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REVIEW

New Technologies to Diagnose and Treat a Multidrug-Resistant *Candida auris:* A Patent Review

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Abstract *Candida auris* is responsible for hospital outbreaks worldwide. Some *C. auris* isolates may show concomitant resistance to azoles, echinocandins, and polyenes, thereby possibly leaving clinicians with few therapeutic options. In addition, this multi-drug-resistant yeast is difficult to identify with conventional methods and has the ability to persist on environmental surfaces causing hospital-acquired infections. The development of new treatment options and tools for identification is critical to control, prevent, and establish an early diagnosis of this emerging pathogen. The aim of this study was to perform a critical patent review to explore and identify the latest advances in therapeutic strategies as well as diagnostic methods for *C. auris*. A total of 19 patents were identified for a preliminary assessment from the Espacenet database. Three patents were excluded as they were out of focus for this review according to their abstract and/or description. The final selection covered 16 patents, which were surveyed by country, year and classified as treatment or diagnostic methods for *C. auris*. As noted in the patent reading, in recent years, the interest of academic, government and industry sectors have shown an increasing tendency focused on research and development of new therapeutic molecules and diagnostic methods to combat this emerging pathogen.

Keywords *Candida auris* · Treatment · Diagnostic methods

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Introduction

Candida auris is an emerging fungus that presents a serious global health threat. Though *C. auris* was first identified in Japan in 2009 [1], a retrospective study revealed that the earliest strain of *C. auris* dates back to 1996 in South Korea [2], and since then, outbreaks have been reported from over 47 countries [3].

Controlling *C. auris* is a major concern for several reasons: (1) It is resistant to multiple classes of antifungal drugs commonly used to treat *Candida* infections, (2) It is difficult to identify with standard laboratory methods and thus can often be misidentified without the use of specific technology leading to

inappropriate management and (3) It can disseminate between patients in healthcare settings. For these reasons, rapid identification of clinical *C. auris* strains is very important so that healthcare facilities can take necessary measures to prevent its transmission [2, 4]. In addition, *C. auris* is exceptionally well adapted to the nosocomial environment, resists common disinfectants, persists on medical equipment and dry surfaces in hospitals for up to 4 weeks, and readily colonizes the axilla, groin, and nares of patients [5].

Ultimately, correct detection and identification of the pathogen along with its antifungal susceptibility profile, followed by strict adherence to appropriate treatment and infection prevention and control strategies, are crucial for limiting the spread of *C. auris* [6]. Furthermore, matrix-assisted laser desorption ionization-time of flight mass spectrometry ("MALDI-TOF MS) and ribosomal DNA sequencing are preferred over conventional diagnostic methods as they can reliably distinguish *C. auris* from other yeasts [6].

Currently, four classes of antifungal agents are available for the treatment of candidiasis: azoles (fluconazole, voriconazole), polyenes, echinocandins (caspofungin, micafungin, and anidulafungin), and flucytosine. The use of echinocandins as first-line therapies subjected to sensitivity testing is recommended [7]. Although echinocandins are effective against most isolates of *Candida* species resistant to other antifungal agents, an increase in the number of *C. auris* strains with reduced susceptibility to one or more echinocandins has been observed [8, 9].

All these factors allow *C. auris* to easily spread in hospitals and cause recalcitrant outbreaks. They also contribute to the high mortality rates (30–60%) observed in the case of *C. auris* invasive infections [10]. The onset of the SARS-CoV-2 pandemic has increased the *C. auris* colonization and candidemia cases [4]. New *C. auris* outbreaks in critically ill COVID-19 patients were also reported, and it was alerted that the SARS-CoV-2 pandemic might facilitate the transmission of nosocomial pathogens, including *C. auris*[11].

Thus, this review aims to provide an overview of new methods and therapeutic options that can bring new hope to patients and healthcare professionals to combat the outbreaks caused by *C. auris.*

Methods

An updated keyword search of "*Candida"* and *"auris*" was performed in the claim search field of Espacenet database on May 30, 2022. This review is based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The patent selection was based on the following inclusion criteria: recent patents published after the first description of *C. auris* in 2009 in Japan to May 2022 in any language and containing "*Candida*" and "*auris*" as the keywords in the title or abstract. Using the same criteria, a literature survey was performed using the PubMed literature database to compare the number of papers on the subject of "*Candida auris*" to the number of patents found in the patent databases. This survey was conducted in May 2022. Patents that did not focus on the "*Candida*" and "*auris*" subject were excluded from the search results. A total of 21 patents were selected for preliminary assessment from Espacenet (Fig. 1). After excluding three patents that were out of scope, 18 patents were selected to be studied in detail. Following this, the patent contents were classified per country, year and type of applicant.

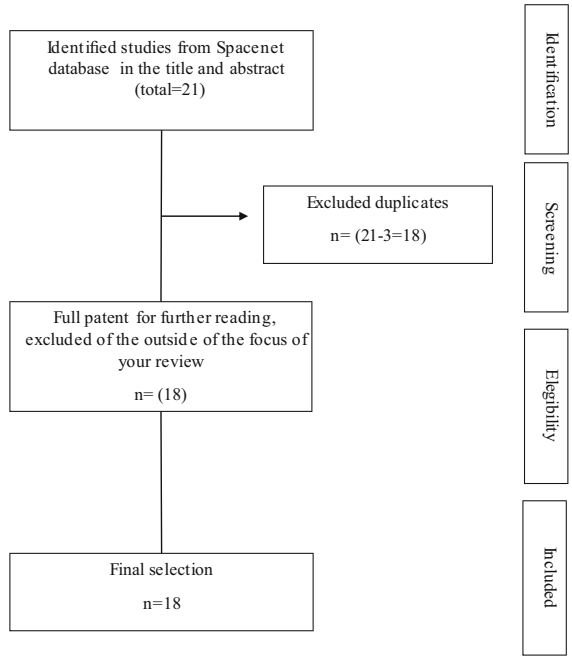

Fig. 1 Flowchart of patent search and screening

Results and Discussion

The identification of new target-specific antifungal therapeutic strategies and the development of novel diagnostic methods against *C. auris* are valuable approaches to combat this emerging multidrug-resistant pathogen. In our review, the patents related to the diagnosis and treatment published by May 2022 were included. Out of 18 reviewed patents, 11 were deposited in 2020, and until May 2022, 4 were described. *C. auris* was first reported in 2009 in Japan, but patents related to *C. auris* appeared nine years later. The total number of patent publications between 2018 and 2020 was also lower compared to the number of scientific articles published during the same period. Using the same combination of words "*Candida auris*" to search in the PubMed database, 882 scientific papers were obtained from 2009 to 2022 (accessed on May 23, 2022). Based on the results, we observed that both the number of patents and the number of scientific publications increased rapidly, emphasizing the importance of *C. auris* as a global health concern. We have to considerer the impact of the COVID-19 pandemic on the patent community. Most of the offices suspended the transmittal of Patent Cooperation Treaty (PCT) documents, limited, or canceled in-person interviews, postponed deadlines, and focused only on patents related to the COVID-19 pandemic [12]. Quarantines and lockdowns have shut down conferences, seminars, and other social events where knowledge is disseminated, collaboration occurs, funding sources are identified, and discoveries emerge. In addition, many clinical trials and early-stage research projects that could lead to life-saving treatments worldwide have been abandoned due to lockdowns or because funding has been discontinued [13]. National Public Radio (NPR) reported an interruption of clinical trials for many important cancer drugs [14]. At present, only 4 clinical studies are registered in the Clinical Trials related to *C. auris* (accessed on May 23, 2022: https://clinicaltrials.gov). In the USA, non-COVID-19 research operations at universities, medical schools, and federal labs (most located in states with severe lockdowns) have also been shut down, leading to the cancellation of basic and applied research on several diseases that kill millions each year [15].

Regardless of the countries which produced patents, the US was responsible for the majority of the number of patents published ($n = 10$), followed by China ($n = 6$), Spain ($n = 1$) and Japan ($n = 1$) (Fig. 2). Though *C. auris* is a global concern causing outbreaks in more than 48 countries (Fig. 2), the patents are mostly based on cases of two countries. Although the US has presented a high number of patent publications, owing to its excellent economy and investment in the field of technological innovation [16] in the past two decades, China has experienced strong and sustained growth in patent applications, surpassing the US and becoming the world's leading patent registrar [17].

Several scientific organizations may request the protection of an invention by filing a patent application. Industries lead the filing ranking with 11 patents (61.1%). In addition, hospitals (02/18, 11.1%), universities (02/16, 11.1%), universities in collaboration with research centers (01/18, 5.5%), only research centers (01/18, 5.5%) and independent researcher (01/18, 5.5%) also file for patents applications.

Based on our findings, the main focus of the patents was categorized into treatment (Table 1) and diagnostic methods (Table 2). Table 1 represents patent publications that focus on the *C. auris* treatment/disinfection. Table 2 describes new methods to identify and diagnose *C. auris* colonization and infection. The treatment and diagnostic methods are discussed in the following sections in detail:

Treatment of *C. auris* Infection or/Colonization

In addition to antifungal resistance, *C. auris* has a special predilection for skin, particularly the axilla and groin. It has the potential to colonize hosts within days to weeks of exposure, and invasive infections may occur within days to months after colonization [10]. Colonization with *C. auris* may persist for many months and possibly indefinitely [4]. This information is helpful for better treatment of patients.

"WO2020232037 (A1)" [18] describes the use of Ibrexafungerp (formerly known as SCY-078) as the first compound of the enfumafungin-derived triterpenoid class of (1 → 3)-β-D-glucan synthase inhibitors (GSIs). There is also an open-label study registered in the clinical trials (https://clinicaltrials.gov/ct2/home) to evaluate the efficacy, safety, tolerability, and pharmacokinetics of oral Ibrexafungerp (SCY-078) as an emergency treatment of patients with candidiasis and candidemia caused by *C. auris*. After oral administration, the enfumafungin derivatives

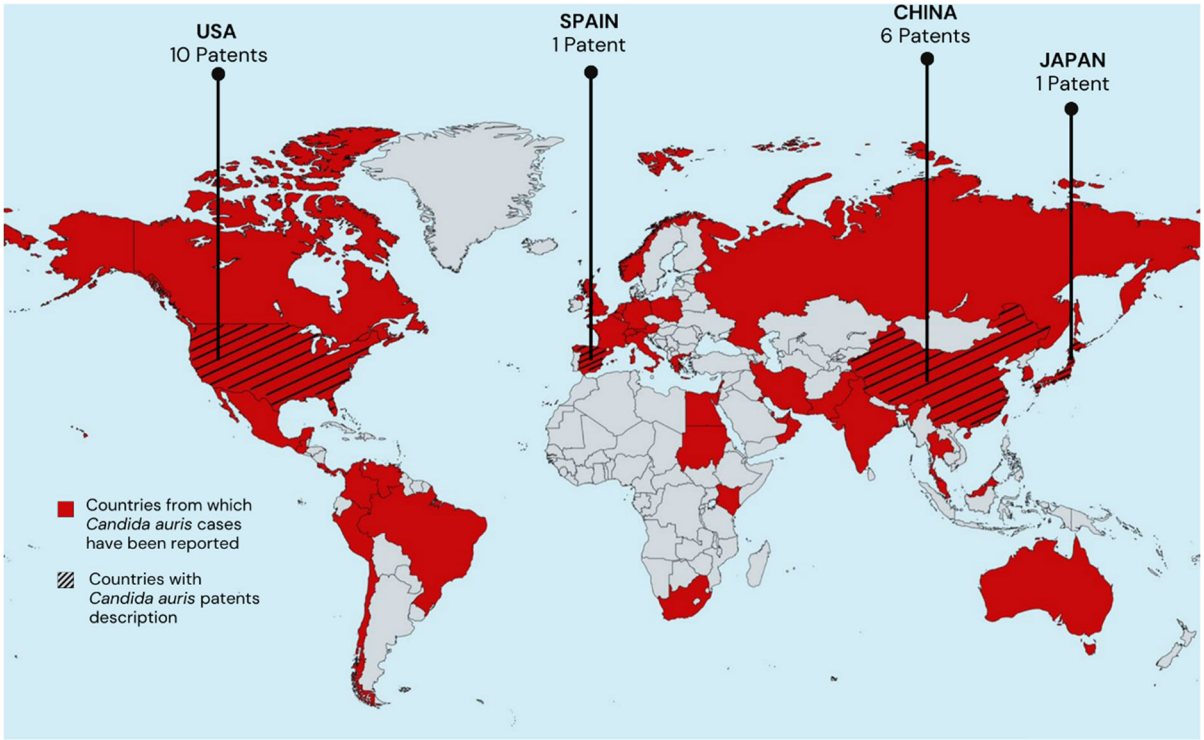

Fig. 2 Worldwide distribution of *C. auris* reported cases-February, 12–2021 and description of the countries where the *C. auris* patents were described until May 2022

were able to significantly reduce *C. auris* infection of the skin, revealed a useful strategy to prevent transmission, and limited the risk of *C. auris* outbreaks [36, 37]. Increased bioavailability of Ibrexafungerp positions them to be an optimal solution for the decolonization of *C. auris* from anatomic areas of a subject [38]. On the other hand, glucan synthase inhibitors, such as echinocandins, have a similar mechanism of action and lower oral bioavailability, and their target site concentrations are much lesser than that of plasma [39]. Thus, they cannot prevent the colonization of *C. auris* at multiple body sites, including nares, groin, axilla, and rectum for 3 months or more after initial intravenous echinocandin treatment [3]. In addition, Ibrexafungerp does not have clinically relevant antibacterial properties and cannot cause a deleterious effect on the normal bacterial microbiome of the skin and mucosa. Ibrexafungerp, with the potential to provide the therapeutic advantages of both intravenous (IV) and oral formulations, being developed as the first oral and intravenous glucan synthase inhibitor (IV GSI) for the treatment and prevention of fungal infections, including serious and life-threatening infections due to *Candida* spp., *Aspergillus* spp. and *Pneumocystis jirovecii* [40]. Ibrexafungerp causes a decrease in the concentration of (1 → 3)-β-D-glucan polymers and weakens the fungal cell wall [37].

"WO2021090739 (A1)" [19] describes a pharmaceutical composition comprising of a therapeutically effective amount of 4-[16]propyl)-1-piperidinyl]propoxy}benzamidine (abbreviated as T-2307) which is effective in treating *C. auris* infection. Results demonstrate that T-2307 is effective against invasive infections caused by *Candida* spp., specifically *C. auris*, as both in vitro and in *vivo* activity were observed against this emerging pathogen. The initial preclinical and early-stage clinical development of T-2307 has been conducted by FUJIFILM Toyama Chemical Co. Ltd. (Tokyo, Japan), which has recently assigned the rights to Appili Therapeutics (Halifax, NS, Canada; ATI-2307) (http://fftc.fujifilm.co.jp/en/news/news191121e.html, accessed on July 07, 2021) for developing and marketing the drug outside of Japan. In vitro study using clinical isolates of *C. auris* showed that the MICs of

Table 1 Patents for treatment and prevention of *Candida auris* infection or/ colonization

	Applicant number (Reference)	Country	Year	Formulation	Compounds	Indication	Application	Compatibility tests	Mechanism of action
1	WO2020232037 (A1) [18]	US	2020	Oral drug	Ibrexafungerp	To promote *C. auris* decolonization of skin or mucosa and prevent *C. auris* infection	Decolonization of skin or mucosa	In vitro studies: MIC: 0.0625 μg/mL to 2 μg/mL In vivo studies: reduction of *C. auris* skin burden in a guinea pig model	Decrease in (1 → 3)-β-D-glucan polymers and a weakening of the fungal cell wall
2	WO2021090739 (A1) [19]	US	2021	Oral and parenteral drug	T-2307	To treat *C. auris* infection	Treatment of *C. auris* infection	In vitro studies: MIC: < 0.008 μg /mL In vivo studies: Improved survival of *immunocompromised* mice	Collapse of the mitochondrial membrane
3	WO2020150532 (A1)[20]	US	2020	Topical drug	PHMB or combination of: PHMB + PAPB + CHG	To treat of mucous membranes, skin, and surfaces infected with *C. auris*	Treatment of *C. auris* infection	In vitro studies: *Inhibition* of *C. auris* growth In vivo studies: decrease in colonization of *C. auris* on mouse skin and mucous surfaces	Disrupting microbial cell membranes and metabolism, interfering with cell function
4	US2020237705 (A1) [21]	US	2020	Topical drug	GML	To treat *C. auris* infection	Treatment of *C. auris* infection	In vitro studies: Kill C. auris at ≥ 50 μg/mL of GML *Inhibition* of Biofilm formation	Unknown
5	CN111954533 (A)[22]	China	2020	Parenteral drug	Taurolidine	To treat *C. auris* blood infection		In vitro studies: MIC? In vivo studies: ? undetermined model	Unknown
6	WO2018204506 (A1)[23]	US	2018	Oral, parenteral and superficial application	CSA-131	To treat or prevent *C. auris* infections and/or preventing colonization by *C. auris*	Open wound, surgical site, catheter (e.g., venous catheter) insertion site, or other such wound	In vitro studies: MIC range:0.1to 1 μg/mL	Membrane disruption

Table 1 continued

	Applicant number (Reference)	Country	Year	Formulation	Compounds	Indication	Application	Compatibility tests	Mechanism of action
7	US2021030852 (A1)[24]	US	2020	Subcutaneously, intramuscularly, intradermally, transdermally, intranasally, orally, or via an infusion application	Als3 polypeptide or fragment or homolog thereof or an anti-Als3 antibody or antigen-binding fragment	To treat, immunize and prevent *C. auris* infection	Immunization	In vivo studies: Serum from mice inoculated with Als3-2 bound the surface of *C. auris* Serum from vaccinated mice enhances opsonophagocytic killing of *C. auris* Serum from vaccinated mice inhibits *C. auris* biofilm formation	N-terminus of Als3p formulated with alum, drawn for *C. albicans* generates cross-reactive antibodies against *C. auris*
8	WO2021178774A1 [25]	US	2021	Abiotic Disinfectant	Hydrogen peroxide + acetic acid to form peroxy acetic acid	Disinfectant system	Disinfection and sterilization	In vitro studies	Not described

US: United State, MIC: minimum inhibitory concentration, PHMB: polihexanide biguanide, biguanide polyaminopropyl biguanide (PAPB), and or chlorhexidine gluconate (CHG), GML: glycerol monolaurate; CSA-131: cationic steroid antimicrobial

T-2307 ranged from $\leq$ 0.008 µg/mL to 0.015 µg/mL, and the drug was active against strains that were resistant to fluconazole [41]. This agent has a novel mechanism of action and causes the collapse of the mitochondrial membrane potential. Recent studies have revealed that this activity is selective for fungi [41].

"WO2020150532 (A1)"[20] refers to a composition comprising of polyhexanide biguanide (PHMB) for the topical treatment of mucous membranes or skin infected with *C. auris*. PHMB alone or in combination with one or more cationic biocides as polyaminopropyl biguanide (PAPB) and/or chlorhexidine (CHG) presented activity against *C. auris*. The results showed that the treatment with the formulation resulted in a significant decrease in the colonization of *C. auris* on murine ear surfaces. The mechanism of action consists of disrupting microbial cell membranes and metabolism, interfering with function, and ultimately destroying the microbial cell [42].

"US2020237705 (A1)" [21] refers to glycerol monolaurate (GML), also known as monolaurin, which kills *C. auris*. In addition, 5% GML gel was able to inhibit biofilm formation of *C. auris*. There is no published study at present confirming the antifungal activity of GML against *C. auris*. However, oral topical treatments of GML have resulted in a significant decrease in colony formation unit of *C. albicans* on tongue tissue compared to the vehicle control. The results show that GML is a promising antifungal compound in vivo and can be used in the future for the treatment of oral candidiasis [43]. There is no mechanism of action described for GML.

"CN111954533 (A)"[22] comprising of taurolidine, refers to a method for treating *C. auris* in blood. When the drug reaches the infection site of *C. auris* from the point of entry, the hydrolysable polymer coating covering the taurolidine core acts as a sacrificial layer and slowly decomposes as the nanoparticles pass through the bloodstream. Eventually, the hydrolysable polymer coating decomposes to the point where the taurolidine core is exposed to blood. The taurolidine nucleus is then hydrolyzed into its active part (hydroxymethyl derivative), which is then targeted to *C. auris* infection. In addition, clinical trials with taurolidine have been conducted to prevent infections in catheters [44]. The mechanism of taurolidine anti-adherence activity is not known.

Table 2 Patents for diagnostic and detection of *Candida auris*

	Applicant Number/ Reference	Country	Year	Indication	Application	Method/Primers
1	WO2020114998 (A1) [26]	US	2020	To identify *C. auris*	Real time PCR assay to detect 5.8S/ ITS2 gene in biological and non biological samples	SEQ ID NO 1: CAUROOl forward primer T G AGCGT GAT GT CTT CT C AC SEQ ID NO 2: CAUR003 forward primer GAGCGTGATGTCTTCTCACC SEQ ID NO 3: CAUR005 forward primer ACT G ATTT GG ATTTT A A A ACT A ACCC A A SEQ ID NO 4 CAUR007 forward primer AACT AACCCAACGTTAAGTT CAAC SEQ ID NO 5: CAUR002 reverse primer CCTGATTTGAGGCGACAACAA SEQ ID NO 6: CAUR004 reverse primer CGT CTGC A AGT CAT ACT ACGT A SEQ ID NO 7: CAUR006 reverse primer CGATGATTCACGTCTGCAAGTC SEQ ID NO 8: CAUR008 reverse primer CAACGCCACCGCGAA SEQ ID NO 9: CAUR101HQ6 probe CTTCGCGGTGGCGTTGCATTCACA SEQ ID NO 10: CAUR103HQ6 probe TT CGCGGT GGCGTTGCATT CACA SEQ ID NO 11: CAUR105HQ10 probe ACA ACGG AT CT CTT GGTTCT CGC AT CG ATG SEQ ID NO 12: CAUR107HQ8 probe CTCGCATCGATGAAGAACGCAGCGAAA
2	CN110951905 (A) [27]	China	2020	To identify *C. auris*	LAMP method to Identify *C. auris*	The primer set includes an outer primer, an inner primer and a loop primer, and the outer primer is SEQ ID NO: 1 to SEQ ID. NO: 2, the inner primers are SEQ ID NO: 3 to SEQ ID NO: 4, and the loop primers are SEQ ID NO: 5 to SEQ ID NO: 6 External primer Cau416-F3: 5'-CCATGCTAACCCTGAAACT-3' (SEQ ID NO: 1) Outer primer Cau416-B3: 5'-CGAAGATACCACAACAACC-3' (SEQ ID. NO: 2) Inner primer Cau416-FIP: 5'-GGCCTTGGAGATGACACCATTTTTGTCGCTTTTGGTGCTC-3' SEQ ID NO: 3) 5'-CTCCTGTTGGTTTGGTTAAGGTCAGTTGCGTGCAGACGAAGG-3' (SEQ ID NO: 4) loop primer Cau416-LF1: 5'-GCAAGCTCAGTAGCCTGGT-3' (SEQ ID NO: 5) Loop primer Cau416-LB1-2: 5'-TTCCCATTTGCTCAAGAACACT-3' (SEQ ID NO: 6)
3	CN110408720 (A) [28]	China	2020	To identify *C. auris* and distinguish it from similar species	High-resolution-ratio melting curve	Upstream primer is 5'-CGTAGTATGACTTGCAGACG-3' Downstream primer is 5'-GCGGGTAGTCCTACCTGAT-3'
4	ES2763043 (A1); ES2763043 (B2) [29]	Spain	2020	To detect and/or quantify of *C. auris*	Biosensor	SEQ ID NO: 2 (5'-TTTTGGGGGGTACGCAAGGCGAATCTACCCGGGGGGTTTT-3 ') or the nucleotide sequence SEQ ID NO: 3 (5'-TTTCTGTGTGTC 3' -TTCTGTGTGTC) EQ ID NO: 2 and SEQ ID NO: 3 specifically recognizes the region 892,198 to 892,217 of chromosome 2 of *C. auris* DNA, and the region 1,056,775 to 1,056,787 of chromosome 3 of *C. auris* gene respectively These sequences are specific for *C. auris* and do not exist in other pathogenic organisms guaranteeing the specificity of the biosensor for *C. auris*

Table 2 continued

	Applicant Number/ Reference	Country	Year	Indication	Application	Method/Primers
5	US2020291488 (A1) [30]	US	2020	To detect the presence of a *C. auris* in a biological or environmental sample	T2MR	5′-CTA CCT GAT TTG AGG CGA CAA CAA AAC-3′ (SEQ ID NO: 4) and the second probe includes the oligonucleotide sequence: 5′-CCG CGA AGA TTG GTG AGA AGA CAT-3′ (SEQ ID NO: 5)
6	US10870829 (B2); US2020270567 (A1) [31]	US	2020	To ident and differentiate *C. auris* from another *Candida* spp	Identification of *C. auris* based on the sensitivity to certain compounds	Medium based on the positive selection system: Growth at Quaternary Ammonium Compound at 37-38°C; Medium based on the negative selection system: Growth of *C. auris* based on distinctive sensitive to tert-butyl-hydroperoxide
7	CN110551840 (A) [32]	China	2019	Rapid and accurate screening to detect *C. auris*	Nucleic acid reagent, kit, system, and method for detecting invasive fungi	Code probe sequence: C-au C-au-P ROX-tgtcgttattgttactactgactctgacggttc-BHQ2
8	CN112041441 (A) [33]	China	2020	To detect *C. auris* from a specimen	LAMP method	The primers (FIP, BIP, F3, B3) and loop primers (loop-B, loop-F) are based on the specific bases of *C. auris* suitable for the LAMP method: FIP: AGGCTACTGAGCTTGCTGGTGTAACCAAACCAACAGGAGAGG BIP: ACGGTTTCAGGGTTAGCATGGCTCAACAAAGTCGCTGGTACA F3: GGGAAAGGAACCCTGACCT B3: GGACACAGCATTCGAAGTGT Ring-B: CACATACTCGAACGGAGTC Ring-F: CATCTCGAAGGCCTCGGT
9	CN110804671 (A) [34]	China	2020	To identify *C. auris*	rDNA (ITS) target genes as biomarkers for *C. auris*	Upstream primer *C. auris*: 5'-TGATGTCTTCTCACCMATCTTC-3' Downstream primer *C. auris*: 5'-TGAGGCGACACAAAACG-3' TaqManProbe: 5'FAM-AATCTTCGCGGTGGCGTTGCATTCA-TAMRA 3'
10	JP2021122236A [35]	Japan	2021	To identify *C. auris*	Culture medium that enables a quick and convenient check for the presence of *C. auris*	Screening medium containing an enzyme substrate contains raffinose and xylose

US: United State, Loop-mediated isotherm amplification (LAMP), T2 magnetic resonance T2MR

"WO2018204506 (A1)"[23] refers to cationic steroidal antimicrobials ("CSAs") and their formulations used for the treatment of fungal infections and colonization on medical devices. CSA-131 showed activity against all four clades of *C. auris* with no variation in activity between the clades. The MIC value distribution of CSA-131 ranged from 0.5 to 1 mg/L [45]. Membrane disruption has been identified as a major mechanism of antifungal activity of CSAs [45].

"US2021030852 (A1)" [24] refers to an immunizing method against *C. auris* infection using agglutinin-like sequence-3 (Als3). It was discovered that *C. auris* harbors homologs of *C. albicans* Als cell surface proteins. It was found that *C. albicans* NDV-3A vaccine, harboring the N-terminus of Als3p formulated with alum, generates cross-reactive antibodies against *C. auris* clinical isolates and protects neutropenic mice from hematogenous disseminated *C. auris* infection. In addition, the NDV-3A vaccine also displayed a protective effect in neutropenic mice when combined with micafungin [46]. A recent study demonstrated that the vaccine was predicted to be stable, soluble, antigenic, non-allergic with desirable physicochemical properties. The results showed the candidate vaccine as a promising alternative therapy for the treatment of *C. auris* [46].

"WO2021178774A1" [25] refers to a combination between hydrogen peroxide plus acetic acid to form peroxy acetic acid to disinfect surfaces contaminated by *C. auris.* Appropriate cleaning practices are also key to the management of *C. auris* infection, as commonly utilized disinfectants are not guaranteed to be active against *C. auris.* The Environmental Protection Agency (EPA) has a list of registered, hospital-grade disinfectants with activity against *C. auris,* including hydrogen peroxide/peroxyacetic acid *(S*elected EPA-Registered Disinfectants. Available online: https://www.epa.gov/pesticide-registration/selected-epa-registered-disinfectants#candida-auris (accessed on 30 May 2022). However, higher concentrations of this disinfectant coupled to longer exposure times were required to lower regrowth, but even then, they were not able to completely eradicate the pathogen [47]

New Diagnostic Methods

Misidentification of *C. auris* with other yeasts (e.g., *C. haemulonii, C. famata, C. guilliermondii, C. lusitaniae, C. parapsilosis*) may occur due to the use of standard biochemical methods and commercially available tests [6]. In fact, its correct identification at the species level requires more advanced techniques, such as DNA sequencing MALDI-TOF MS or both. Whether the microorganism has been isolated from sterile and non-sterile body sites, it is observed that asymptomatic colonization represents a risk for *C. auris* transmission [48].

"WO2020114998 (A1)" [26] provides primers and probes to identify *C. auris*. It includes oligonucleotide primers and fluorescent-labeled hydrolysis probes that hybridize to a specific target within the *C. auris* genome. This region can be specifically identified using TaqMan® amplification and detection method. As a result of the analysis, a *C. auris* target was chosen, which was 5.8S/ITS2 rRNA gene (GenBank accession number AB375772). The disclosed methods may include performing at least one cycling step using one or more pairs of primers that includes amplifying one or more portions of the target gene of the nucleic acid molecule from a sample.

"CN110951905 (A)" [27] and "CN112041441 (A)"[33] provides a method for quick and accurate detection of *C. auris*. Both comprises a primer set and a detection kit used to amplify and detect the target sequence of *C. auris* in the test body by the by the loop-mediated isothermal amplification (LAMP) method. LAMP approach was proven to reliably identify all of the tested *C. auris* strains, distinguishing these isolates from other species (even very closely related species) with a 100% specificity. The results were obtained within a short time, without any technical complications related to the use of the amplification instrument [49]. This technique is expected to save the time of the clinicians required for cultivation and DNA extraction, thus allowing an early diagnosis. Portable LAMP amplification equipment has been made commercially available. Overall, this assay should be particularly valuable for *C. auris,* a pathogen that is an important target of environmental control in health care facilities[49].

"CN110408720 (A)" [28] was developed in order to provide a method for the identification of *C. auris*. With the help of a high-resolution melting curve *C. auris* can be identified and distinguished from other similar species. Signature melting profiles were generated for *C. auris*, *C. duobushaemulonii*, *C. haemulonii*, and *C. lusitaniae*, enabling their unambiguous

discrimination. Excellent results were achieved with assays during the development phase, as well as during the proficiency panel validation [50].

"ES2763043 (A1); ES2763043 (B2)"[29] describes a biosensor for the detection of *C. auris* DNA and/or diagnosis of infection caused by *C. auris*. The biosensor is based on a porous material comprising of a reporter molecule and single-stranded DNA oligonucleotides that specifically recognize a particular region of *C. auris* DNA. Thus, when the DNA of *C. auris* is present in the medium, the oligonucleotides recognize the said region, bind to it, and the reporter is released, which is then detected. Recently, the detection of *C. auris* by using a fluorogenic nanosensor has been reported [51]. A nanoporous anodic alumina scaffold is filled with fluorescent indicator rhodamine B and the pores are blocked with different oligonucleotides capable of specifically recognizing *C. auris* genomic DNA. *C. auris* is detected even at low concentrations, thus allowing to obtain a diagnostic result in clinical samples within an hour with no prior DNA extraction or amplification steps [51].

"US2020291488 (A1)" [30] provides a method to determine if *C. auris* is present in a biological or environmental sample. An assay for a rapid detection method based on the culture-independent T2 Magnetic Resonance (T2MR) technology has been used to detect *C. auris* from whole blood and common swab matrices at concentrations < 10 CFU/mL. Testing with clinical samples indicates that this test can be used to identify *C. auris* and other species from patient blood samples without the requirement of blood culture. This rapid and sensitive test enables the detection of *C. auris* in candidemia patients and assists in the screening, isolating, and monitoring of the spread of this emerging multidrug-resistant pathogen. In addition, the T2MR method can be used to detect *C. auris* from clinical skin swab samples [52].

"US10870829 (B2); US2020270567 (A1)" [31] refers to a system to identify *C. auris* which is based on two aspects related to the sensitivity to a different medium. The first is the positive selection of *C. auris* based on its distinctive resistance to quaternary ammonium compounds (especially at elevated incubation temperatures). The second is the negative selection of *C. auris* based on its distinctive sensitivity to tert-Butyl-hydroperoxide. *C. auris* can be identified in a sample by the use of a positive-selection culture medium which fosters *C. auris* colony growth while suppressing the growth of other yeasts. The isolate can be confirmed as *C. auris* by using a negative-selection culture medium that suppresses *C. auris* colony growth while permitting the growth of other yeasts. There is no published study describing this method to date.

"CN110551840 (A)" [32] refers to a nucleic acid reagent, kit, system, and method for the detection of invasive fungi. The nucleic acid reagent comprises specific primers and a specific code probe sequence. At least nine invasive fungi, including *C. auris,* can be detected, resulting in a fast, comprehensive, sensitive, specific, and automatic detection.

"CN110804671 (A)"[34] proposes the use of rDNA genes as biomarkers for *C. auris,* which includes its ITS1-ITS4 nucleotide sequence. It was found that the rDNA genes ITS1-ITS4 of *C. auris* are conserved, and some of the sequences are specific and can be used as ideal primers and templates for the study of nucleic acid-based detection of *C. auris*. Using the rDNA gene (SEQ IDNO:17) sequence as a biological target to establish a real-time fluorescent quantitative PCR detection method for *C. auris* will help in the rapid diagnosis of *C. auris* infections in clinics.

"JP2021122236A" [35] refers to a screening medium containing an enzyme substrate contains raffinose and xylose. *C. auris* nonassimilated carbon sources as xylose and assimilated raffinose as carbon sources[53].

Conclusions and Perspectives

The whole process of discovering and developing new drugs and diagnostic methods are extensive and expensive. Launching a new drug into the pharmaceutical market can take about 13 years and costs around two billion US dollar. Deeper insights into fungal proteomics, genomics, enzymology, key factors for fungal survival and virulence, and molecular mechanism of resistance would definitely aid in development of better drugs and vaccines against these pathogens. The funds, technical and regulatory hassles could be overcome by concerted efforts in this direction. It's highly desirable to concentrate on developing newer reliable and rapid tests to diagnose and monitor fungal infections, especially against emerging fungal pathogens as *C. auris*. The vaccines development is urgent and necessary. In addition,

proper microbiological identification, rigorous epidemiological surveillance, adequate treatment and prevention and containment strategies, combined with higher awareness on the side of physicians, microbiologists and healthcare workers, are indispensable to limit further spreading of this pathogen.

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Declarations

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