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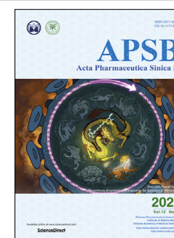

REVIEW

Small molecules for combating multidrug-resistant superbug *Candida auris* infections

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KEY WORDS

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Abstract *Candida auris* is emerging as a major global threat to human health. *C. auris* infections are associated with high mortality due to intrinsic multi-drug resistance. Currently, therapeutic options for the treatment of *C. auris* infections are rather limited. We aim to provide a comprehensive review of current strategies, drug candidates, and lead compounds in the discovery and development of novel therapeutic agents against *C. auris*. The drug resistance profiles and mechanisms are briefly summarized. The structures and activities of clinical candidates, drug combinations, antifungal chemosensitizers, repositioned drugs, new targets, and new types of compounds will be illustrated in detail, and perspectives for guiding future research will be provided. We hope that this review will be helpful to prompting the drug development process to combat this fungal pathogen.

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1. Introduction

There are approximately 200 species in the genus *Candida*, and these are the main causal agents (*e.g.*, *Candida albicans*) of worldwide invasive fungal infections (IFIs)[1]. *Candida auris* was first isolated in 2009 and since then has rapidly spread globally[2]. *C. auris* is characterized by a high level of multi-drug resistance and has emerged as a major and urgent healthcare threat[3]. *C. auris* infections have been reported in more than 45 countries and have caused serious hospital outbreaks, with crude mortality rates as high as 72%[4]. *C. auris* can be transmitted by direct or indirect contact[5]. Persistent skin colonization, environmental adaptation and contamination, and nosocomial transmission have contributed to the global pandemic of *C. auris*[6].

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C. auris is a member of the *Candida haemulonii* clade and is distantly related to common fungal pathogens such as *C. albicans* and *Candida glabrata*[7,8]. To date, the origins of *C. auris* are still largely unknown. Based on genetic studies using whole-genome sequencing (WGS), *C. auris* strains are classified into four major geographic clades, namely, clade I (the South Asian clade), clade II (the East Asian clade), clade III (the South African clade), and clade IV (the South American clade)[9]. Recently, a potential fifth clade of *C. auris* was isolated from Iran[10]. Considerable differences in genetics and phenotypes have been observed among *C. auris* strains from different clades.

The characteristics and mechanisms of *C. auris* infections slightly differ from those of other *Candida* species. The body sites of *C. auris* colonization mainly include skins, mucosa and gastrointestinal tract, overlapping with those of other *Candida* species, such as *C. albicans*, *C. glabrata*, *Candida parapsilosis*, and *Candida tropicalis*[11−13]. However, *C. auris* exhibits a stronger capacity for skin colonization than other *Candida* species. The number of colonized patients was 2−3 folds more than that of infected patients, which causes clonal inter- and intra-hospital transmission and healthcare-associated infections[14−16]. The colonization of *C. auris* on skin or other sites may not cause infections, which could possibly lead to the contamination of the nosocomial and healthcare environment and pose a risk on immunocompromised individuals[12,17]. Thus, guidelines on the prevention of spread of *C. auris* are much stricter than those of other *Candida* species. Routine screening on colonization sites of patients and medical staff and improved environmental decontamination may interrupt healthcare-associated transmission[18]. Chlorine-containing disinfectants and 2% chlorhexidine are currently used in clinical practice for environmental decontamination and skin decolonization, respectively[19]. Moreover, recent studies showed that *C. auris* may behave differently as other *Candida* species to induce innate immune responses[20−22]. *C. auris* tends to significantly reduce the innate immunoinflammatory response than *C. albicans* due to the thicker mannan layer of the cell wall[21], facilitating its colonizations and infections in hosts.

Unfortunately, therapeutic options for the treatment of *C. auris* infections are rather limited. Only three major classes of antifungal agents (Fig. 1), namely, azoles (**1**−**5**), polyenes (**6**), and echinocandins (**7**−**9**), are clinically available for the treatment of IFIs. Additionally, the nucleoside analogue 5-flucytosine (**10**) is generally used in adjunctive therapy. However, most *C. auris* strains were reported to be resistant to fluconazole (**1**), and multi-drug resistance has also observed against two, three, or even four classes of antifungal agents[15]. *C. auris* is the only *Candida* species in which several isolates have been identified to be resistant to all four classes of antifungal drugs[11]. The order of drug resistance is fluconazole > amphotericin B (**6**) > echinocandins[23]. Thus, echinocandins (*e.g.*, caspofungin, **7**) are commonly recommended as the first-line therapy for the treatment of *C. auris* infections[24]. Even so, several cases of deaths were reported for patients after the administration of echinocandins[17,25]. In addition to intrinsic resistance, rapid development of multidrug resistance has also been documented during antifungal treatments[15]. Thus, there is an urgent need to develop effective therapeutics to treat life-threatening and multidrug resistant *C. auris* infections.

The biology, pathogenicity, epidemiology, resistance mechanisms and active compounds of *C. auris* have been reviewed previously[3,26−34]. Continuing our efforts in the discovery of novel antifungal agents against resistant fungal pathogens[35,36], this review focuses on the small molecules and potential drug targets with which to tackle *C. auris* infections. After a brief introduction of resistance profiles and mechanisms, the activity of clinical candidates and drug combinations is discussed. Then, we provide a detailed illustration of drug discovery strategies and active lead compounds for combating *C. auris* infections, focusing on antifungal chemosensitizers, drug repurposing, new targets, and new chemotypes. Finally, perspectives for future research on drug development for this superbug fungal pathogen are provided.

2. Susceptibility of *C. auris* to antifungal agents

Several studies have investigated the susceptibility of *C. auris* to antifungal agents using different sets of isolates[23,37]. On the basis of a susceptibility test against 350 isolates collected in India, 90% of the isolates were resistant to fluconazole (MIC: 32−64 μg/mL); 8% were resistant to amphotericin B (MIC: 2 μg/mL), and 2% were resistant to echinocandins (MIC: 8 μg/mL)[23]. In another test of 296 *C. auris* isolates, a similar resistance trend was observed in which 80% of the strains were resistant to fluconazole, 23% to amphotericin B, and 7% to micafungin (**8**)[37]. Notably, 24% of the tested strains were resistant to at least two classes of antifungal agents, and 1% were resistant to all three of the classes[37]. The resistance profiles appeared to be clade-specific. For example, *C. auris* isolates in clade III were reported to be more resistant to fluconazole and voriconazole (**2**) than isolates in clade I. Newer azoles such as posaconazole (**5**, MIC range: 0.06−1 μg/mL) and isavuconazole (**3**, MIC range: 0.008−4 μg/mL) showed improved *in vitro* activity against *C. auris*[11,38]. Elevated MIC values were observed for the new azoles (*e.g.*, voriconazole) compared with those against other *Candida* species[39].

3. Resistance mechanisms of *C. auris*

The antifungal drug resistance mechanisms of *C. auris* are similar to those observed in other *Candida* species, including overexpression or mutation of the drug target, overexpression of efflux pumps, reductions of drug intake, and biofilm formation (Fig. 2)[32]. Azole antifungal agents act by inhibiting lanosterol 14α-demethylase (CYP51, encoded by the *ERG11* gene), a key enzyme in the biosynthesis of ergosterol of the fungal cell membrane. In *C. auris* strains resistant to azoles, no significant overexpression of the *ERG11* gene was observed, and substitution mutations in CYP51 were generally clade-dependent: F126T (clade III), Y132F (clade IV), and Y132F or K143R (clade I)[9,23,37,40,41]. Higher expression of multidrug efflux pumps was also involved in decreased susceptibility of *C. auris* to azoles[42]. The ATP-binding cassette (ABC) family and the major facilitator superfamily (MFS) are two major transporters associated with antifungal resistance[43] that are conserved in *C. auris*[9]. Increased expression of the *CDR1* gene of the ABC transporter and the *MDR1* gene of the MFS transporter contributed to the azole resistance of *C. auris*[42,44,45].

Amphotericin B exerts fungicidal activity by binding to ergosterol in fungal cell membranes and thereby altering the membrane permeability, resulting in the leakage of vital cytoplasmic components. Overexpression of genes involved in ergosterol biosynthesis,

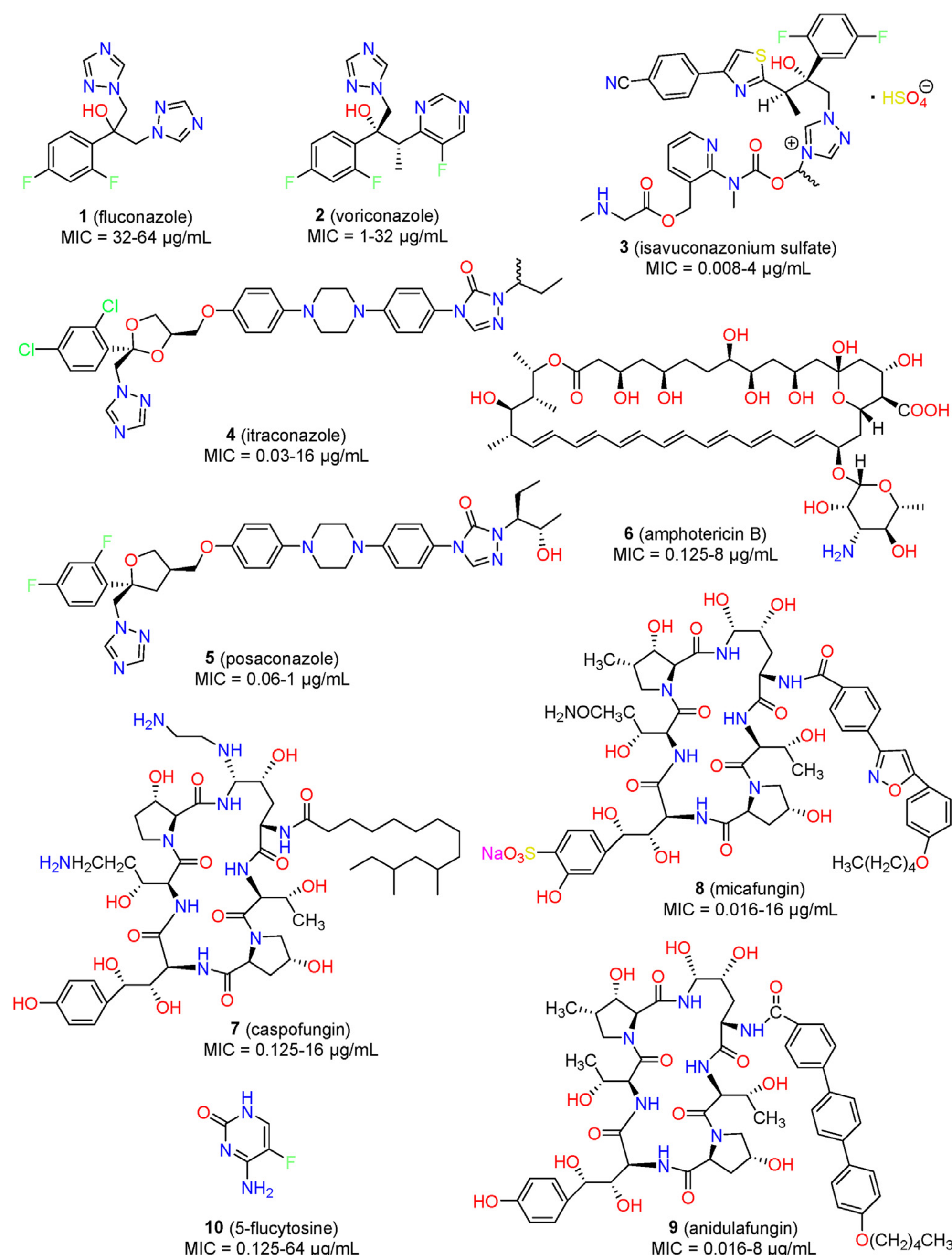

Figure 1 Chemical structures of clinically available antifungal agents.

such as *ERG1*, *ERG2*, *ERG6*, and *ERG13,* was reported to be related to amphotericin B resistance in *C. auris* strains[9]. Although significant mutation for amphotericin B resistance is rare, a point mutation in transcription factor FLO8 has been observed in a resistant *C. auris* isolate[46].

Echinocandins act on the fungal cell wall via inhibition of 1,3-β-glucan synthase (encoded by the *FKS1* gene). In *C. auris*, *FKS1* substitution mutations S639F, S639P, S639Y, and S652Y were responsible for echinocandins resistance[23,47,48]. The compound 5-flucytosine inhibits fungal DNA and RNA synthesis and is activated in fungal cells by Fur1. In *C. auris*, a substitution mutation F211I in the *FUR1* gene was detected in an isolate resistant to 5-flucytosine[41].

The increased expression of ABC and MFS transporters also contributes to the formation of biofilms that are highly resistant to antifungal agents[49]. Most antifungal agents, such as fluconazole, voriconazole, and amphotericin B, showed higher MIC values against *C. auris* biofilms than against planktonic cells[50]. Although planktonic cells are susceptible to echinocandins, these compounds are ineffective against biofilms[50]. Similar to other *Candida* species, *C. auris* is able to form biofilms that are largely composed of mannan polysaccharides and glucan[50,51]. *C. auris* formed significantly less biofilm than *C. albicans* with a limited amount of extracellular matrix[52]. *C. auris* seems to be unable to form true hyphae, and its biofilms consist largely of yeast cells[50,53]. The phenotypic, biochemical, and functional features of *C. auris*

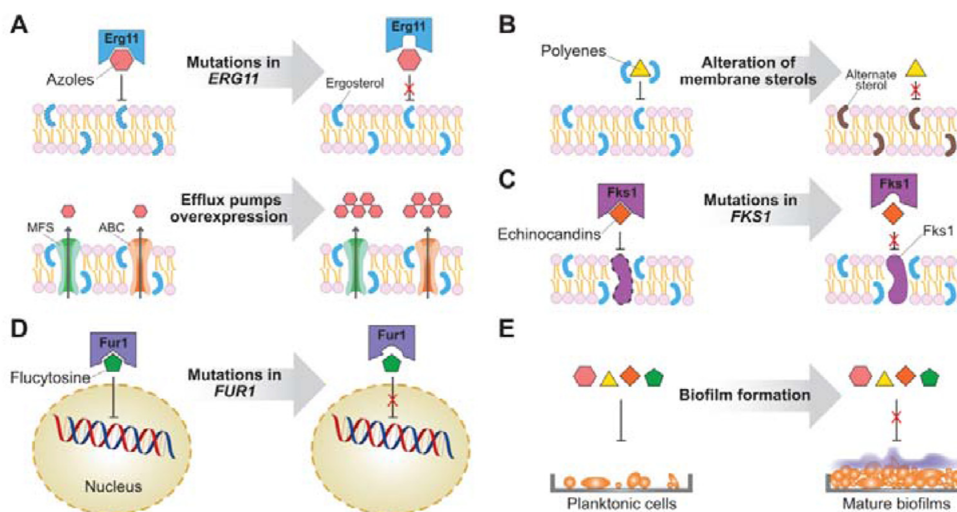

Figure 2 Resistance mechanisms to antifungal agents in *C. auris*. Mutation of targets, overexpression of efflux pumps, and alteration of membrane components are associated with the resistance of *C. auris* to azoles (A), polyenes (B), echinocandins (C), and flucytosine (D). The formation of biofilms is a general mechanism of antifungal resistance (E).

biofilms seem to be clade- or strain-specific. Differences in the extent of biofilm formation were observed among various *C. auris* isolates. Compared with *C. albicans*, *C. auris* formed more consistent biofilms in colonization models, suggesting higher virulence and resistance[54].

4. Investigational antifungal agents for the treatment of *C. auris* infections

Currently, several new antifungals have entered into the clinical research, including VT-1598 (**11**), PC945 (**12**), rezafungin (**13**), ibrexafungerp (**14**), SCY-247 (**15**), fosmanogepix (**16**), manogepix (**17**) and T-2307 (**18**), which have demonstrated promising results against *C. auris* (Fig. 3). Herein the *in vitro* and *in vivo* anti-*C. auris* activities of these investigated antifungal agents are discussed. The antifungal assays and expression levels of activity are summarized in Table 1.

4.1. New CYP51 inhibitors: Triazole antifungal agents VT-1598 and PC945

VT-1598, a tetrazole-based fungal CYP51 inhibitor, has entered the clinical evaluation[63]. Currently, phase I clinical trial of VT-1598 has been completed and no more clinical trial is ongoing. Compared with traditional triazole antifungal agents, VT-1598 showed better selectivity between fungal CYP51 and mammalian cytochrome P450 enzymes, resulting in reduced drug−drug interactions[64]. VT-1598 demonstrated potent *in vitro* activity against a collection of 100 *C. auris* isolates (MIC range: 0.03 μg/mL; MIC_{50} = 0.25 μg/mL; MIC_{90} = 1 μg/mL)[65]. VT-1598 also showed dose-dependent *in vivo* efficacy in a neutropenic murine model of *C. auris* infections. At the doses of 15 and 50 mg/kg (once daily), oral VT-1598 treatment achieved significant improvement in survival, with median survival of 15 days and >21 days, respectively[65]. Moreover, VT-1598 also significantly reduced kidney and brain fungal burdens, suggesting that VT-1598 deserved further evaluation as a potential option for treating *C. auris* infections.

PC945 is a novel triazole antifungal derivative designed for inhaled administration of *Aspergillus fumigatus* infections[66]. PC945 also showed excellent antifungal activity against a collection of 50 *C. auris* clinical isolates, with GM MIC, MIC_{50} and MIC_{90} values of 0.058, 0.063, and 0.25 μg/mL, respectively[67]. PC945 also completely inhibited *C. auris* growth, with GM MIC and MIC_{90} values of 0.16 and 0.5 μg/mL, respectively. Notably, PC945 showed better anti-*C. auris* activity than fluconazole, voriconazole, and posaconazole.

4.2. New glucan synthase inhibitors: Rezafungin and ibrexafungerp

Rezafungin (CD101), an optimized echinocandin derivative, is currently under clinical development[68]. Compared with marketed echinocandin-like antifungal agents (*e.g.*, caspofungin and micafungin), rezafungin possessed a better safety profile and improved pharmacokinetic properties such as an longer half time ($t_{1/2}$ > 130 h) and higher plasma drug exposure, enabling once-weekly intravenous therapy[69]. Several studies have confirmed that rezafungin had excellent *in vitro* and *in vivo* activities against *C. auris* infections[70−75]. In a susceptibility assay of a collection of 100 *C. auris* isolates, the MIC values of rezafungin ranged from 0.03 to 8 μg/mL[70]. The MIC_{50} and MIC_{90} values were 0.125 and 0.5 μg/mL, respectively[70]. Similar *in vitro* activity was observed in a test of rezafungin against 122 Indian *C. auris* isolates (MIC range: 0.016−16 μg/mL; MIC_{50} = 0.25 μg/mL; MIC_{90} = 1 μg/mL)[73]. In a mouse model of disseminated *C. auris* infections, rezafungin (20 mg/kg ip) showed potent *in vivo* efficacy and effectively reduced the fungal burden[71]. In particular, rezafungin showed superior activity compared to amphotericin B and micafungin, even with less frequent dosing[71]. The PK/PD advantage of rezafungin was further validated in a *C. auris* neutropenic mouse model[72]. The PK/PD index of rezafungin suggested that the clinically evaluated dose (400 mg, iv, once a week) may be a useful option to treat patients infected with *C. auris* infections, although further clinical trials are warranted[72].

Ibrexafungerp (SCY-078) is an orally active inhibitor of glucan synthase that exhibited *in vitro* and *in vivo* inhibitory activity against

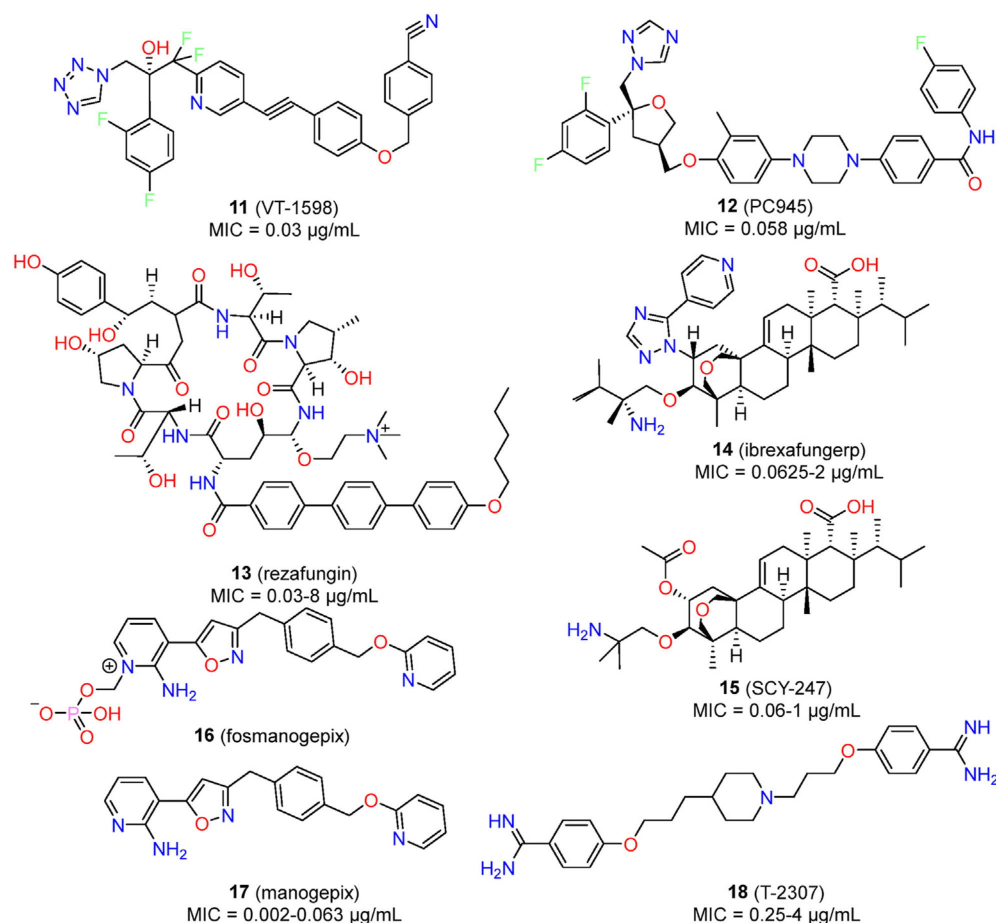

Figure 3 Chemical structures of investigated antifungal agents for the treatment of *C. auris* infections.

Candida species, including echinocandin-resistant isolates[76]. Ibrexafungerp differs from echinocandin-like glucan synthase inhibitors in that it can be administrated both orally and intravenously, and it is active against the most common mutations of the target gene *FKS*[77]. A susceptibility assay indicated that the MIC values of ibrexafungerp ranged from 0.0625 to 2 μg/mL against a collection of 100 *C. auris* isolates, with MIC_{50} and MIC_{90} values of 0.5 and 1 μg/mL, respectively[78,79]. Furthermore, ibrexafungerp showed similar MIC values against *C. auris* isolates resistant to echinocandin antifungal agents[78]. Larkin et al.[52] and Arendrup et al.[79] reported similar MIC results for ibrexafungerp. Ibrexafungerp was able to completely inhibit the growth of *C. auris*, with an MIC_{90} value of 1 μg/mL[52]. Moreover, ibrexafungerp interrupted cell division of *C. auris* and inhibited biofilm formation (0.5−4 μg/mL) by reducing metabolic activity and biofilm thickness[52]. In a neutropenic murine model of *C. auris* infections, oral treatment with ibrexafungerp (20, 30, and 40 mg/kg, twice daily) resulted in dose-dependent improvements of survival and reductions in fungal burden, while caspofungin showed similar potency, and fluconazole was ineffective[80]. In an *in vivo* guinea pig cutaneous model of *C. auris* infections, oral dosing with ibrexafungerp (10 mg/kg) was effective in controlling skin infections and significantly reduced the fungal burden and the severity of lesions[62]. Ibrexafungerp is currently in phase II open-label clinical trials to evaluate efficacy and safety in patients infected with *C. auris* (identifier: NCT03363841). In an emergency-use phase III clinical trial, ibrexafungerp therapy successfully cured two patients without drug-related adverse events, highlighting its potential for further clinical evaluation[81].

SCY-247 is an analogue of ibrexafungerp that showed broad-spectrum antifungal activity and an excellent safety profile, and it is suitable for both intravenous and oral administration[82]. Ghannoum's group[83] compared *in vitro* anti-*C. auris* activity between SCY-247 and ibrexafungerp. In a panel of 44 *C. auris* isolates, SCY-247 (MIC range: 0.06−1 μg/mL, MIC_{50} = 0.5 μg/mL, MIC_{90} = 0.5 μg/mL) showed similar MIC values to ibrexafungerp (MIC range: 0.06−2 μg/mL, MIC_{50} = 0.5 μg/mL, MIC_{90} = 0.5 μg/mL)[83]. The fungicidal activity of SCY-247 (MFC_{90} = 4 μg/mL) was slightly better than that of ibrexafungerp (MFC_{90} = 8 μg/mL)[83]. The *in vivo* potency of SCY-247 against *C. auris* infections has not been reported. However, SCY-247 (40 mg/kg) exhibited a 100% survival rate in a murine model of disseminated infections of *C. albicans*[83], suggesting that the efficacy of SCY-247 to treat *C. auris* deserves further evaluation.

4.3. Fungal cell wall Gwt1 inhibitor: Manogepix

Manogepix (APX001A) is an inhibitor of fungal Gwt1 (glycosylphosphatidylinositol-anchored wall transfer protein 1) that showed broad-spectrum antifungal activity[84]. Fosmanogepix (APX001), the prodrug of manogepix, is currently being evaluated

Table 1 Assays and expression of the activity for the research and development of novel antifungal agents against *C. auris*.

Activity	Assay	Ref.
In vitro susceptibility[a]	Clinical and Laboratory Standards Institute (CLSI)	55
	European Committee on Antimicrobial Susceptibility Testing (EUCAST)	55
Synergistic activity[b]	Fractional inhibitory concentration index (FICI)	56
	Bliss independence model	57
Biofilm inhibition[c]	Inhibition of biofilm formation: XTT reduction assay	50
In vivo potency[d]	*Caenorhabditis elegans* infections model (preliminary screen)	58
	Galleria mellonella infections model (preliminary screen)	59
	C. auris candidemia mouse model: survival curve, reduction of fungal burden (log_{10} CFU/g) and ED_{50}	60
	Pharmacokinetic/pharmacodynamic (PK/PD) index	61
	Guinea pig cutaneous infections model	62

[a]*In vitro* activity was generally expressed by minimum inhibitory concentration (MIC); MIC_{50}, MIC_{80}, MIC_{90}: the lowest concentration inhibiting fungal growth by 50%, 80%, and 90%, respectively; geometric mean (GM) MIC, mode MIC; MFC: minimum fungicidal concentration.

[b]FICI < 0.5: synergism; $0.5 \leq$ FICI ≤ 4; FICI >4: antagonism.

[c]Sessile MIC ($SMIC_{50}$): the concentration inhibiting 50% of biofilm formation; XTT: 2,3-bis(2-methoxy-4-nitro-5-sulfophenyl)-2*H*-tetrazolium-5-carboxanilide.

[d]ED_{50}: doses required to produce 50% of the maximal effect; PK/PD index: AUC (concentration−time curve)/MIC value.

in clinical trials to treat various fungal infections[85]. The efficacy of APX001A to treat *C. auris* infections has been well characterized[61,86−91]. Hager et al.[88] determined the inhibitory activity of APX001A against 16 *C. auris* clinical strains. APX001A had MIC values in the range of 0.002−0.063 μg/mL (MIC_{50} = 0.004 μg/mL; MIC_{90} = 0.031 μg/mL), values that demonstrated greater potency than 10 tested antifungal agents[88]. The excellent activity of APX001A was further confirmed in a large collection of *C. auris* containing 100 geographically distinct isolates[87]. The MIC values ranged from <0.005 to 0.015 μg/mL, and the MIC_{50} and MIC_{90} values were 0.002 and 0.008 μg/mL, respectively[87]. Zhu et al.[90] evaluated the *in vitro* inhibitory activity of APX001A against 200 New York *C. auris* isolates. APX001A demonstrated lower MIC values (MIC range: 0.004−0.06 μg/mL; MIC_{50} = 0.03 μg/mL; MIC_{90} = 0.03 μg/mL) than 10 clinical antifungal agents[90]. APX001 also showed potent *in vivo* efficacy to treat *C. auris* infections and was more effective than caspofungin and anidulafungin (**9**)[61,88,89]. In a murine model of disseminated *C. auris* infections, APX001 effectively prolonged the survival time of the treated mice (100% survival, 78 mg/kg TID) and significantly reduced the fungal burden of kidney, lung, and brain[88]. In a pharmacokinetics (PK) and pharmacodynamics (PD) study of APX001, the ED_{50} (50% of the maximum effect) to treat *C. auris* infections was 77 mg/kg[61]. Even delayed therapy with fosmanogepix showed good potency, significantly reducing the kidney fungal burden at the dose of 260 mg/kg (BID)[89]. These *in vitro* and *in vivo* data supported further clinical evaluation of fosmanogepix as an anti-*C. auris* agent. An open-label clinical study of APX001 for the treatment of patients with candidemia caused by *C. auris* was started in 2019 (identifier: NCT04148287). Although the trial was terminated due to the impact of COVID-19, the objectives of the study were successfully met. However, the clinical data have not been disclosed to date.

4.4. Fungal mitochondria modulator: T-2307

T-2307 is an antifungal agent currently under clinical development for the treatment of IFIs[92,93]. T-2307 acts by targeting respiratory chain enzymatic complexes III and IV and selectively disrupting yeast mitochondrial function, leading to the collapse of the mitochondrial membrane potential[94]. *In vitro* activity of T-3207 against 23 *C. auris* isolates revealed that the MIC values ranged from ≤0.008 μg/mL to 0.015 μg/mL using 50% inhibition as the endpoint[95]. The MIC values were clearly higher when 100% inhibition was used as the endpoint (0.25 μg/mL to 4 > μg/mL)[95]. Overall, the geometric mean MIC of T-2307 (0.011 μg/mL) was significantly lower than those of fluconazole (14.6 μg/mL) and caspofungin (0.24 μg/mL). In a neutropenic mouse model with *C. auris*, treatment with T-2307 (3 mg/kg, subcutaneous, once daily) significantly improved median (21 days) and percent of survival (70%)[95]. T-2307 (3 mg/kg) also effectively reduced kidney and brain fungal burden, and the effect was more potent than with caspofungin (10 mg/kg).

5. Synergistic drug combinations to treat *C. auris*

Due to limited therapeutic options for *C. auris*, the identification of effective drug combinations provides an alternative for clinical treatment (Fig. 4). Taking advantage of different mechanisms of action, such drug combinations are expected to achieve synergistic effects, thus increasing therapeutic efficacy and overcoming the resistance of *C. auris* to antifungal agents. Currently, more than 100 drug combinations have been evaluated for synergistic effects against *C. auris* infections[96]. The combinations have included antifungal agents, non-antifungal agents, and bioactive compounds (synthetic molecules and natural products).

5.1. Combinations of antifungal agents

Among the combinations of antifungal agents, voriconazole with micafungin, flucytosine with amphotericin B, and flucytosine with micafungin have shown synergistic effects regarding inhibition of the growth of *C. auris* (Table 2). Fakhim et al.[56] evaluated the synergism between echinocandins and azoles against 10 multidrug-resistant *C. auris* clinical isolates. Synergistic effects were observed for the combination of micafungin and voriconazole against all of the tested isolates (FICI range: 0.15−0.5)[56]. Another study systematically evaluated 864 antifungal drug combinations against 15 *C. auris* isolates[97]. Flucytosine (1.0 μg/mL) was able to potentiate the activity of other antifungal agents, including azoles, echinocandins, and amphotericin B[97]. However, in another study by Bidaud et al.[98], indifferent interactions between flucytosine and other antifungal agents were observed. Thus, the therapeutic effects of drug combinations remain to be further evaluated by *in vivo* studies.

More recently, the synergistic activity of isavuconazole and voriconazole in combination with anidulafungin was evaluated

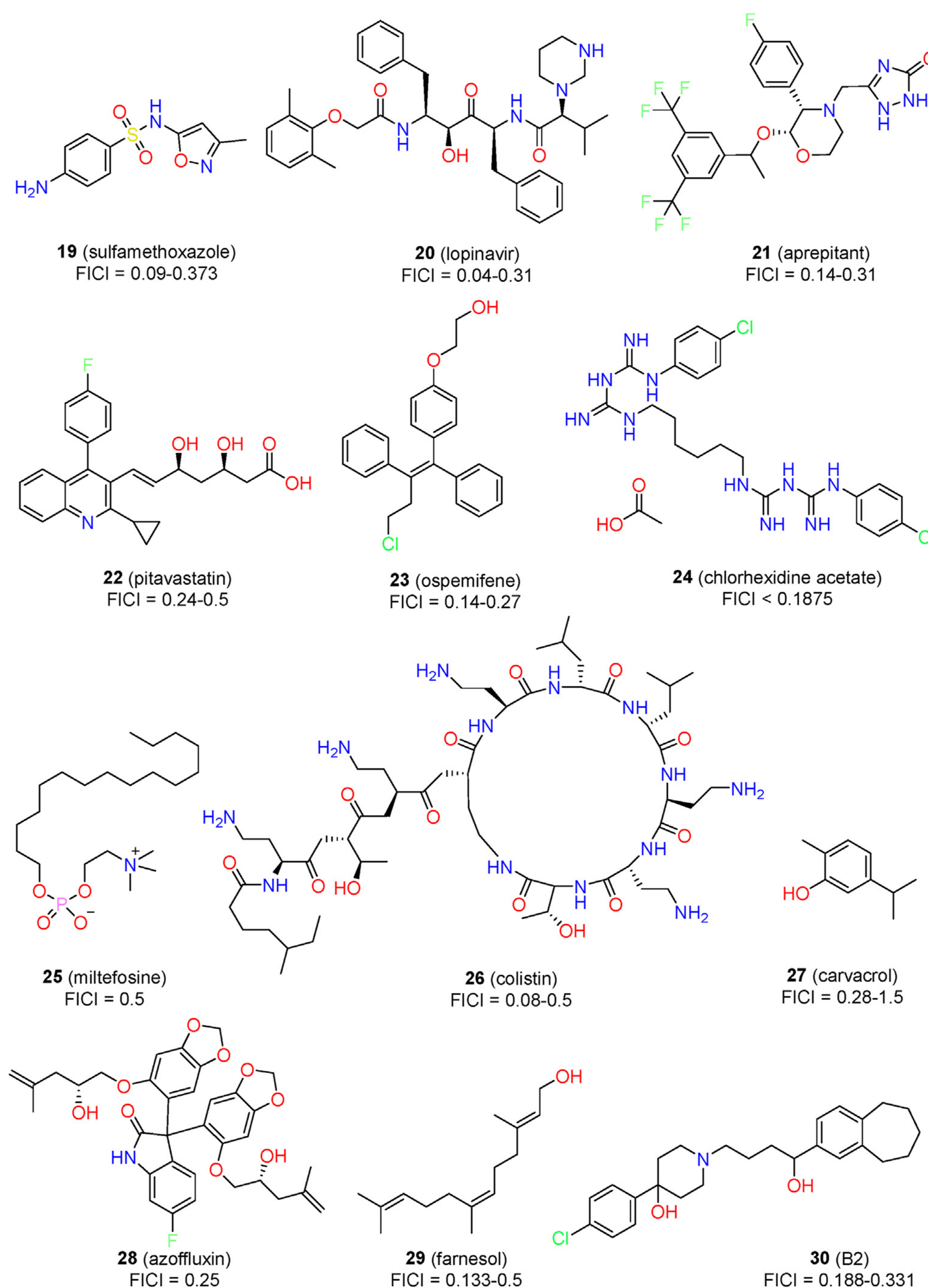

Figure 4 Chemical structures of marketed drugs and chemosensitizers for the combination treatment of *C. auris* infections.

against a collection of 36 *C. auris* isolates[38]. The isavuconazole–anidulafungin combination (active in 11/36 isolates) showed stronger synergistic effects than the voriconazole–anidulafungin combination (active in 5/36 isolates). Similar synergistic interactions between isavuconazole and echinocandin-like antifungal agents were also observed in an assay with six clinical *C. auris* isolates[99]. In addition to the synergistic effects against planktonic isolates, isavuconazole was also able to potentiate the activity of caspofungin in inhibiting the biofilm formation of *C. auris* (FICI range: 0.023–0.5, 12/14 sessile isolates)[57]. In a mouse infections model of *C. auris*, single uses of caspofungin (1 mg/kg, daily) or isavuconazole (20 mg/kg, daily) were statistically ineffective. When used in combination, the kidney fungal burden was significantly decreased by more than three log volumes[57]. Thus, isavuconazole had direct and synergistic activity against *C. auris*, providing a promising option for further evaluation.

In a time–kill curve assay against six *C. auris* isolates, monotherapy with echinocandins (anidulafungin and caspofungin) was ineffective, while high concentrations of amphotericin B (≥1 μg/mL) only showed fungistatic activity[100]. When used in combination, higher fungal killing activity was observed[100]. Lower doses of amphotericin B (0.5 mg/L) and anidulafungin or caspofungin (2 mg/L) achieved rapid synergism with potent fungicidal activity[100].

Table 2 Synergistic combinations of antifungal drugs against *C. auris*.

Drug	Antifungal drug	FICI	Isolate[a]	Ref.
Antifungal drug				
Micafungin	Voriconazole	0.15−0.5	10/10	56
Anidulafungin	Isavuconazole	0.25−0.38	11/36	38
	Voriconazole	0.25−0.38	5/36	38
Amphotericin B	Caspofungin	ND[b]	6/6	100
	Anidulafungin	ND	6/6	100
Non-antifungal drug				
Sulfamethoxazole	Fluconazole	0.156	1/1	101
	Voriconazole	0.09−0.5	3/8	101
	Itraconazole	0.186−0.373	3/4	101
Lopinavir	Itraconazole	0.04−0.09	10/10	58
	Voriconazole	0.19−0.31	6/10	58
	Fluconazole	0.13−0.31	3/10	58
Aprepitant	Itraconazole	0.14−0.31	8/10	102
Pitavastatin	Fluconazole	0.25−0.5	5/5	103
Ospemifene	Itraconazole	0.14−0.27	5/5	104
Chlorhexidine acetate	Fluconazole	<0.1875[c]	2/2	105
Miltefosine	Amphotericin B	0.5	3/12	106
Colistin	Caspofungin	0.08−0.14	15/15	107
	Isavuconazole	0.3125−0.5	15/15	107
Chemosensitizer				
Azoffluxin	Fluconazole	0.25	1/1	108
Carvacrol	Amphotericin B	0.28−1.5	7/25	109
Farnesol	Caspofungin	0.156−0.5	3/4	110
	Micafungin	0.133−0.281	4/4	110
	Anidulafungin	0.14−0.375	4/4	110
B2	Itraconazole	0.188	1/3	111
	Voriconazole	0.311	1/3	111

[a]Number of isolates: active isolates/tested isolates.
[b]ND: not determined.
[c]Synergistic effect against biofilm inhibition.

5.2. Combinations of antifungal agents and non-antifungal agents

Seleem's group performed systemic screening of known drugs and identified several synergists that were able to potentiate the activity of antifungal agents against *C. auris*[58,101−104]. Inspired by the effects of sulfa antibacterial drugs to reverse azole resistance against *C. alibicans*[112], the sulfa drugs were also confirmed to possess synergistic activity with azole antifungals to inhibit the growth of *C. auris* isolates[101]. Among them, sulfamethoxazole (**19**) exhibited the best synergistic activity with voriconazole (FICI range: 0.09−0.5) and itraconazole (**4**, FICI range: 0.186−0.373)[101]. Sulfamethoxazole alone was inactive against *C. auris* (MIC ≥256 μg/mL). When sulfamethoxazole (128 μg/mL) was used in combination with voriconazole (0.5 μg/mL), the survival of the infected nematodes was prolonged by about 70% in an *in vivo* model using *C. elegans*. The underlying mechanisms of the synergism was possibly associated with interference with the expression of the target protein CYP51 and the fungal folate pathway[101].

After screening 1547 compounds, Seleem's group found that the antiviral agent lopinavir (**20**) was a potent chemosensitizer that could potentiate the activity of fluconazole against resistant *C. auris* isolates[58]. At a therapeutically acceptably concentration (10 μg/mL), lopinavir showed good synergistic effects with fluconazole, voriconazole, and itraconazole (Table 2). The strongest synergism was observed between lopinavir and itraconazole (FICI range: 0.04−0.09). The drug combination also showed good *in vivo* efficacy in a *C. auris*-infected model using *C. elegans*, improving the survival rate by 90% and reducing the fungal burden by 88.5%. The mechanism of the synergism was investigated by comparative transcriptomic analysis. The drug combination may act by interfering with the expression of several transporters that are related to glucose permeation and drug efflux[58].

The same group identified aprepitant (**21**, an antiemetic agent) as a potent synergist of itraconazole by assaying the azole chemosensitizing activity of a compound library containing about 1600 FDA-approved drugs[102]. Aprepitant was able to reduce the MIC value of itraconazole by up to eight-fold against *C. auris* (FICI range: 0.14−0.31). The drug combination was fungicidal and significantly inhibited biofilm formation (95%) and mature biofilms (52%). The combination of aprepitant and itraconazole also showed *in vivo* activity in a *C. elegans* infections model, significantly prolonging the survival rate by ∼90% and reducing the fungal burden by ∼92%. The mechanism of synergistic effects was associated with interfering with metal ion homeostasis and the ROS detoxification ability of *C. auris*[102].

In a screen of synergists against azole-resistant *C. albicans*, the pitavastatin (**22**)-fluconazole combination was identified to have broad-spectrum synergistic activity[103]. In particular, pitavastatin displayed potent fluconazole chemosensitizing activity against 5 *C. auris* isolates (FICI range: 0.25−0.5). The combination of pitavastatin-fluconazole effectively inhibited the biofilm-forming abilities and reduced the CFU burden by 14%−92% in an *in vivo C. elegans* model with *C. auris*[103]. The mechanism of synergism was associated with interference with the efflux machinery.

Eldesouky et al.[104] assayed nine stilbene compounds for their synergistic activity with azole drugs against azole-resistant fungal isolates. The ospemifene (**23**)−itraconazole combination displayed the most potent chemosensitizing activity against a variety of fungal pathogens, including *C. auris* (FICI range: 0.14−0.27). The drug combination reduced *C. auris* CFU burden by 96% in a *C. elegans* infections model. Ospemifene exerted synergistic activity by directly interfering with fungal efflux systems such as ABC and MFS transporters and facilitating the entry of azoles into fungal cells.

Chlorhexidine acetate (**24**) is a broad-spectrum antibacterial agent. When used alone, its MIC_{80} values against *C. auris* isolates CBS12373 and CBS10913 were 8 and 2 μg/mL, respectively[105]. When chlorhexidine acetate was used in combination with fluconazole, significant synergism was observed in the growth curve assay[105]. In particular, the drug combination showed strong synergism against the biofilm formation of *C. auris* strains (FICI <0.1875).

The antileishmanial drug miltefosine (**25**) possessed both *in vitro* and *in vivo* antifungal activities, with an MIC value of 2 μg/mL against 12 *C. auris* isolates[106]. When used in combination with amphotericin B, miltefosine showed marginal synergistic effects against 3 out of 12 isolates (FICI = 0.5)[106]. In contrast, indifferent interaction was observed for the miltefosine and fluconazole combination against all of the tested isolates.

Colistin (**26**), an antibiotic, had synergistic activity with caspofungin against several azole-resistant *Candida* spp[113]. For *C. auris*, colistin used alone was totally ineffective (MIC >64 μg/mL)[107]. Synergistic activities were observed for the

combination of colistin and caspofungin, with FICI values in the range of 0.08 to 0.14[107]. In contrast, the combination of colistin with micafungin showed indifferent interactions (FICI range: 0.51−1.01). Colistin also had *in vitro* synergistic interactions with amphotericin B (FICI range: 0.1563−0.375)[114] and isavuconazole (FICI range: 0.3125−0.5)[115] against *C. auris* strains.

5.3. Chemosensitizers potentiating the activity of antifungal agents

Cowen's group[108] screened a diverse chemical library and identified azoffluxin (**28**, a bis-benzodioxolylindolinone derivative) as an effective synergist with fluconazole against *C. auris*. Azoffluxin exerted species-selective synergistic activity against *C. auris* that reduced the MIC value of fluconazole more than eight-fold (FICI = 0.25). The synergistic activity was also observed in *C. auris* clades I, II, and IV, whereas azoffluxin was ineffective against clade III. In a mouse infections model of systemic *C. auris*, azoffluxin (10 mg/kg, subcutaneously, four times daily) significantly enhanced fluconazole (32 mg/kg, intraperitoneally, twice daily) activity in reducing the fungal burden. Unexpectedly, azoffluxin alone also reduced the fungal burden despite it showing no *in vitro* inhibitory activity against *C. auris* growth. Further mechanistic studies revealed that the inhibition of the efflux pump Cdr1 was associated with the potency of azoffluxin. Thus, Cdr1 may be an effective target for development of novel therapeutics.

Shaban et al. evaluated the anti-*C. auris* activity of four phenolic natural products, and carvacrol (**27**) was found to be the most potent compound[109]. Carvacrol had direct activity against at the highest concentration (125 μg/mL) and exerted synergistic and additive effects in combination with fluconazole, caspofungin, amphotericin B, and nystatin. Carvacrol also inhibited virulence factors of *C. auris*, including proteinase production and adherence ability. Although echinocandins were used as the first-line therapy for the treatment of *C. auris* infections, their activity against *C. auris* biofilms was significantly lower than that against *C. albicans*[50]. Farnesol (**29**) is a quorum-sensing antibacterial molecule that has been demonstrated to enhance the activity of echinocandins against *C. auris* biofilms[110]. The synergism was observed for caspofungin (FICI range: 0.156−0.5), micafungin (FICI range: 0.133−0.281), and anidulafungin (FICI range: 0.14−0.375).

The antipsychotic drug haloperidol exhibited direct inhibitory effects against *C. albicans*[116]. Our group designed a series of haloperidol derivatives that showed improved antifungal activities[111,117]. The compound **B2** (**30**) exhibited potent synergistic activity against *C. auris* when used in combination with itraconazole (FICI = 0.188) or voriconazole (FICI = 0.313)[111].

6. Drug repurposing

Drug repurposing has become an effective approach to rapidly identifying new therapeutics for emerging infectious disease[118−120]. Three independent HTS studies have been performed to identify potential agents against *C. auris* from among marketed drugs (Fig. 5)[121−123]. Several hits were shown to possess potent anti-*C. auris* activity when used alone or in combination with antifungal agents (Table 3).

Among such drugs, the effects of ebselen (**31**) have been well characterized in two screens[122,123]. Ebselen is an antioxidant agent with diverse biological activities; it is currently undergoing clinical trials for various applications[124,125]. Ebselen had IC_{50} values in the range 0.2345−1.47 μg/mL against 10 *C. auris* clinical isolates[123]. Moreover, ebselen effectively inhibited biofilm formation of *C. auris* (IC_{50} range: 5.864−9.781 μg/mL)[123]. Ebselen was unable to synergize with fluconazole, amphotericin B, or caspofungin[123], while it showed moderate synergism with anidulafungin[122]. However, the *in vivo* potency of ebselen against *C. auris* has not been reported. In addition to *C. auris*, ebselen also showed broad-spectrum antifungal activity[123,126,127]. The antifungal target and mechanism of ebselen have not been fully characterized. The diverse activity of ebselen may be related to its electrophilic nature, meaning that it could interact with cysteine-rich proteins. In fungal cells, the antifungal activity of ebselen was associated with the inhibition of plasma membrane H^+-ATPase, regulation of glutathione (GSH), and reactive oxygen species (ROS) production[126−128].

Suloctidil (**32**), an antiplatelet drug, has been reported to be active against *C. albicans* and *C. neoformans*[129,130]. Suloctidil also showed significant inhibitory activity against *C. auris*, with MIC values ranging from 4 to 8 μg/mL[122]. In addition, suloctidil was able to synergize with voriconazole against *C. auris*, with FICI values ranging from 0.11 to 0.5. The synergistic antifungal activity of suloctidil may be due to vacuolar biogenesis and membrane trafficking[131].

Myriocin (**33**), a serine palmitoyltransferase inhibitor, showed IC_{50} values of 0.94 and 0.47 μmol/L against *C. auris* 0384 and *C. auris* 0385, respectively. Moreover, myriocin demonstrated a synergistic effect with flucytosine against 13 clinical isolates of *C. auris* (FICI range: 0.49−0.53)[121].

Sertraline (**34**), an antidepressant agent, was reported to possess broad spectrum antifungal activity, including against *C. auris*[132−135]. Sertraline significantly inhibited the growth of *C. auris*, with MIC values ranging from 20 to 40 μg/mL[132]. Sertraline displayed fungicidal activity against *C. auris* and effectively inhibited virulence factors such as the yeast to hyphae formation and biofilm formation[132]. The possible mechanism of action of sertraline was associated with cell membrane damage in *C. auris*[132]. CYP51, the target of azole antifungal agents, was suggested to be the target of sertraline by molecular docking. However, there is still a lack of experimental evidence to support this hypothesis. Recently, our group designed a series of sertraline derivatives by scaffold hopping[136]. Compound **D16** (**35**) showed potent activity against three *C. auris* isolates (MIC range: 4−16 μg/mL). Antifungal mechanistic studies revealed that compound **D16** blocked the biosynthesis of ergosterol through the inhibition of $\Delta^{5,6}$−desaturase, a potential target for the development of anti-*C. auris* therapeutics[136].

Mefloquine (**36**) is an antimalarial agent that was reported to possess moderate antifungal activity[137]. Montoya et al. further evaluated the activity of mefloquine derivatives, and they identified several compounds with improved potency. Among these, compound 4377 (**37**) showed the best activity against five *C. auris* isolates (MIC range: 2−4 μg/mL)[138]. However, this compound was still less active than caspofungin and amphotericin B. Mefloquine derivatives acted by multi-targeting mechanisms in which interference with the functions of mitochondria and vacuoles was preliminarily confirmed[138].

Disulfiram (**38**), an aldehyde dehydrogenase enzyme inhibitor for the treatment of alcohol dependence, was identified as an antifungal agent against *C. auris*[139]. Disulfiram exhibited superior activity against *C. auris* over fluconazole, with MIC values ranging from 1 to 8 μg/mL. In addition, disulfiram showed inhibitory activity against biofilm formation of *C. auris* by increasing fungal cell aggregation, with $SMIC_{50}$ values ranging from 32 to 128 μg/mL[139]. Preliminary

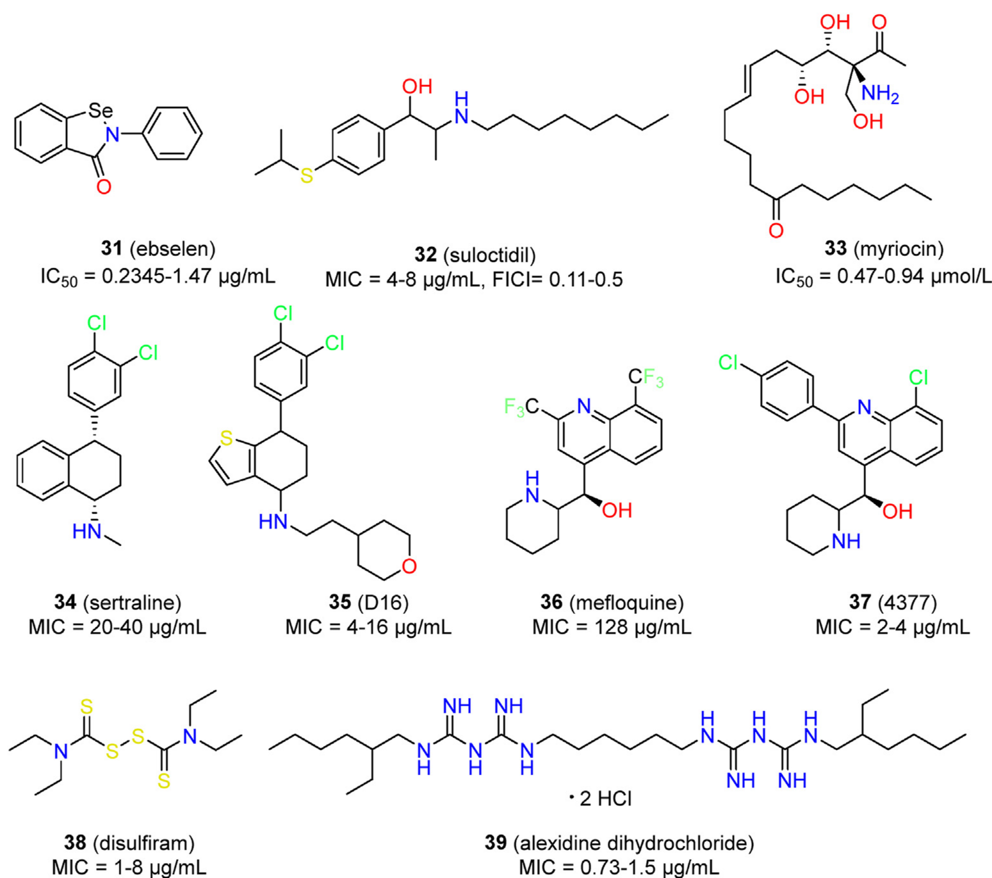

Figure 5 Chemical structures of marketed drugs and derivatives with inhibitory activity against *C. auris* infections.

mechanism studies indicated that disulfiram could combat drug resistance by inhibiting the ABC transporter proteins[140].

Alexidine dihydrochloride (**39**), an anticancer drug act by inhibiting mitochondrial tyrosine phosphatase, has been reported to possess antifungal and anti-biofilm activity against *C. auris*[141]. Alexidine dihydrochloride had MIC values in the range of 0.73−1.5 μg/mL against *C. auris*, and displayed low toxicity on lung epithelial cells and HUVECs (IC_{50} > 7.37 μg/mL). Moreover, alexidine dihydrochloride effectively inhibited biofilm formation and mature biofilm of *C. auris*, with $SMIC_{50}$ values of 6 and 3 μg/mL, respectively[141].

7. New targets for the development of anti-*C. auris* agents

7.1. Phosphatidylinositol−phosphatidylcholine transfer protein: Sec14p

Bugni's group performed anti-*C. albicans* high-throughput screening of the microbiomes of marine animals through an integrated platform of metabolomic and genomic tools[142]. Turbinmicin (**40**), a highly oxidized polyketide, was identified to possess broad-spectrum inhibitory activity against *Candida* spp., *Fusarium* spp., *Scedosporium* spp., and *Rhizopus* spp. (MIC range: 0.03−0.5 μg/mL). In particular, turbinmicin was effective against *C. auris* (strain number: B11211) with an MIC value of 0.25 μg/mL. Further evaluation indicated that turbinmicin was fungicidal with low toxicity, and the maximum tolerated dose (MTD) in a mouse model was above 256 mg/kg. Turbinmicin also showed dose-dependent *in vivo* potency for the treatment *C. auris* infections. At the dose of 4 mg/kg, turbinmicin treatment led to a 3.6 log_{10} reduction in fungal burden compared with a blank control. The mode of action of turbinmicin was preliminary clarified by screening knockdown and knockout gene libraries of *Saccharomyces cerevisiae*. Sec14p, a phosphatidylinositol−phosphatidylcholine transfer protein, was validated as the molecular target of turbinmicin (Fig. 6A). Turbinmicin binds to the phospholipid binding pocket of Sec14p through hydrophobic and hydrogen bonding interactions (Fig. 6B).

The promising *in vitro* and *in vivo* antifungal activity and favorable mammalian safety profile have made turbinmicin a valuable lead compound. However, turbinmicin was administrated by intraperitoneal injection; this limited its further clinical development. After removal of the side chain by ester hydrolysis, the antifungal activity was reduced. Thus, structure optimization of turbinmicin into an orally active antifungal agent is required. To facilitate extensive SAR investigation, the difficulty involved in total synthesis should be solved. However, Sec14p may be further exploited as a drug target to design drug-like inhibitors against *C. auris* infections. Ergoline[143], benzamide[144], and picolinamide[144] derivatives have been reported to be fungal Sec14p inhibitors. However, the antifungal activities of these Sec14p inhibitors were rather weak[143,144]. Fortunately, the crystal structure of Sec14p has been solved[144]; this could improve the efficiency of designing potent Sec14p inhibitors.

7.2. Casein kinase: Yck2

By screening a library of 736 protein kinase inhibitors, the arylpyrazolopyridine derivative GW461484A (**41**) was identified as a

Table 3 Natural peptides and synthetic derivatives with inhibitory activity against *C. auris*.

Peptides	Description	Antifungal activity	Ref.
Crotamine	Natural peptide	MIC range: 40−80 μmol/L	164
Myr-B	Myristoylated lipopeptide	MIC: 16 μg/mL; MIC range: 16−32 μg/mL; *In vivo* potency in a *Galleria mellonella* infection model.	165
Peptide 3	Cyclic temporin L peptide analogue	MIC: 50 μmol/L; MFC: 50 μmol/L; 50% biofilm inhibition at 6.25 μmol/L; *In vivo* potency on the infected *G. mellonella* larvae without significant toxicity.	59
Pom-1	A fragment of Closticin 574	Planktonic cells IC_{50}: 13.8 μg/mL Biofilm IC_{50}: 4.2 μg/mL	166
Pom-2	A fragment of cecropin D-like peptide	Planktonic cells IC_{50}: 8.4 μg/mL Biofilm IC_{50}: 2.2 μg/mL	166
NCR169C17-38	A derivative of specific cysteine-rich (NCR) peptide	MIC: 6.25 μmol/L; Additive effect with fluconazole	167
NCR335C17-33	A derivative of specific cysteine-rich (NCR) peptide	No direct activity; Synergic effect with fluconazole FICI: 0.375	167
Cm-p5	Natural peptide	MIC: 11 μg/mL	168
Dimer 1 and 2	Cyclic and helical-stabilized analogues of the antifungal peptide Cm-p5	Inactive against planktonic cells Biofilm IC_{50}: 10−21 μg/mL	169
CR-184	Cathelicidin-inspired AMPs	Abolish metabolic activity at the concentration <1 μmol/L	170
θ-Defensins	18-Amino-acid macrocyclic peptides	MIC range: 3.125−6.25 μg/mL	171
AF4	Lipopeptide homologues	MIC: 3.48 μg/mL; MFC: 3.48 μg/mL; Inhibition of biofilm formation: $SMIC_{50}$ = 6.96 μg/mL	172

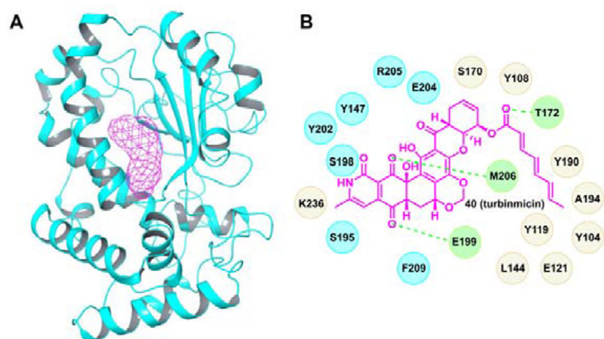

Figure 6 Crystal structure of Sec14p (A, PDB code: 6F0E) and a proposed binding model of turbinmicin with Sec14p (B). The magenta mesh indicates turbinimicin, and the dashed green lines represent hydrogen bonding interactions.

sensitizer to reverse caspofungin resistance against *C. albicans*[145]. Interestingly, GW461484A also potentiated the activity of caspofungin against a multidrug-resistant *C. auris* isolate with an FIC_{80} (fractional inhibitory concentration 80 index) value lower than 0.156, whereas it had little effect on the anti-*C. auris* activity of fluconazole. Furthermore, Yck2 was identified to be the molecular target of GW461484A by chemogenomic and biochemical profiling[145]. Yck2 belongs to the protein family of CK1 (casein kinase 1) that has been associated with the morphogenesis and virulence of *C. albicans*. Structural biology studies indicated that GW461484A interacted with the ATP-binding pocket of Yck2 through hydrogen bonding and hydrophobic interactions (Fig. 7). Although the biological functions of Yck2 are still unknown, Yck2 represents a valuable target for the development of *C. auris* therapeutics. *In vivo* antifungal potency of GW461484A was not determined due to poor metabolic stability. The pyrazolopyridine Yck2 inhibitors remain to be further optimized and evaluated against *C. auris* infections.

7.3. Acetohydroxyacid synthase

Acetohydroxyacid synthase (AHAS), an enzyme in the biosynthesis pathway of branched-chain amino acid, has been demonstrated as a promising target for the development of antifungal agents against *C. auris*[146,147]. Guddat et al.[147] expressed and obtained the AHAS from *C. auris* (*Cau*AHAS), and identified several sulfonylurea and triazolopyrimidine herbicides as potent antifungal inhibitors against *C. auris* (MIC_{50} < 5 μmol/L), with the K_i values of < 2 μmol/L for *Cau*AHAS. Among them, bensulfuron methyl (BSM, **42**), a sulfonylurea inhibitor, exhibited the best fungicidal potency with the MIC_{50} values of 0.09 μmol/L. BSM was also an excellent inhibitor for preventing the biofilms formation of *C. auris* ($SMIC_{50}$ = 0.6 μmol/L). Cell viability assays revealed that BSM was non-cytotoxic to human embryonic kidney (HEK)-293 cells at the concentrations of < 100 μmol/L[147]. The possible binding model of these inhibitors with *Cau*AHAS was identified by homology modelling based on the crystal complex of *C. albicans* AHAS with chlorimuron ethyl (CE, **43**), an analogue of compound **42**. CE interacted with the binding sites of *Cau*AHAS by hydrophobic, hydrogen bonding and $\pi-\pi$ stacking interactions (Fig. 8). These data indicated that *Cau*AHAS was a viable target for treating *C. auris* infections.

7.4. New chemical scaffolds against C. auris

7.4.1. Rocaglates

Cowen's group screened a library containing 2454 compounds to identify anti-*C. auris* compounds, and the hits shared a common rocaglate scaffold (**44**)[148]. Representative compound CMLD010515 (Fig. 9) displayed inhibitory activity against *C. auris* (active concentration: < 12.5 μmol/L) and was demonstrated to be fungicidal. Interestingly, the anti-*C. auris* activity was species-specific, because the rocaglates were inactive against pathogenic related *Candida* species such as *C. albicans*. The antifungal mechanisms of rocaglates were preliminary elucidated; these involved inhibition of translation

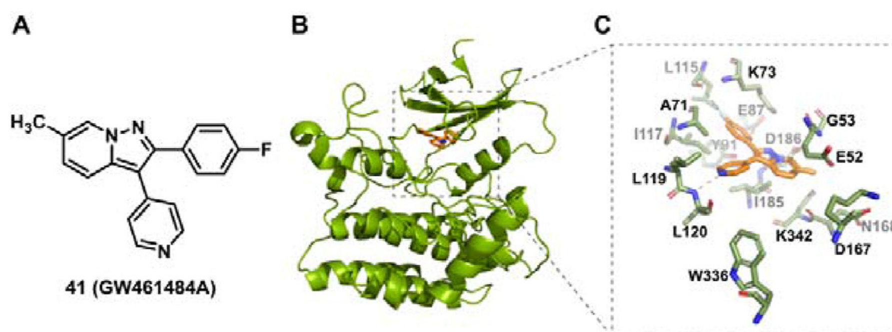

Figure 7 Chemical structure of GW461484A (A), crystal structure of Yck2 (B, PDB code: 6U6A), and the binding mode of GW461484A with Yck2 (C). The orange molecule indicates compound GW461484A.

initiation in *C. auris*, triggering an apoptosis-like cell death program and blocking vacuolar homeostasis[148].

7.4.2. *Hydroxyquinolines: Nitroxoline*

The hydroxyquinoline derivate nitroxoline (**45**) is an antibacterial agent used for urinary tract infections. It also has shown inhibitory activity against *C. auris*, with MICs ranging from 0.125 to 1 μg/mL (35 isolates: MIC_{50} = 0.25 μg/mL, MIC_{90} = 0.5 μg/mL)[149]. It was more potent than amphotericin B (MIC > 1 μg/mL in 4/35 isolates) and fluconazole (MIC > 4 μg/mL in 31/35 isolates). Nitroxoline was proposed as a potential treatment option for *C. auris* candiduria. However, its *in vivo* efficacy remains to be confirmed.

7.4.3. *Halogenated salicylanilides*

In an antivirulence phenotypic screen, halogenated salicylanilides 1 and its analog niclosamide (**46**, **47**) exhibited potent inhibitory activities against *C. albicans* filamentation and biofilm formation[150]. Both were also active against the biofilms of *C. auris* in a dose-dependent manner[150]. Mechanistic studies revealed that the mitochondrial protein import machinery may be involved in the activity of halogenated salicylanilides.

7.4.4. *Pyrimidinedione: MYC-053*

The pyrimidinedione derivative MYC-053 (**48**) showed broad spectrum effects against *Candida* spp., *Cryptococcus* spp., and *Pneumocystis* spp. It had an MIC value of 4 μg/mL against 5 *C. auris* isolates, and it was also active against several strains resistant to fluconazole and caspofungin[151].

7.4.5. *Macrocyclic amidinoureas: BM1*

BM1 (**49**) is a derivative of macrocyclic amidinoureas whose chemical structure features an amphiphilic macrocycle, a methylene linker, and a terminal alkenyl guanidine[152]. BM1 showed potent inhibitory activity against various fluconazole-sensitive and fluconazole-resistant *Candida* spp., including *C. auris* isolates. The MIC value of BM1 against 18 *C. auris* isolates was in the range of 8 μg/mL to 64 μg/mL[153]. However, the antifungal activity of BM1 against *C. auris* was significantly lower than that against *C. albicans* (MIC range: 0.125−2 μg/mL). The activity of BM1 against resistant fungi was associated with the overexpression of ABC transporters[153]. BM1 showed *in vivo* efficacy for treating infections by drug-resistant *C. albicans*[152], whereas the *in vivo* potency against *C. auris* is still unknown.

7.4.6. *Oxadiazolylthiazoles*

Hagras et al. synthesized a series of oxadiazolylthiazole derivatives and identified selective antifungal agents[154]. Diaminocyclohexyl derivative **50** showed broad-spectrum *in vitro* antifungal activity, including against *C. auris*. It had MIC values of 4, 2, and 2 μg/mL against *C. auris* 381, *C. auris* 383, and *C. auris* 384, respectively. Moreover, compound **50** showed low toxicity against human colorectal adenocarcinoma (Caco-2) and monkey fibroblast-like kidney epithelial (Vero) cells, with CC_{50} values larger than 64 μg/mL.

7.4.7. *Phenylthiazoles*

Mohammad et al. assayed 85 synthetic phenylthiazole derivatives for inhibitory activity against drug-resistant *C. albicans*[155]. Thiazole-

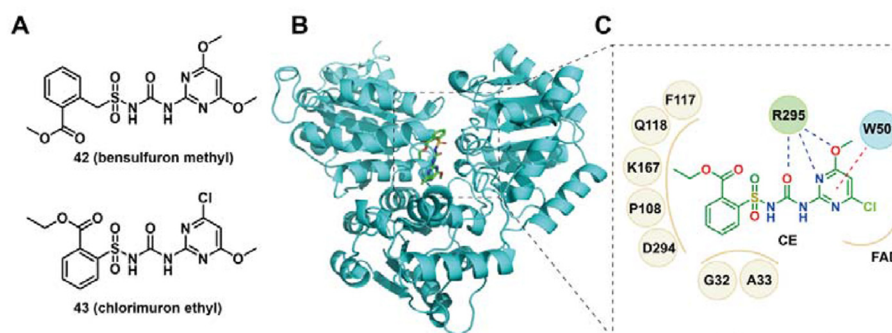

Figure 8 Chemical structure of BSM and CE (A), crystal structure of AHAS (B, PDB code: 6DEL), and the binding mode of CE with AHAS (C). The green molecule indicate compound CE. Solid brown lines, dashed blue lines, and dashed red lines represent hydrophobic, hydrogen bonding and $\pi-\pi$ stacking interactions, respectively.

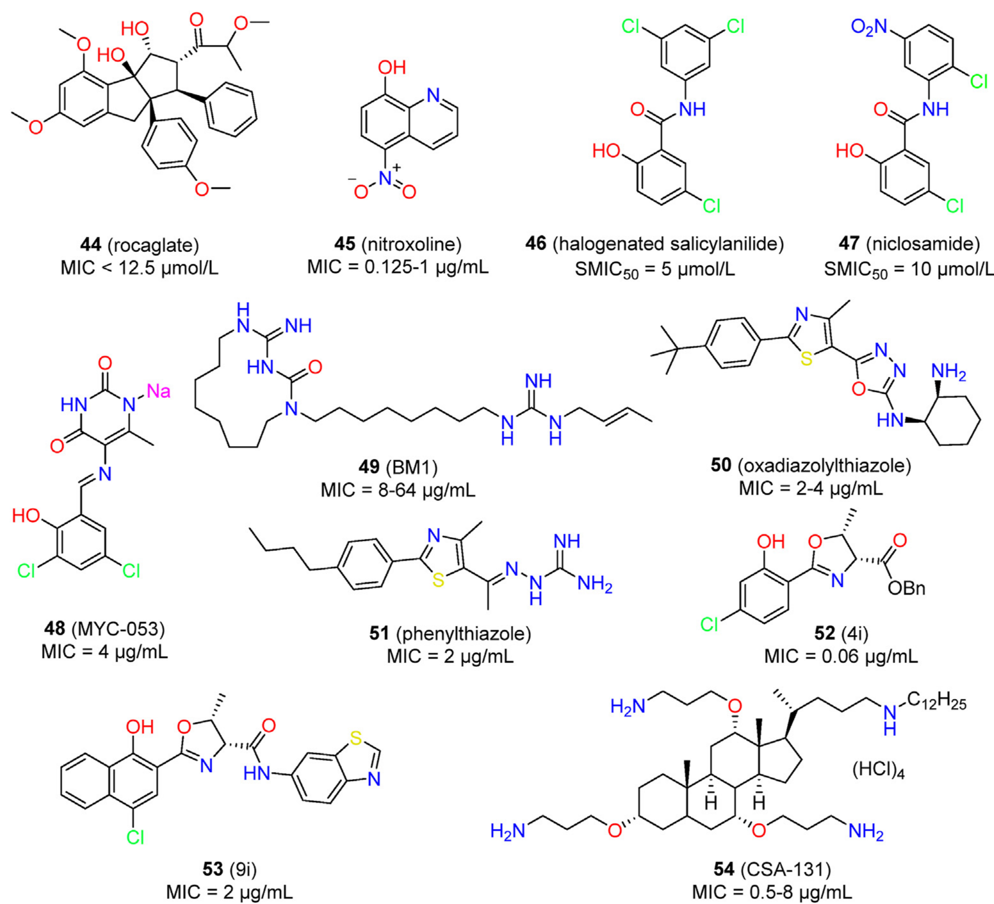

Figure 9 Chemical structures of new chemotypes with inhibitory activity against *C. auris*.

aminoguanidine derivative **51** showed the most potent antifungal activity, with a broad spectrum. Compound **51** had an MIC value of 2 μg/mL against eight *C. auris* isolates, a value that was more potent than fluconazole (MIC > 64 μg/mL) and comparable to amphotericin B (MIC range: 0.50−2 μg/mL). Compound **51** showed rapid fungicidal activity against *C. auris* viability within 30 min. At the concentration of 2 μg/mL, compound **51** effectively inhibited biofilm formation of *C. auris* (91.2% reduction), and it was equally effective as amphotericin B (92.4% reduction). In contrast, the cytotoxicity of compound **51** against mammalian cells was significantly lower than that of amphotericin B. In a *C. elegans* model with *C. auris*, compound **51** prolonged the survival of infected nematodes by about 70% at the concentration of 10 μg/mL.

7.4.8. 2-Aryloxazolines

Stefani's group synthesized a series of 2-aryloxazoline derivatives and assayed these for inhibitory activity against *C. albicans*[156]. Most compounds showed comparable or superior antifungal activity to fluconazole. The compounds **4i** (**52**) and **9i** (**53**) were also effective against *C. auris* isolates CBS 10913 (MIC = 0.06 μg/mL) and CBS 12766 (MIC = 2 μg/mL).

8. Antimicrobial peptides

Antimicrobial peptides (AMPs) are emerging as an attractive area in antifungal therapy due to the important roles in human innate immunity and host defense and the low risk of inducing MDR[157]. Several antifungal AMPs have also shown potent activity against *C. auris* (Table 3).

Histatin 5 (Hst 5) was reported to possess good antifungal activity against *C. albicans*[158]. In a susceptibility assay of 10 *C. auris* clinical isolates, Hst 5 showed fungicidal activity against the majority of tested isolates, killing 55%−90% of *C. auris* cells at the concentration of 7.5 μmol/L[159]. The high tolerance of *C. auris* strains to oxidative stress was possibly associated with the killing effect of Hst 5[159].

Human cathelicidin peptides LL-37 showed both direct and synergistic activities against *C. auris*[160]. The growth inhibitory activity of LL-37 was moderate in a collection of 10 clinical strains (MIC range: 25−100 μg/mL; MFC range: 50−200 μg/mL). LL-37 also effectively synergized with antifungal agents such as fluconazole (80% of strains, FICI range: 0.27−0.5), amphotericin B (100% of strains, FICI range: 0.13−0.31), and caspofungin (100% of strains, FICI range: 0.13−0.26). The antifungal mechanistic studies revealed that LL-37 acted by disrupting the cell membrane, causing oxidative stress, and arresting the S phase of cell cycle of *C. auris*[160].

AMPs are generally the substrates for proteases and are prone to be degraded *in vivo*. Thus, non-peptide AMP mimics were designed to overcome the limitations of peptide molecules. Ceragenins feature a bile acid scaffold and a lipid chain that mimics the common amphiphilic secondary structure of AMPs and that has shown broad-spectrum antifungal activity[161,162]. The compound ceragenin CSA-131 (**54**) had potent fungistatic and fungicidal activity against a set of 100 *C. auris* clinical isolates (MIC range: 0.5−8 μg/mL; MFC

range: 2−64 μg/mL) and was generally more potent than fluconazole, caspofungin, and amphotericin B[163]. The antifungal activity of CSA-131 was clade independent without variation between the four clades (overall mode: 1 μg/mL; MIC_{90} = 1 μg/mL). Notably, no loss of inhibitory activity was observed for those isolates resistant to fluconazole and/or echinocandin. CSA-131 also effectively inhibited the activity of *C. auris* biofilm formation ($SMIC_{50}$ range: 2−4 μg/mL). In an *ex vivo* infections model of mucosal tissues, topical use of CSA-131 (2% gel and cream formulations) resulted in significant reductions of fungal burdens.

9. Perspectives and conclusions

Although some progress has been made, we still do not clearly know where *C. auris* originated or why *C. auris* has independently and simultaneously spread worldwide. Our understanding of the virulence, risk factors, and mechanisms of drug resistance remains in its infancy. In some cases, the results obtained from different clades (strains) of *C. auris* are controversial or contradictory. Thus, there is still a long way to go before we can fully understand this novel fungal pathogen. To tackle the threat of *C. auris*, improvement in early diagnosis, control measures, and education of healthcare providers will help to reduce the incidence of infections. More importantly, the development of effective therapeutics is urgently needed to improve clinical outcomes and decrease mortality.

Although echinocandins have been recommended as the first-line therapy, the options for effective treatment of *C. auris* infections are rather limited. Several antifungal agents in clinical development have been shown to be effective against *C. auris* through *in vitro* and *in vivo* evaluations. These compounds have also shown favorable pharmacokinetic and safety profiles with a low risk of drug−drug interactions in clinical trials. However, only two clinical trials have been started for *C. auris* infections (ibrexafungerp and APX001) with as yet undisclosed data. Therefore, more clinical studies are required to validate the potential usefulness of these candidates in clinical practice.

Synergistic drug combinations have been suggested as a potential option for the treatment of *C. auris* infections. Although a number of active combinations have been reported, it is premature to predict their clinical utility, because most have only been evaluated *in vitro*. Additional evaluation in animal models or eventually in clinical trials is required to identify useful combinations for pan-resistant *C. auris*.

Drug repurposing has been demonstrated to be a useful approach to accelerate the drug development process, particularly for emerging infectious diseases. Several “non-antifungal” drugs have been shown be active in inhibiting the growth of *C. auris* when used alone or in combination the antifungal agents. However, such known drugs could hardly be used directly in clinical application due to limited potency and side effects. An important value of drug repurposing is to offer drug-like lead compounds for the optimization of therapeutic efficacy and safety profiles. For example, our group has designed a series of new derivatives of sertraline and piperidol as antifungal agents, and it has also identified new leads with improved antifungal activity and reduced original activity of approved agents[111,136]. Thus, further structural optimization and exploration of the SARs of the hits from anti-*C. auris* screening may improve the efficiency of drug development. Also, the clinical values of broad-spectrum antifungal agents or *C. auris* selective inhibitors still remain to be further explored.

With better understanding of the virulence and resistant mechanisms of *C. auris*, the discovery and identification of new targets is highly important for developing effective therapeutics with new modes of action. Sec14p and Yck2 have been preliminarily identified as potential targets for *C. auris* infections. These targets were identified through chemogenomic profiling of active compounds. Biology-inspired discovery of new targets is still rare, possibly due to limited knowledge concerning *C. auris*. Another problem for the new antifungal targets is the inconsistency between molecular and antifungal activity. After proof-of-concept validation, extensional medicinal chemistry exploration of the inhibitors would contribute to identifying selective and drug-like inhibitors. Recently, a large number of anti-*C. auris* compounds were identified by phenotypic antifungal screening, and their molecular targets are mostly unknown. These bioactive compounds could be used as chemical probes to look for new targets by chemogenomic profiling; this would provide an alternative for target discovery in *C. auris*. With a better understanding of *C. auris*, increased medicinal chemistry effort, and more preclinical and clinical trials, highly effective antifungal drugs will become a reality for the treatment of patients with severe *C. auris* infections.

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Author contributions

Yahui Huang and Wanzhen Yang performed the literature search and data collection. Chunquan Sheng conceived the concept of the study. Jie Tu designed and regenerated the conceptual pictures. Jie Tu, Na Liu and Chunquan Sheng prepared and revised the manuscript. All authors have read and approved the final manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

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