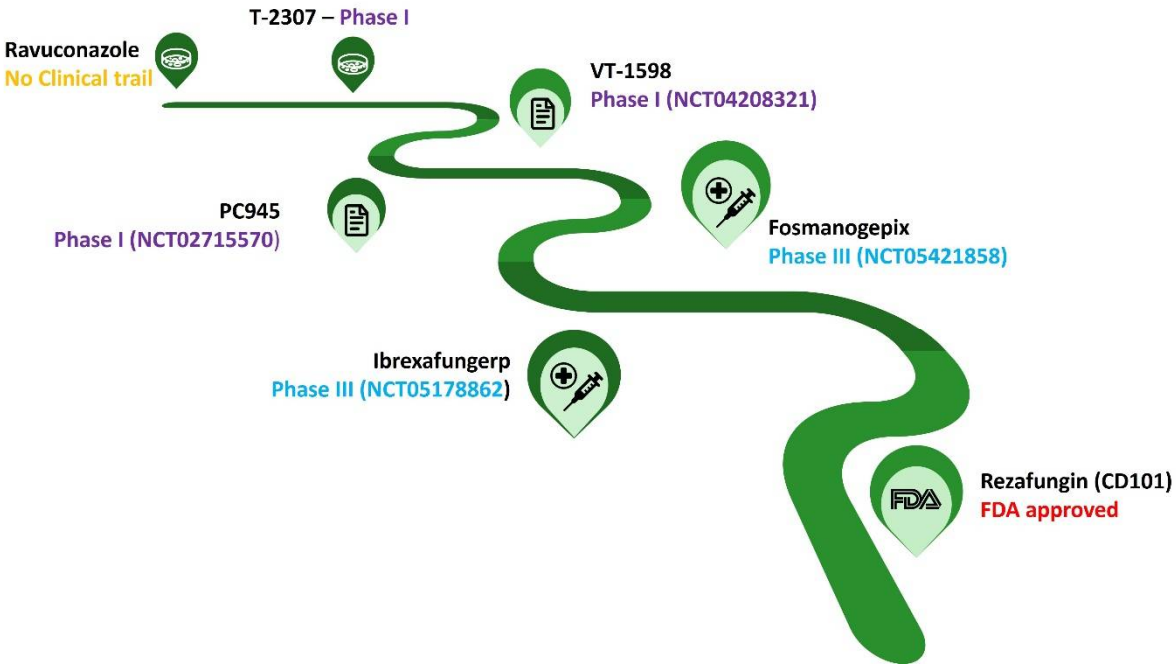

Figure 2. Current treatment options for *C. auris* medicated prophylaxis. As of December 2023, only one molecule was approved by US-FDA to manage *C. auris* and other *Candida* medicated infections. Rezafungin is a modified version of anidulafungin, the occurrence of structural modification aimed to reduce the hepatotoxicity of the molecules while its efficiency was retained. The data presented here is based on the recent information provided by Wang et al., 2024 [27].

Ibrexafungerp (IBX) was focused by the researchers because of the superior antifungal behaviour. It is a class of (1,3) β-d-glucan synthase inhibitors like echinocandins, a semi-synthetic derivative of enfumafungin. The mode of binding of IBX was not disturbed by FKS mutations, also its mode of binding was different than echinocandins which limited cross-resistance. During the preclinical investigations, it was confirmed its potential as a therapeutic agent for managing highly resistant *Candida* infections. IBX remined active against fluconazole and echinocandin resistant *Candida* isolates and multidrug-resistant *C. auris*. However, IBX expressed concentration-dependent fungicidal activity on different clinically important fungi, including *C. auris* [28–31].

Fosmanogepix (known as APX001) is also a promising antifungal agent exhibiting potential to treat *C. auris* infections. While not yet commercially available, clinical trials provided encouraging results regarding its efficacy and safety against this multidrug-resistant fungus. Fosmanogepix demonstrated strong activity against *C. auris* strains in laboratory tests, including those resistant to standard antifungals like echinocandins. Phase II trials evaluating fosmanogepix for *C. auris* infections showed high treatment success rates. A study published in 2022 reported 80% success in clearing *Candida* from blood cultures with patient survival at the end of treatment. Apart from *C. auris*, fosmanogepix exhibited a broad spectrum of activity against other *Candida* species and molds, making it a valuable tool for wider fungal infections. Clinical trials indicated that fosmanogepix was well-tolerated with minimal side effects. Serious adverse events or treatment discontinuations were not reported. Fosmanogepix is available in both intravenous and oral forms, offering flexibility in treatment administration based on patient needs and disease severity [32]. Multiple Phase III clinical trials are currently investigating fosmanogepix for different fungal infections, including invasive candidiasis caused by *C. auris*. These trials will further evaluate its efficacy and safety on a larger patient population. Fosmanogepix is not yet approved for clinical use in any country. While the promising results from Phase II trials are encouraging, further research and evaluation through Phase III trials are still required [33].

Another novel antifungal agent is T-2307 that belongs to the triterpenoid class. As like other *Candida* species, *C. auris* was also sensitive to T-2307. In addition, it exhibited potent in vitro activity against a broad spectrum of fungal pathogens. Its mechanism of action was associated with inhibition of fungal cell wall biosynthesis [34–36]. Phase I clinical trial evaluating the safety and tolerability of

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T-2307 in healthy volunteers was recently completed, showing promising results. Phase II clinical trials to assess its efficacy in patients with fungal infections are planned to begin in 2024. Considering its promising preclinical data and ongoing clinical trials, T-2307 could be approved for clinical use against *C. auris* infections within the next few years.

2.2. Chemicals as an Emerging Weapon Against C. auris

Whilst some antifungal agents are in clinical trials phase, the scientific community has worked intensely to discover other therapeutic options. Here several new compounds with activity against *C. auris* are listed (Table 1) and discussed. Toepfer and team investigated the compound clorgyline and its derivatives, which worked as multi-target inhibitors of Cdr1 and Mdr1 efflux pumps of *C. albicans* and *C. glabrata. Especially,* clorgyline analogs M19 and M25 expressed high ability to inhibit the efflux pump activity of *C. auris* [37]. Recent investigations have discovered the active of pyrazole moiety compounds against fluconazole-resistant *C. auris* isolates. These compounds exhibited a broad spectrum, high potency, high selectivity, low cytotoxicity and anti-drug resistance [38]. Novel tetrazoles featuring isoxazole moiety were also identified as highly selective antifungal agents, displaying outstanding antifungal activity against fluconazole-resistant strains of *C. albicans*, *C. glabrata* and *C. auris* [39]. A novel benzoanilide antifungal (compound A1) showed potent activity against *C. auris* cells through blocking of virulence biosynthesis and alterations in cell wall by inhibition of glycosylphosphatidylinositol (GPI) and GPI-anchored proteins [40]. Furthermore, a compound named NSC319726 (thiosemicarbazone zinc chelator) exhibited MIC values ranging from 0.125 to 0.25 mg/L for *C. auris* isolates belonging to five different clades, expressing fungistatic activity in time-kill curves [41].

Table 1. Minimal Inhibitory Concentration (MIC) of different classes of chemically derived compounds against *C. auris.*

Group	Compound	MIC/MIC range (μg/ml)	Reference
Clorgyline analogs	M19	86.7 - 98.3 μM	Toepfer et al., 2023 [37]
	M25	137 - 228 μM	
Novel Tetrazoles Featuring a Pyrazole Moiety	8, 11, 15, 24, 25	< 0.0625 – 4, 0.125 – 8, < 0.0625 – 2, 0.5 – 64, < 0.0625 - 16	Chi et al., 2023 [38]
Novel tetrazoles featuring isoxazole moiety	10d, 10h, 13r, 13u	0.008, < 0.008, 0.0313, 0.0313	Ni et al., 2023 [39]
Benzoanilide group	Compound A1	0.5 - 2.0	Tu et al., 2023 [40]
Piperidine based 1,2,3-triazolylacetamide derivatives	pta1, pta2, pta3, pta4, pta5, pta6	0.48 - 0.97, 0.24-0.48, 0.12-0.24, >250, >250, >250	Srivastava et al., 2020 [41]
Pyrrolidine-based 1,2,3-triazole	P1 – P10	0.97 - 62.5	Wani et al., 2023 [42]
Nitroxoline		0.125 to 1	Fuchs et al., 2021[43]
NSC319726 is a thiosemicarbazone		0.125 to 0.25	Li et al., 2021 [44]
Manogepix	Flu^R	0.002 to 0.063	Maphanga et al., 2022 [45]
	Flu and $Amp\ B^R$	0.004 to 0.031	
	Pan^R	0.004 μg/mL and 0.008	

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Manogepix	PanR - New York	0.008 to 0.015	Zhu et al., 2020 [46]
Gold(I)−Phosphine Complex 4		3.9 to 7.8	Dennis et al., 2019 [47]
Gold(I)−Phosphine Complex 6		1.95	
Phenylthiazole Compound 1	-	0.25–2	Mohammad et al., 2019[48]
Ceragenins	CSA-44, CSA-131, CSA-142, CSA-144	0.5 – 1, 0.5 – 1, 2 to 8, 0.5 - 2	Hashemi et al., 2018 [49]

Flu^R – Fluconazole resistant; Amp B^R – Amphotericin B resistant; Pan^R – Resistant to more than two antifungals.

Lohse and their colleague have aimed to develop antifungal metabolites from a group of FDA (Food and Drug Administration) approved compounds. The selection of these compounds was based on MIC values of <10 μM. Among the hydroxyquinolines tested, clioquinol was more active than others, however the authors were unable to guaranteed their mechanisms of action [42]. In another study, hydroxyquinoline derivative known as nitroxoline, was also active against 35 isolates of *C. auris* with the MIC range of 0.125 to 1 μg/mL. The resultant MIC values were lesser than the activity of fluconazole and Amp B. At last, nitroxoline was recommended for the treatment of *C. auris* mediated candiduria. However, in vivo and clinical efficiency remains questionable [43].

Many authors focused on the study of Manogepix, a *pyridine-isoxazole-based antifungal agent.* Manogepix was active against most clinical isolates of *C. auris* belonging to South Africa. Over 300 *C. auris* isolates were studied, including 335 fluconazole resistant, 19 fluconazole and Amp B resistant, 1 Amp B resistant and 2 pan resistant. MIC values of manogepix ranged from 0.002 to 0.063 μg/mL for fluconazole resistant isolates, 0.004 to 0.031 μg/mL for fluconazole and Amp B resistant isolates, and 0.004 μg/mL and 0.008 μg/mL for pan-resistant isolates. The activity of manogepix was more than 3 folds than azoles, 4 folds than echinocandins, and 9 folds than Amp B [44]. Manogepix also showed activity against clinical isolates from the New York Outbreak with MIC values of 0.008 to 0.015 mg/L against pan-resistant isolates [45]. Now, some studies have addressed the efficiency of manogepix with anidulafungin against *C. auris* [46].

Various studies have reported the biological role of metallic gold or its salt. Among them, gold(I)−phosphine complexes and gold salt auranofin were tested against a panel of 28 fungal strains including *Candida* spp., *Cryptococcus* spp., *Aspergillus* spp., and *Fusarium* spp. Notably, two (complex 4 and 6) square-planar gold(I) complexes produced a remarkable antifungal activity in most of the tested isolates. In relation to *C. auris* isolates, complex 4 and 6 resulted in MIC ranges between 3.9 to 7.8 and 1.95 μg/mL respectively. However, auranofin did not produce considerable results (MIC >31.3 μg/mL) in *Candida* species [47].

The activity of new promising antifungal compounds has also investigated against *C. auris* in biofilm stage. Among several phenylthiazole small molecules, compound 1 emerged as the most potent antifungal, inhibiting the growth of *C. albicans* and *C. auris* strains at concentrations ranging from 0.25 to 2μg/mL. This compound reduced 50% of biofilm produced by *C. auris* with similar activity to Amp B [48]. A class of molecule ceragenins were also found to inhibit both planktonic and biofilm form of *C. auris*. Promisingly, they led to significant reductions of fungal infections in ex vivo mucosal tissues [49].

2.3. Essential Oils Are the Potential Sources of Novel Antifungal Skeletons

Essential oils are the fatty acids moieties derived from bioactive plants. These chemical substances alone or in combination with other drugs produce significant biological activities among the different targets. Thus, essential oils have been extensively studied as antimicrobial agents against bacteria and fungus, including *C. auris* strains.

 doi:10.20944/preprints202405.1513.v1

For instance, Parker et al. demonstrated the effectiveness of selected essential oils against *C. auris* and found the superior activity for the oils from Cinnamon leaf, clove bud, lemongrass and basil. The effective eradication of *C. auris* occurred with MIC values ranged from 0.01% to 1.0%. The same study reported the interactions between conventional antifungal drugs and essential oils. Clove bud oil synergistically interacted with fluconazole and flucytosine to combat *C. auris* [50].

Essential oil extracted from the seeds of *Withania somnifera* was also tested against *C. auris*, producing IC50 at 5.96 mg/mL and fungistatic mechanism confirmed by killing assay. Its mechanism of action was associated with disturb in the membrane integrity of *C. auris* cells, evidenced through ergosterol binding and sorbitol protection assays. However, seed oil was inactive against mature biofilm formed by *C. auris* [51].

In a more detailed study, Di Vito et al. tested 15 essential oils against 10 clinical strains of *C. auris*. The results indicated that *Cinnamomum zeylanicum* essential oil was most effective against *C. auris* (MIC; 0.06% v/v) in synergy with antifungal drug fluconazole. Further they verified that cinnamaldehyde was the sole reason for the antifungal activity [52]. In the same year, another group of researchers identified the antifungal potency of *Cinnamomum cassia* essential oil [53], this oil also rich in chemical constitute like cinnamaldehyde [54]. The level of cinnamaldehyde in plants may vary depending upon the species; however, *C. cassia and C. zeylanicum* has 85.3% and 90.5% cinnamaldehyde respectively [55].

2.4. Natural Products against Candida auris

The world of medicine is increasingly turning to nature's bounty for solutions to modern health challenges. In the realm of fungal infections, a fascinating arsenal of weapons lies hidden within plants, microbes, and even marine organisms. These diverse and potent molecules, meticulously crafted by living organisms, offer a promising alternative to traditional antifungal drugs. With the rising tide of fungal resistance to existing therapies, natural products present a glimmer of hope in the fight against these tenacious pathogens. A list of natural products with anti-candidal activity are listed in Table 2 and Figure 3.

Table 2. Antifungal natural products against *C. auris* .

Species	Molecule	MIC range (µg/ml)	Ref
Turbinmicin-producing bacterium *Micromonospora* sp. WMMC-415	Turbinmicin	0.125-0.50	Zhang et al., 2020 [56]
Hypoxylon rubiginosum and *Hypoxylon texense*	Penta-O-galloyl-β-D-Glucose	1-8	Marquez et al., 2023 [57]
Hormonema carpetanum	Enfumafungin	64	Cheng et al., 2023 [58]
	Enfumafungin B	> 64	
	Enfumafungin C	> 64	
Sphaceloma sp from the leaf of *Poplar* sp	Persephacin	2.5	Du et al., 2023 [59]
Myrothecium inundatum	Myropeptin C	16	Jagels et al., 2023 [60]
	Myropeptin D	16	
	Myropeptin E	16	
	Myropeptin A1	4	
Hypomyces pseudocorticiicola FKA-73	Hakuhybotrol	>128	Watanabe et al., 2023[61]
	Cladobotric acids F	>128	
	Pyrenulic acid A	16	

 doi:10.20944/preprints202405.1513.v1

	F2928-1	2	
	Cladobotric acids E	2 to 4	
	Cladobotric acids H	16 to 32	
	Cladobotric acids A	4 to 8	
Lactobacillus paracasei 28.4	Culture extract	3.75 to 7.5 mg/mL	Rossoni et al., 2020 [62]
	Carvacrol	125-500	Ismail et al., 2022 [63]
	Geraniol	225	Fatima et al., 2023 [64]
	Nikkomycin Z	0.125 to >64	Bentz et al., 2021[65]
	6-shogaol	16-32	Kim & Eom, 2021) [66]

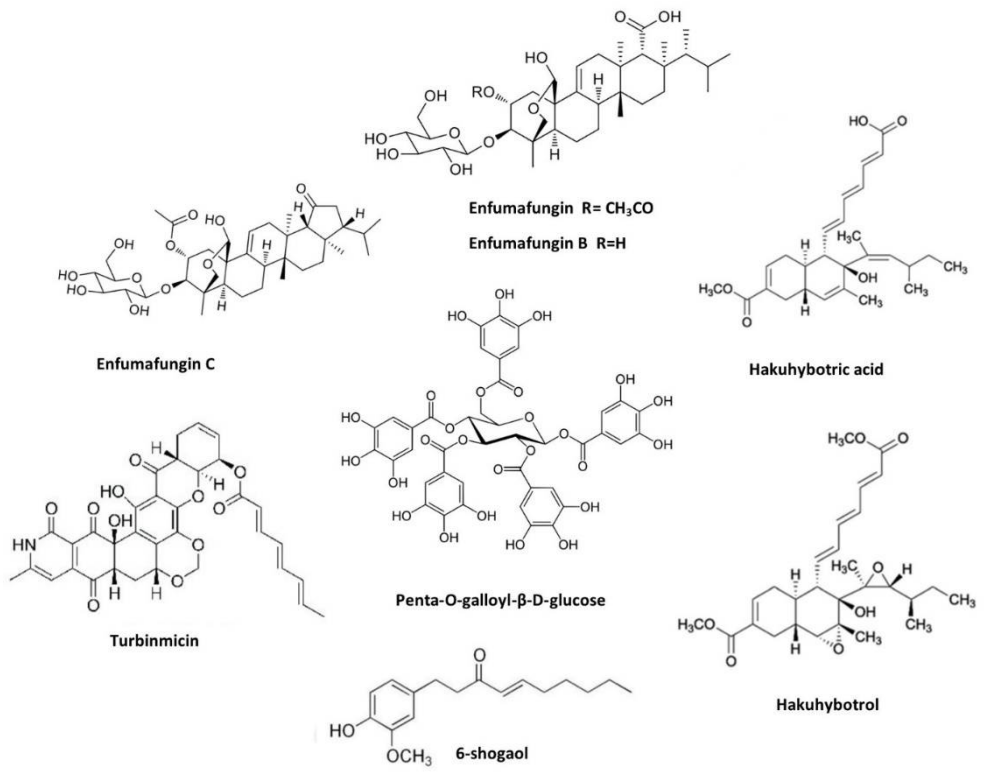

Figure 3. Scheme of potential molecules from different sources of natural products against *C. auris.*

Among the compounds from plants, great focus has been given to Carvacrol, a phenolic monoterpenoid found in essential oils of oregano, thyme, pepperwort, wild bergamot, and other plants. Due to its broad spectrum of biological responses [56]. Carvacrol was active against *C. auris* by modulating the expression level and action of certain antioxidant enzymes [57]. As like carvacrol, geraniol is another monoterpene alcohol found in geranium oil as a major component. Recently, Fatima and her colleague utilized geraniol against *C. auris*. Geraniol displayed fungicidal activity and

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inhibition effect on metabolically active biofilm of *C. auris*. Subsequently, geraniol improved the survival rate of *C. elegans* infected by *C. auris* [58].

Penta-O-galloyl-β-D-glucose (PGG), a bioactive product of many plants (firstly isolated from the leaves of *S. terebinthifolia*) was also investigated against *C. auris*. Chemically, PPG is hydrolysable tannin reported with plenty of biological activities such as antibacterial, anticancer, and antiviral activities. PPG demonstrated anticandidal activity with the MIC ranges of 1-8μg/mL against drug-resistant *C. auris* [59]. Kim and Eom explored the antifungal and anti-biofilm properties of 6-shogaol against *C. auris*. Shogaols are pungent constituents of ginger similar in chemical structure to gingerol [60]. 6-shogaol demonstrated effectiveness in inhibiting the growth of *C. auris* at the concentration range of 16-32μg/mL, further it showed promise activity in preventing the formation of biofilms and controlled the secreted aspartyl proteinase activity [61].

In relation to natural compounds from microbial sources, Rubiginosin C obtained from the stromata of the ascomycetes *Hypoxylon rubiginosum* and *Hypoxylon texense*, effectively inhibited the formation of biofilms of *C. auris* and *C. albicans* [62]. In the last years, many studies focused on the compound Enfumafungin, a triterpene glycoside found in the culture supernatant of *Hormonema carpetanum*. This compound was acted as a probe to produce biologically active antifungal Ibrexafungerp. Enfumafungin analogues were isolated; they are enfumafungin B and C. Both compounds were effective against clinically relevant *C. auris* with the MIC of 64 μg/mL. Further molecular docking studies confirmed that these compounds binded in transmembrane region of FKS1 of β-(1,3)-D-glucansynthase [63].

In another study, Persephacin isolated from the endophytic fungus *Sphaceloma* sp showed activity against a wide spectrum of fungal species (*C. albicans*, *C. glabrata*, *C. parapsilosis*, *C. krusei*, *C. kefyr*, *C. tropicalis* and *C. auris*). Persephacin resulted in the MIC values around 2.5 μg/mL, which was equal to the activity expressed by Amp B [64]. A group of new linear lipopeptides (Myropeptin C−E and Myropeptin A1) isolated from saprotrophic filamentous fungus *Myrothecium inundatum*, also produced good inhibition in *C. auris* cells. In vitro hemolysis, cell viability, and ionophore assays indicated that these compounds target mitochondrial and cellular membranes, inducing cell depolarization and cell death [65]. Subsequentely, Hakuhybotrol along with six known cladobotric acids F, E, H, A, pyrenulic acid A and F2928-1 were isolated from culture broth of *Hypomyces pseudocorticiicola* FKA-73. Most of these compounds showed promising antifungal activity against azole resistant and sensitive strains of *C. auris.* In particular cladobotric acids F and E were able to cause a high inhibition in the fungal growth [66].

Although most antifungal compounds from microbial sources were isolated from fungus, some studies investigated compounds from bacterial cultures. For example, culture extract of *Lactobacillus paracasei* 28.4 inhibited several *C. auris* strains, acting against planktonic cells, biofilms, and persister cells. Further experiments confirmed that supplementation derived from *L. paracasei* 28.4 protected *G. mellonella* from *C. auris* infection [67].

Finally, compounds from marine sources have also been investigated against *C. auris*. Turbinmicin, a potent lead obtained from the marine reservoir (Turbinmicin-producing bacterium *Micromonospora* sp. WMMC-415.), displayed antifungal properties in several in vitro and in vivo experiments. Turbinmicin expressed fungal-specific mode of action, targeting Sec14 of the vesicular trafficking pathway, a unique target yet to be investigated [68]. A subsequent investigation showed that Turbinmicin exhibited a MIC value of 0.125 mg/mL and an inhibitory action on mature biofilm of *C. auris* [69].

2.5. Peptide-Based Strategies for Eradicating C. auris

Antimicrobial peptides (AMPs) are another alternative group of components reported with superior biological property. They are an active form of smaller segment of protein produced by various organisms that includes plants, insects, human and other small animals. They have its own function when it presents within the host; therefore, they expressed some unexceptional behaviour towards medically important pathogens like bacteria, fungi, and virus. On the other hand, antimicrobial resistance mechanism of AMPs has not yet been elucidated. Wider investigations identified some direct or indirect mechanisms of AMPs against pathogens, with capacity to reduce the virulence traits. As per the information available [70], there are more than 3940 AMPs reported until now that include 3146 natural peptides, 190 predicted and 314 synthetic AMPs. In more specific,

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HsAFP1 (*Heuchera sanguinea*); NaD1 (*Nicotiana alata* flowers); Psd1 (*Pisum sativum* seeds); Psoriasin, CGA-N46, β-Defensin-1 to 4, Histatin-5 from *Homo sapiens*; Gomesin, Heliomicin, Jelleine I to IV, Lasioglossin I to III from insects and arachnids; and NFAP2 from filamentous fungi *Neosartorya fischeri* were reported with anticandidal activity [71]. The list of AMPs with its significant biological role and its origin was presented in Table 3.

Among the microorganisms, both fungi and bacteria produce potent antimicrobial peptides. The fungus *Neosartorya fischeri* produces two different peptides; they are NFAP and NFAP2 with 57 and 52 amino acids length, respectively. Cystine residues present in these structures have remarkable importance, since they significantly improve the stability of the peptides at high temperature [85,86]. They were identified as potent molecules against fluconazole (FLC)-resistant *C. albicans* [87] and *C. auris* [88]. Notoriously, NFAP2 interacted with most of the azoles and echinocandins, producing significant FICI values [88]. The bacteria *Bacillus subtilis* produces a lipopeptide (AF4) that showed broad spectrum of antifungal activity on more than 110 fungal isolates. Recently, AF4 at 8 mg/L was found to kill most of *C. auris* cells. Mode of killing was associated with severe cellular membrane disruption and elevated generation of Reactive Oxygen Species (ROS) [76].

Table 3. Antifungal peptides against *C. auris* derived from different classes of organisms.

S. no	Origin	Name	MIC (µg/ml)	Ref
1	*Homo sapiens*	Human β-defensin-3	3.125 to 12.5	Shaban et al., 2023[72]
2	*Homo sapiens*	Cathelicidin peptides LL-37	25-100	Rather et al., 2022 [73]
3	*Homo sapiens*	Histatin-5	7.5 µM	Pathirana et al., 2018[74]
4	Barley plant	Defensin-like Protein 1 (D-lp1)	0.047–0.78 mg/mL	Kamli et al., 2022 [75]
5	*Bacillus subtilis*	AF_4	8	Ramesh et al., 2023[76]
6	American rattlesnake (*Crotalus durissus terrificus*)	Crotamine	40–80 µM which is equal to 0.2 - 0.4 mg/ml	Dal Mas et al., 2019 [77]
7	*Pomacea poeyana* - freshwater snail	Pom-1, Pom-2	8.5, 8.4	Raber et al., 2021[78]
8	Scorpion venom	ToAP1, ToAP2	>100 µM, 50 - >100 µM	Pinheiro et al., 2023[79]
9	Brilacidin	Semi synthetic	80	Dos Reis et al., 2023 [80]
10	Chemically prepared, Myristoylated and Non-Myristoylated Peptides	Pep-A, Myr-A, Pep-B, Myr-B, Pep-C, Myr-C	>256, >256, >256, 16-32, >256, 16-64	Bugli et al., 2022 [81]
11	Symbiotic NCR Peptide Fragments	NCR169C 17–38	6.25 µM	Szerencsés et al., 2021[82]
		NCR169C 17–38 ox	12.5 µM	
12	Analogue of the Peptide Cm-p5			
	Monomers	Cm-p5, Cyclic, Hcy	11, 27, Not active	Vicente et al., 2019[83]
	Dimer	Dimer 1 (parallel)	30	

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		Dimer 2 (anti-parallel)	31	
13	Rhesus macaque θ-defensin (RTD)	RTD – 1, RTD - 2	6.25, 6.25	Basso et al., 2018[84]
	Olive baboon θ-defensins (BTD)	BTD – 2, BTD – 4, BTD - 8	3.125, > 25, 3.12 - 6.25	

Human body is also a potent source of antifungal peptides, so far many peptides with different biological functions were reported from the human body. Peptides like human β-defensin-3 [72], human cathelicidin peptides LL-37 [73] and salivary histatin-5 [74] were recently reported with antifungal activity on *C. auris* (Table 3). Human β-defensin-3 and cathelicidin peptides LL-37 produced 100% and 70% of synergy with fluconazole [72,73]. Anticandidal activity of human histatin-5 was also documented against other non albicans species like *C. glabrata*, *C. parapsilosis*, *C. tropicalis*, *C. krusei*, *C. guilliermondii* and *C. tropicalis* [89]. In addition, some studies highlighted the ex vivo effects of histatin-5 on mouse models, by reducing the fungal burden in both oral and vaginal infections models [90,91].

Plant defensins are potent molecules that protect plants from infections by effectively combating microbes without harming host cells. Certain plant-derived peptides, like HsAFP1 [92], NaD1[93], Psd1 [94] and D-lp1 [75] exhibited strong activity against *C. auris*. Among them, D-lp1completely inhibited biofilm formation and virulence of *C. auris* [75]. As like plant AMPs, other living organisms were found to be a source of antifungal molecules. Crotamine (from south American rattlesnake) acted on multidrug-resistant *C. auris* without harming cells [77]. Pom-1 and Pom-2 peptides from *Pomacea poeyana* (Cuban freshwater snail) inhibited bacteria like *Pseudomonas aeruginosa* and fungi including *C. auris* [78,95]. Scorpion venom peptides ToAP1 and ToAP2 showed promising antifungal effects against *C. auris*, alone and associated with other antimicrobial drugs [79] (Table 3).

2.6. Antifungal Immune Therapy against C. auris

Apart from AMPs, there are some other proteinous molecules that arouse interest as therapeutic strategy towards *C. auris* due to its immunological properties. These group of molecules can be derived from immune system of humans or certain animals. Amongst them, complement receptor 3-related protein (CR3-RP) is one of the key surface antigens expressed during the biofilm formation of *Candida* species. Previous investigation identified the presence of CR3-RP moieties on the surface of *C. auris*. Upon *in vitro* exposure to prepared anti-CR3-RP, *C. auris* cells failed to form biofilm, confirming the ability of anti-CR3-RP for eradicating *C. auris* biofilms [96]. Similarly, Singh et al. utilized anti-Hyr1p monoclonal antibody (mAb) to control the *C. auris* infection. The anti-Hyr1p mAb prevented the biofilm formation and enhanced opsonophagocytic killing of *C. auris* by macrophages. In vivo studies showed that anti-Hyr1p mAb protected 55% of mice from the systemic infection causes by *C. auris* [97]. Other than these, NDV-3A (a vaccine based on the N-terminus of Als3 protein formulated with alum) also showed effects against *C. auris*, blocking the formation of biofilms and encouraging the macrophage-mediated killing of *C. auris* [98].

A new humanized antibody H5K1 was recently identified and found to be active against *C. auris*. H5K1 expressed significant results when tested alone or in combination with Caspofungin and Amp B [99]. Recent findings suggested that H5K1 specifically binds to β-1,3-glucans derived from *C. auris*, causing perturbation and remodeling of the fungal cell wall and facilitating the loss of cellular membrane integrity [100]. In support to this investigation, other *Candida* cell-surface-specific mAbs were investigated in mouse model of *C. auris* invasive infection. For example, the specific monoclonal antibody C3.1, that targets β-1,2-mannotriose (β-Man3) of *C. auris*, was able to improve the survival of animals and reduce the fungal burden in vital organs. In the same study, other peptide-specific mAbs such as 6H1 and 9F2 were reported with targeting two hyphal specific protein 1 (Hwp1) and phosphoglycerate kinase 1 (Pgk1), respectively. It's also showed the same outcome as like C3.1 in comparison with control group. All together 6H1+9F2 cocktail enhanced the therapeutic outcome than monotherapy. Therefore, all the three antibodies reported here might be an alternative to treat *C. auris* mediated infections [101].

Intravenous immunoglobulins (IVIG) have been considered an alternative therapeutic strategy to treat the patient who present primary antibody deficiencies. They are the therapeutic product of

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normal human IgG [102–104]. Xin et al. recently demonstrated the role of IVIG in prevention and control of *C. auris* and *C. albicans* mediated disseminated candidiasis in animal models. Treatment with IVIG prolonged the survival and reduced the fungal burden in organs of treated animals. In combination, IVIG enhanced the therapeutic index of Amp B in comparison with monotherapy [105].

Immuno-informatics-based approaches offer an alternative and burgeoning avenue for designing suitable vaccine candidates against fungal infections. Recently, subtractive proteomics approaches were employed to design vaccines against *C. auris*. Khan et al. adopted this method and generated multi-epitope vaccine candidates, which elicited immune responses against *C. auris* infection by inducing various immune factors such as IgM, IgG, IL-6, and Interferon-α [106]. Similarly, Gupta and colleagues developed a vaccine based on novel CD4+ epitopes through genome-wide scanning and a reverse vaccinology approach. This vaccine had a reduced chance to become ineffective because rapidly evolving genes of *C. auris* were eliminated from the epitope selection process [107].

2.7. Photosensitizers Based Antimicrobial Photodynamic Therapy (APDT)

APDT is a promising approach as an adjuvant therapy for fungal infections. As advantage, APDT simultaneously targets different biomolecules of pathogens. Thus, it doesn't have any specific mechanism of action which restrict to development of cross resistance. Therefore, APDT is considered an alternative therapeutic strategy against multiple clinically important organisms that includes *C. auris*. APDT involves the association of a photosensitizer with irradiation by a light source, that results in generation of ROS, a prime factor responsible for effectiveness of APDT.

Phenothiazinium based photosensitizers are promising agent proven to be inactivated the *C. auris* cells. Methylene blue, toluidine blue, new methylene blue, and the pentacyclic derivative S137 were assessed as photosensitizers for APDT on *C. auris* (CDC B11903). Their efficacy was evaluated using MIC and the *G. mellonella* insect model. Based on the findings, the pentacyclic derivative S137 was identified as a potent treatment for *C. auris* [108]. Previously, it had demonstrated strong inhibition of *C. albicans* [109]. In another study researchers utilised red, green, and blue visible lights alone and in combination with photosensitizers (new methylene blue, toluidine blue O and rose bengal) against *C. auris*. The results showed that blue light alone disturbed the mature biofilm, but it was significantly improved when the photosensitizer was combined. On the other hand, red or green light alone had no effect on *Candida* biofilm. The biofilms were disturbed only in combination of light and photosensitizers [110].

Recently, Silva and their coworkers assessed the impact of methylene blue and 1,9-dimethyl methylene blue in addition with red LED on *C. auris*. At 3 μM regardless of the light dose, 1,9-dimethyl methylene blue reduced the metabolic activity of *Candida* cells. Furthermore, it promoted high level of ROS, lipid peroxidation and mitochondrial membrane damage. In contrast methylene blue was active only in concentration of 100 μM when exposed to highest dose of light. Further, studies evidenced that 1,9-dimethyl methylene blue was capable of inhibiting biofilm formation and mature biofilm formed by *C. auris* [111]. Earlier studies by Stefanek and his team confirmed the positive effect of methylene blue with a red laser on the biofilm of *C. auris*. They observed a maximum of 90% biofilm inhibition after 300 seconds of irradiation compared to the growth control. Interestingly, in the presence of 0.25 mM methylene blue, the expression of both the MDR1 and CDR1 genes was affected [112].

2.8. Repurposing of Drugs with Antifungal Properties

Drug repositioning or repurposing is a process of utilizing commercially available drug for treating diseases outside the scope of its original indication. Drug repurposing is considered an important approach to manage emerging diseases caused by bacteria, fungi and virus [113,114]. The availability of various information rather than therapeutic indexes is a valuable point to consider in the repurposing process. Drug repurposing reduce the time and cost of new drug development since it has previous data on toxicity profiles and preclinical parameters [115]. Therefore, repurposing of drug is recognized as an alternative to combat antifungal drug resistance, and several commercial non-antifungal drugs with activity against *C. auris* has been reported (Figure 4). Among them, Sertraline (an antidepressant agent comes under serotonin reuptake inhibitors) showed active against

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three different isolates of *C. auris*, possessing efficient antifungal activity by supressing the action of yeast to hyphae conversion and biofilm formation [116].

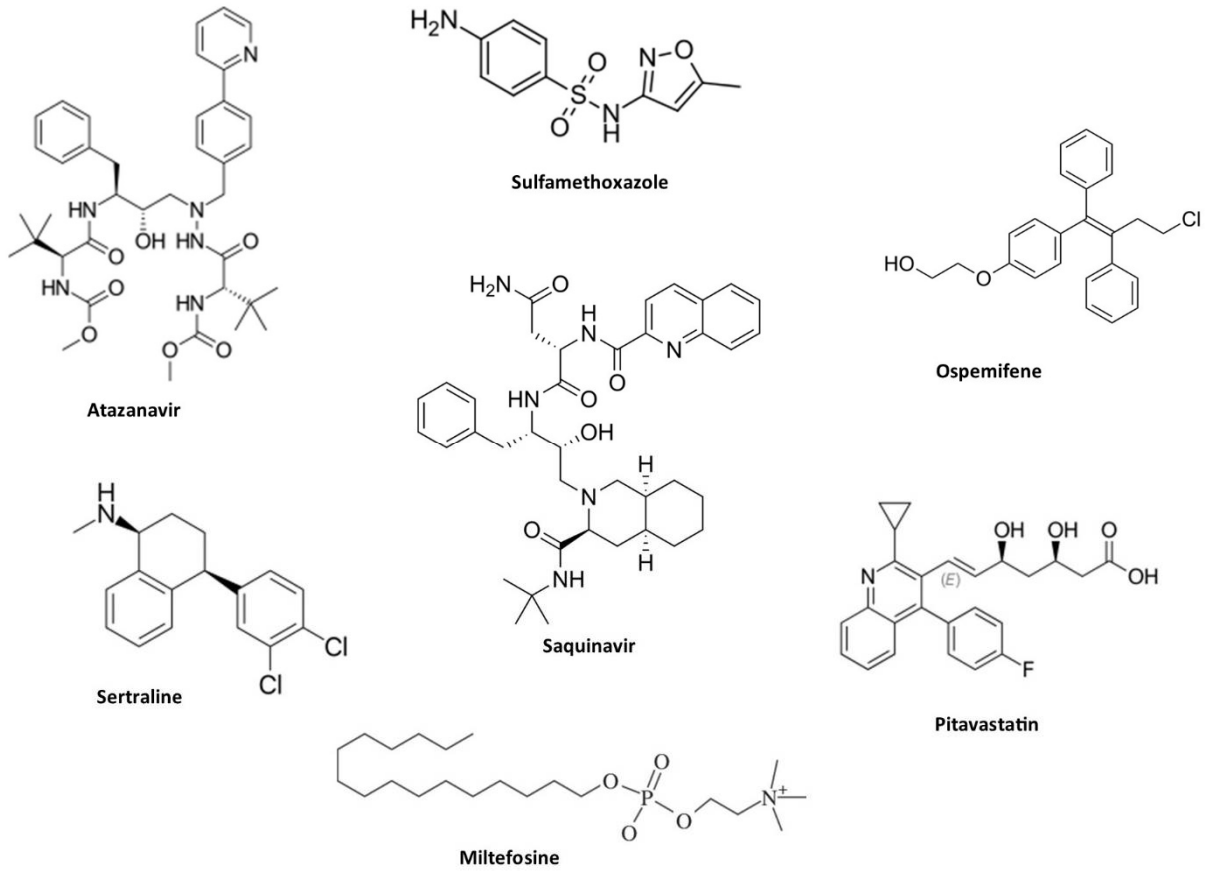

Figure 4. The list of commercial drug molecules used to manage other disease conditions showing antifungal action against *C. auris*.

Synergistic drug interactions have also been investigated to increase the success of drug repurposing [117]). Pitavastatin, a cholesterol-lowering drug, proved to be a potent azole chemosensitizer. It reduced *Candida* biofilm formation and lowered MIC ranges when combined with fluconazole against *C. auris* [118]. Aprepitant, an antiemetic drug, showed ability to disrupt metal ion homeostasis in *C. auris*, synergizing with azoles to reduce MIC by up to eight-fold and inhibit biofilm formation by 95±0.13% [119]. Miltefosine, an antiparasitic drug licensed for leishmaniasis, demonstrated potential against *C. auris* and other *Candida* strains, especially in combination with other antifungal drugs [120,121]. Colistin, an antibiotic used for multidrug-resistant Gram-negative infections like pneumonia, showed synergistic effects when combined with caspofungin, with FICI values ranging from 0.08 to 0.14. However, combining colistin with micafungin yields indifferent results, with FICI values ranging from 0.51 to 1.01 [122]. Synergistic combinations between HIV protease inhibitors and azoles were also found to be active against drug-resistant *C. auris*. Lopinavir combined with itraconazole achieved potent effects, increasing the survival rate of *C. auris*-infected *C. elegans* by up to 90% and reducing fungal burden by 88.5% [123]. Additionally, lopinavir and ritonavir interacted synergistically with itraconazole, effectively combating disseminated candidiasis in a rat model [124]. Atazanavir resensitizes *C. auris* to azoles by inhibiting efflux pumps, glucose transport, and ATP synthesis [125]. Moreover, the combination of saquinavir and itraconazole significantly reduced fungal burden in murine models, with an 88% decrease in colony-forming units compared to itraconazole alone [126].

Recently, some studies validated the synergistic potential of azoles in combination with Chlorhexidine, used as skin antiseptic and mouthwash due to its broad-spectrum antibacterial effects. It was reported that chlorhexidine can bind to cellular membrane phospholipids, causing changes in osmotic pressure and cell lysis [127]. When combined with fluconazole, chlorhexidine

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significantly reduced the viability of both planktonic and biofilm forms of *C. auris* [128]. These results suggest the combined use of chlorhexidine and azoles to control the *C. auris* infections in cutaneous and mucosal surfaces.

2.9. Nanotechnology Mediated Antifungal Therapy

Metallic nanoparticles have been investigated as antimicrobial agent against a large number of microorganisms. The detailed investigations and its potent antifungal property of different nanoparticles was presented in this review. In the last decades, researchers have extensively worked to develop different metallic nanoparticles like Ag, Zn, and Au targeted to combat pathogenic microorganisms.

In relation to *C. auris*, most studies focused on silver-based nanoparticles. Humberto and colleagues verified that silver nanoparticles effectively limited the biofilm development at 0.48 ppm, suggesting their use for controlling *C. auris* in healthcare settings [129]. Another study investigated silver nanoparticles against multidrug-resistant *C. auris*, showing strong antifungal properties with <0.5 μg/mL on planktonic cells and MIC <2 μg/mL on preformed biofilm [130]. Consistent findings also revealed a significant reduction in viable *C. auris* cells, in both planktonic and biofilm form, upon treatment with silver nanoparticles [131].

More recently, several functionalised silver nanoparticles have been produced by green synthesis using plants compounds as metal ions reducing agents. Polyphenol-capped metallic silver nanoparticles, such as those derived from *Cynara cardunculus* extract, exhibited an antifungal effect on *C. auris* by inducing mitochondrial toxicity and DNA fragmentation at 50 μg/mL [132]. Trimetallic (Ag-Cu-Co) nanoparticles, synthesized with compounds from *Salvia officinalis*, also showed potent antifungal properties, inducing apoptosis and G2/M phase cell cycle arrest in *C. auris*, with MIC values ranging from 0.39–0.78 μg/mL and minimum fungicidal concentration ranging from 0.78–1.56 μg/mL [133].

Besides silver nanoparticles, various other metal nanoparticles had proved action against *C. auris*. For example, bismuth nanoparticles have shown promising effects in combating multidrug-resistant *C. auris*, exhibiting anticandidal activity with MIC ranging from 1 to 4 μg/mL, and disrupting both cells and biofilms of *C. auris* [134]. Caspofungin loaded zinc oxide nanoparticles have demonstrated antifungal activity against caspofungin-resistant *C. auris.* Interestingly, caspofungin-ZnO nanoparticles did not develop acquired or cross resistance in *C. auris* [135].

2.10. Liposomal Technology for Efficient Drug Delivery

Liposomal technology represents a promising avenue for antifungal therapy, using different approaches to prepare liposomal vehicles. The key-point among these methods is the careful selection of lipid moieties for encapsulating a specific drug. This selection influences the surface charge of the liposome, enabling tailored delivery of potent molecules. The advantages of liposomal technology are manifold, including i**mproved bioavailability, reduced toxicity and targeted delivery**. For instance, liposomal formulations of amphotericin B offer enhanced solubility and reduced nephrotoxicity compared to conventional amphotericin B, confirming the potential of liposomal technology in optimizing therapeutic outcomes.

De Alteriis et al. examined the role of liposomal technology to improve the antifungal effects of essential oil from *Lavandula angustifolia*, reaching antibiofilm activity of persister-derived biofilm of *C. auris* [136]. Similarly, *Lippia sidoides* essential oil was loaded in lipid carriers, and improvements in the MIC values were observed on *C. auris* [137]. In line with earlier investigations, Jaromin et al. utilized liposomal formulation to improve and modulate the surface characteristics of PQA-Az-13, which is the combination of indazole, pyrrolidine, and arylpiperazine scaffolds substituted with a trifluoromethyl moiety. Here, addition of liposome displayed a mean size of 76.4 nm, a positive charge of +45.0 mV with excellent stability, and no toxicity to normal human dermal fibroblasts. PQA-Az-13 showed MIC between 0.67 and 1.25 μg/mL against *C. auris* and demonstrated promissing results in in-vitro biofilms and ex vivo skin colonization models [138].

3. Conclusion and Future Perspectives

The treatment of *C. auris* infections faces multiple challenges that are associated with multidrug resistance, global spread, limited therapeutic options, biofilm formation, diagnostic failure, lack of

 doi:10.20944/preprints202405.1513.v1

standardized treatment guidelines, underreporting, and surveillance issues. The future of antifungal development is promising with a range of new strategies addressed to the control of *C. auris* and other emerging fungi. Unlike bacteria, fungi are eukaryotes and share its genetic traits with human genome. Thus, the identification of fungal-specific pathways are required to provide selective targets to fungi, reducing the risk of side effects in humans and minimizing toxicity.

For this, researchers have been working to design compounds with new modes of action, exploring the chemical structures of existing antifungal drugs or investigating new molecules from natural sources, such as plants, microorganisms, insects and other small animals. Another approach is the selection of specific drug carrier such as metallic and liposomal nanoparticles, that can be designed to deliver antifungal drugs directly to *C. auris* cells, minimizing side effects and improving its efficacy. Face to the advances in the light-based technologies, the antimicrobial photodynamic therapy raises as a promising therapy that simultaneously acts on multiple cell targets in different pathogens. This mechanism of action makes APDT an important adjuvant therapy to control skin and mucosal fungal infections.

Additionally, some researchers are focusing on the drug repurposing strategies. Adapting drugs already approved for other conditions can be a faster and cheaper way to bring new antifungals to market, especially against emerging or resistant fungal threats. While still in early stages, research on fungal vaccines is ongoing, focusing on stimulating the immune system to recognize and fight fungal infections. Tailoring antifungal treatment based on individual patient characteristics and the specific fungal strain involved in the infection can improve outcomes and reduce the risk of resistance.

Finally, combining different therapies can be an effective approach to reach multiple cellular targets and to obtain synergistic interactions, increasing the antifungal efficacy and preventing the emergence of resistant *C. auris* strains. Although several approaches discussed here had showed promising antifungal activity against *C. auris*, few researchers extended their results to animal models and clinical trials. Overall, hope that the data gathered in this review can provides support and insights into the advances of new treatments for *C. auris* infections.

Acknowledgments: The present work was carried out with the support of the Coordination for the Improvement of Higher Education Personnel - Brazil (CAPES) - 88887.890668/2023-00. We are grateful to the Brazilian National Council for Scientific and Technological Development (CNPq 310265/2022-3) and office of Naval Research Global (N62909-20-1-2034).

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