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CANDIDA AURIS: MULTIDRUG RESISTANCE AND NEW TREATMENT STRATEGIES

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ABSTRACT

Candida auris is an emerging public health threat fungal pathogen of high virulence and mortality rates throughout the world causing outbreaks in hospitals, hence it has become both an unfathomable and challenging nosocomial infection. The prevalence of this yeast infection is mostly seen in immunocompromised patients admitted to intensive care units in use of antibiotics, immunosuppressive drugs and catheters. As it exhibits an amplified resistance to recurrent antifungal drugs, along with its delayed diagnostic rates due to its similarities to other *Candida* species, in addition to how quickly it spreads, this pathogen takes part in a major concern within healthcare centers. *C. auris*' high virulence is mainly on account of the biofilm formation in medical devices as a consequence of its phenotypic plasticity and ability to adapt to the most challenging and fraught conditions remaining viable in innumerable surfaces for up to two weeks. A better understanding of those aspects is imperative in order to control and provide alternative treatment strategies. In light of this, the aim of this study was to systematically investigate publications related to *C. auris*' relevance, focusing on the epidemiological strains prevalent all over the world, not only as a nosocomial rising infection and its concern in global public health, but also focus on its resistance mechanisms to available antifungal treatment in addition to propose future investigation on new promising treatment strategies.

Keywords: biofilm, candidiasis, nosocomial

INTRODUCTION

Candida auris is an invasive fungal yeast from the *Ascomycota* phylum and also the largest medically important genus first described in 2009 as a single strain isolated from the external ear canal of an elderly 70-year-old Japanese woman admitted to the Metropolitan Geriatric Hospital in Tokyo [1]. Since its first report as a novel species, *C. auris* has frequently been isolated throughout the world in health care centers causing life-threatening infections showing a wide range of resistance to the conventional antifungal therapy treatment. Furthermore, *C. auris* has developed the ability to evade the innate immune system as well as it perseveres on various surfaces of hospital settings [2]. *C. auris* illustrates the first fungal pathogen designed as a global health threat even being denominated as a "superfungus" owing to not only its ease to spread from patient-to-patient, its multidrug resistance and mortality rates, but also the heightened ability to resist disinfection measures including quaternary ammonia compounds which are widely used in hospitals [3]. As a sample of the level of threat this pathogen poses, the Centers for Disease Control and Prevention (CDC) [4] has released along with The United States Environmental Protection Agency (EPA) [16] alternatives in cleaning and disinfecting specifically to *C. auris*.

In spite of being isolated from multiple anatomic sites, this

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yeast is a mighty skin colonizer, which increases its transmission within hospitalized patients. The infection can spread to internal organs via bloodstream causing candidemia resulting in almost 70% mortality rate [5]. In addition to this, *C. auris* can also be detected in hospital surfaces and indwelling medical devices leading to its persistence in hospital settings remaining viable in dry surfaces for up to 4 weeks [6,3]. Besides, identifying and diagnosing this yeast has been put to question due to how easily it´s misidentified with other *Candida* spp. Recently, only matrix-assisted laser desorption ionization-time of flight (MALDI-TOF) mass spectrometry and ribosomal DNA sequencing are able to differentiate it from other yeasts [6].

The prevalence of *C. auris* infection is primarily seen in immunocompromised patients inside intensive care units due to their vulnerability by both the use of catheters and immunosuppressive medication. Also shown as a risk factor is the use of antibiotic therapy by hospitalized patients, as most of the fungal infections are considered as opportunistic. Diabetic and organ transplantation patients are also on the verge of the risk [5]. The considerable challenge of this infection is its multi-drug resistance ability alarmingly being reported as resistant to at least two of the three classes of current antifungal therapy, such as azoles, echinocandins, and polyenes, at an extremely high rate reaching up to 93% [5,7]. As an alternative, echinocandins are now becoming the first choice in treating this infection. Although mutations in the FKS1 gene, responsible for encoding the synthesis of β-1,3 glucan, an important constituent of the fungal cell wall, of some strains of *C. auris* has concerned specialists around the globe since it might confer resistance to echinocandins [5].

Furthermore, *C. auris*' ability to form biofilms on medical surfaces is an imperative factor to its resistance. The studies mention two critical ones. Essentially, in the early stages of the biofilm formation, the matrix itself can, both in length and in complex mannan-glucan constitution, guarantee resistance to the conventional drug therapy, specially reported one, fluconazole [5]. This mechanism is known by efflux pumps. The second factor includes the inability to inhibit ergosterol synthesis, which is an important component of fungal cell membranes, acquired by *C. auris* mutations in the ERG11 gene conferring resistance to azoles [5]. Changes in the membrane level are considered responsible for its resistance to amphotericin [5,3]. Once the *C. auris* infection has been acquired, there are only two proposed courses of action to lessen mortality: identification and control measures associated with an effective antifungal treatment [8]. In light of *C. auris*'s multidrug resistance and risk factors posing a global threat, this review aims to present its resistance mechanisms as well as new treatment strategies to hinder the rise of this emerging pathogen.

MATERIALS AND METHODS

In this study, a systematic review was performed comprising an electronic literature search through the following databases: *Pubmed*, *Google Scholar*, *ScienceDirect*, *Lilacs*, and *Scielo*. It was accomplished by the present authors and limited to articles that had been published up until October 2022. During the search, keywords such as "*Candida auris*", "emerging pathogens", "multi-drug resistant", "nosocomial infections", "biofilm", "therapeutic strategies", and "promising targets" were used. The criteria applied for their usability were based on their applicability to the topic relating epidemiologic data, drug resistance, virulence, overview and promising treatment strategies, comprising articles, dissertations and indexed articles in both Mycology and Microbiology medical databases published in English (Fig.1)

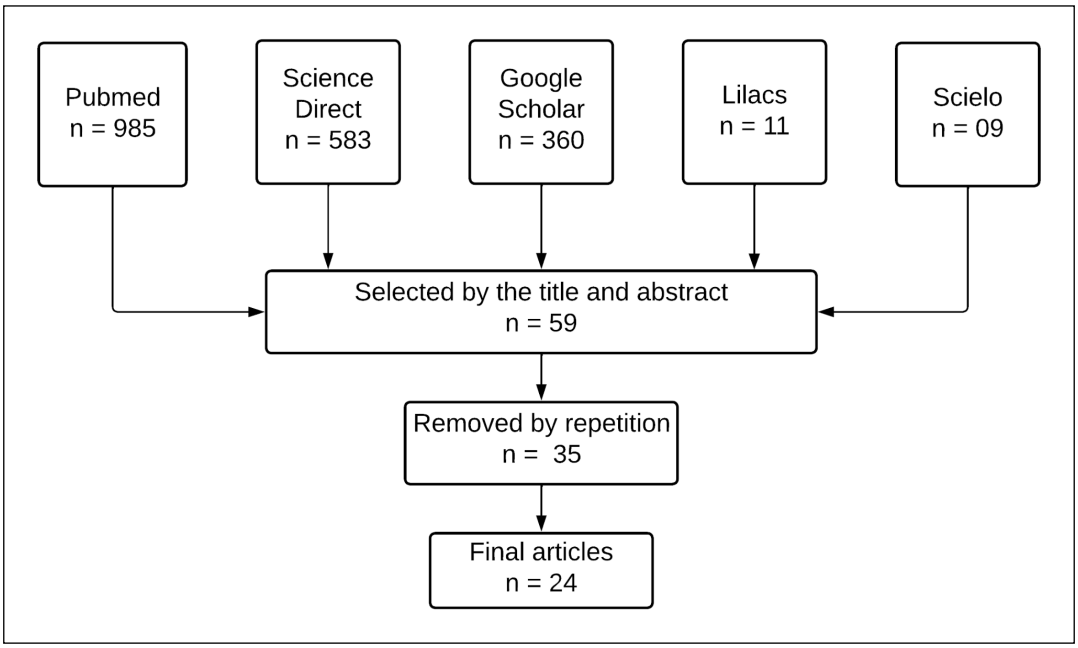

Figure 1: Flowchart outlining the criteria followed in this review.

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In accordance with the bibliographic search, all the results found were sorted out by year of publication and relevance consisted of research articles, reviews of literature, case reports and clinical trials.

RESULTS AND DISCUSSION

In *Pubmed* database 985 results were found by the keyword "*Candida auris*"; 360 results in *Google Scholar*; 583 results in *ScienceDirect*; 11 results in *Lilacs* whereas in *Scielo* only 9 results were found from 2017 to 2021. Within the previous research, 24 articles published between 2020 and 2022 embodied the eligible criteria to convey a recent overview of this pathogen focusing on its resistance mechanisms and promising new treatment strategies.

Epidemiology of C. auris

Candida auris, as a novel species, has become a global hazard on account of being a multidrug resistant yeast causing nosocomial outbreaks in several hospital settings mostly found in hospitalized patients in use of broad-spectrum antibiotic therapy as well as both antifungal therapy and immunosuppressive treatment which has a major impact on its emergence and high virulence. This yeast has been firstly identified in 2009 from the external ear canal of an elderly 70-year-old Japanese woman admitted to the Metropolitan Geriatric Hospital in Tokyo [1]; yet retrospective isolates had been reported dating back to 1996 from candidemia isolates in Korea [9,10]. Therefore, this novel species had been named as *Candida auris* due to *auris* being Latin for ear. Since then, more than 40 countries have reported the multiresistant *C. auris*' isolates. According to the phylogenetics analysis of the isolates found and reported all over the continents, four different clades of *C. auris* have been identified based on the geographic zones in which it had been previously collected [6]. For that reason, clade I originated from South Asia; clade II from East Asia; clade III from South Africa and clade IV from South America [6]. A fifth clade appeared as potential, however it was included in 2019 by Chow et al. [11], ergo, clade V reported from Iran [12].

The origin of this microorganism hasn´t been completely understood although a few theories were speculated. One of them includes the participation of the global warming phenomena in the selection of this novel species [5,13]. Casadevall et al. [14] posed the hypothesis that *C. auris* is the first example of an emerging pathogen provenient from global warming. They suggest that *C. auris*' inability to grow anaerobically is a strong indication that it was in fact an environmental fungus before becoming pathogenic to humans. They also state that *C. auris* existed as a saprophytic fungus on wetlands ecosystems leading to the acquisition of both salinity and thermal tolerance on account of climate changes. Thermotolerant *C. auris* might have been transported to the cities by migrating birds reaching rural areas and therefore having interspecies transmission that were led to health care facilities by human urban migration. Chakrabarti et al. [6] suggests that other reasons for the emergence of *C. auris* might have been the lack of specific phenotypic methods of diagnosis which could have missed its identification. In addition, it was stated in this study that the selection caused by the extensive use of agricultural fungicides might be a cause for *C. auris*' emergence. Nearly 13 years have passed since its first identification and multiple cases have been reported over all the continents with great prevalence. The CDC has classified *C. auris* as an emerging global threat able to cause invasive infection and death [4]. After 2009, cases emerged in South Africa and India and right after that in Kenya and China, 2010 to 2011 [6]. In 2013 cases emerged in Venezuela and Colombia and soon reached Europe [6]. In the UK, outbreaks were reported between 2015 and 2017 [6]. By then, CDC had started tracking the reports worldwide and soon reported large outbreaks in New York, New Jersey and Chicago from 2013 to 2017 [6,4]. In 2020, it reached Mexico [6] and Brazil's first outbreak [15]. The Brazilian Health Regulatory Agency (ANVISA) released an emergency risk alert reporting its first outbreak in 2020 originated from an ICU catheter isolate in Bahia, a northeastern Brazilian state [15]. 15 cases had been reported, culminating in 2 deaths [15]. In 2021, a second outbreak was also reported in Bahia and a third one was confirmed in the beginning of 2022 in Pernambuco, northeast Brazil [15]. It has also spread through the Middle East, North Africa and South Asia and over 49 countries have already filed reports on outbreaks [6,13]. Nowadays, although being tracked by regulatory agencies worldwide, cases have risen in such proportion that are no longer being updated [4] (Fig.2). In the following map, the prevalence of *C. auris* is shown portraying how widespread it has become. The CDC released a note informing that the last updates made on the map were up until February 15th of 2021 due to the large number of cases that became difficult to keep track of [4].

C. auris virulence and pathogenicity

The genus *Candida* includes over 200 species being those of the most significant medical importance. Usually, *Candida* spp. are commensal colonizers with prevalence in the gastrointestinal tract and mucosal surfaces [5]. Nonetheless, *C. auris* has tropism for the skin allowing the spread from person-to-person contact extremely difficult to control which elucidates the urgent sanitary control measures within nosocomial facilities [13]. The *C. auris* infection can originate from various clinical sites such as skin, nares, wounds, central vascular and urinary catheters, parenteral nutrition; those posing as the most common risk factors. Besides, being admitted for a prolonged time, having associated comorbidities such as diabetes, kidney, respiratory or neurological diseases, also undergoing prior antibiotic and antifungal therapy, having an organ transplant and being immunocompromised are also specific risk factors among *C. auris* infections [3,13]. As catheters play an important factor in hospitalized patients, their use is mostly the main source for many *C. auris* infections, especially responsible for the candidemia in which *C. auris* reaches the patients' bloodstream. The ability of *C. auris* in forming biofilm on catheter surface makes it easily disseminated into the bloodstream and poses a high virulence challenge as an invading pathogen [3].

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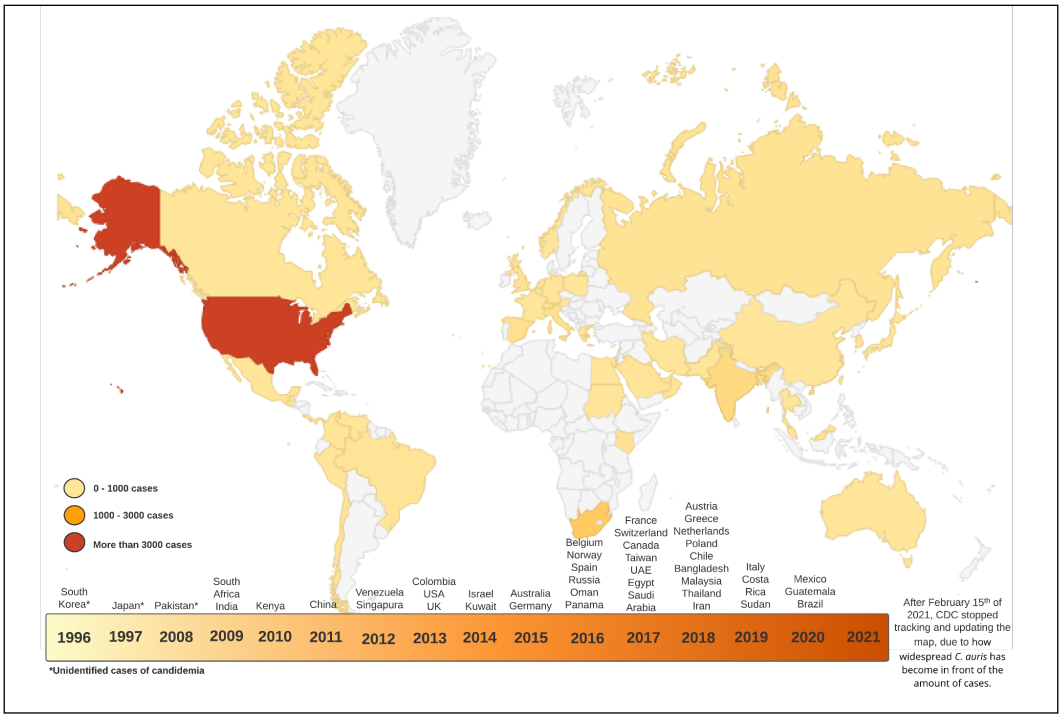

Figure 2: *C. auris* global reported prevalence. Adapted from CDC/Tracking *Candida auris* and Chakrabarti et al. [4,5]

Once it reaches the bloodstream *C. auris* can diffuse to internal organs.

The skin serves as a physical barrier whereas the innate immune system comprising macrophages, neutrophils and monocytes play part in the host defense mechanism. Due to *C. auris* shape shifting across the host cells and its adaptability to stressful conditions, along with the changes present in the host microbiota, by antibiotic therapy or use of immunosuppressive drugs as an example, allows this yeast to colonize and acquire nutrients becoming a nosocomial threat [5]. Its ability to evade the host innate immune system is seen by the inactivation of neutrophil extracellular traps [13]. Health care personnel can also be carriers of *C. auris*, therefore the use of medical equipment and indwelling devices must undergo appropriate disinfection, adequate and frequent hand disinfection as well as quarantine for colonized patients and frequent screening of those who may have been in direct contact with *C. auris* infection [5]. Since disinfection is also challenging, new strategies regarding the control and management of it are being tested and evaluated, such as pulsed-xenon ultraviolet light. Maslo et al. [21] suggests 99.6% reduction on *C. auris* after using a 10 minute cycle within 2 meter range. Associating concentrated solutions of chlorine and vapor hydrogen peroxide along with antimicrobial photodynamic therapy have been reported as strategies to assess proper disinfection as shown by Bandara et al.[22].

C. auris grows as yeast cells constituting both spherical or oval shape. It has the ability to survive in the most inhospitable environment, such as high salinity concentrations and high temperature (42°C) in comparison with other *Candida* spp; can also persist in hospital surfaces in numerous conditions such as dry, wet, nonporous, plastic and metallic ones up to 4 weeks [13]; and it is resistant to quaternary ammonia compounds, commonly used disinfectant agent in hospitals [3]. Those survival adaptations pose an urgent threat in dealing with outbreaks in medical settings. The CDC has released along with The United States EPA [16] alternatives in cleaning and disinfecting specifically to *C. auris* : List P Antimicrobial Products Registered with EPA for Claims Against *Candida auris* [16,5,18,17]. Additionally, *C. auris* shows a remarkable adaptability response in which its phenotypic plasticity allows this yeast to present itself in three different switching systems: this shape shifter yeast can swift from typical yeast, filamentation competent yeast and also filamentous yeast form adapting to stressful environmental changes such as damaged DNA, high sodium concentrations and genotoxicity stress [18]. According to Bravo Ruiz et al. [18], these changes in the *C. auris*' cellular structure appear as a response to its interaction to the host immune cells as well as with organ cells and antifungal drugs. Therefore, it is reasonable to assess that once the infection is installed, it can last months inside the patients. Horton et al. [3] confirms that many patients remained colonized for close to 200 days, making it harder to control.

C. auris main virulence factor is the biofilm formation which allows this yeast to spread by replicating on skin and consequently entering the bloodstream causing candidemia. *C. auris'* biofilm is frequently found in indwelling devices such as catheters, cardiac-implanted devices, dentures and other prostheses [3]. Moreover, the *C. auris'* ability to form biofilms may partake in its multidrug resistance. In fact, the composition of its biofilm comprising of high

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density, a complex mannan-glucan extracellular matrix, protein markers and its own gene expression adapting to inhospitable conditions make this yeast´s biofilm even more daring than its planktonic form [23]. Biofilm also guarantees molecular integrity protecting it from outside stressors by blocking their action [6]. On human skin, on account of its thriving growth conditions, *C. auris* rapidly forms biofilms in sites like axillas, groins and adheres to medical devices like catheters and endotracheal tubes gaining fast access to the host's bloodstream [6]. The significant challenge of this infection is its multi-drug resistance ability being reported as resistant to at least two of the three classes of current antifungal therapy depending on its geographical origin strain [5,13]. This ability according to Chow et al. [11] is due to its gene expression taking an important role in its adaptive abilities in face of the host's. The most important ones being the iron assimilation, oxidative stress, both cell wall and membrane integrity and oligopeptide transporters [11,13].

Another challenge concerning this emergent pathogen is its identification and diagnosis due to its similarity with other *Candida* spp. This delay in identifying the proper strains increases transmission and the risk of another outbreak cannot be discarded. Preventing and controlling methods are imperative to avoid and contain outbreaks. Nowadays, the standard diagnostic tests able to differentiate *C. auris* from other yeasts are MALDI-TOF mass spectrometry and ribosomal DNA sequencing [6]. The necessity in updated databases and new DNA sequencing makes diagnosing *C. auris* still a challenge. A study performed by Huang et al. [19] aiming to increase diagnostic capacity showed the skin microbiome analysis collected previously from surveillance swabs from colonized patients. They were able to detect *C. auris* more frequently than those detected in culturing suggesting accuracy and potential sensitivity in opposition to culture-base tests [19,20].

Multidrug resistance

When facing a fungal infection there are three main classes of antifungal drugs available for clinical and therapeutic treatment: the azoles, polyenes and echinocandins. *C. auris* engages in four basic mechanisms of multidrug resistance: drug target mutations; drug intake or efflux, target overexpression and biofilm formation [10,6].

Azoles

The azoles action mechanism is to inhibit an enzyme lanosterol 14-α-demethylase required to synthesize ergosterol, an imperative constituent of the fungal cell membrane [10,6]. This specific enzyme is encoded by the ERG11 gene; mutations in this gene are accountable for azoles resistance [10]. Azole-resistant *C. auris* strains often carry mutations in ERG11 gene and are also related to its geographic clade [10,6]. According to Chakrabarti et al [6], those resistant strains when exposed to Fluconazole overexpress the ERG11 gene increasing its resistance. Besides, the overexpression of drug efflux pumps, in which decreases the antifungal drug concentration within the fungal wall, partakes great influence in the resistance to azoles, as an example, the CDR1 gene as a dominant azole efflux pump [10,3,13]. On the other hand, Casadevall et al. [14] states that *C. auris* overexpresses HSP 90, a molecular chaperone, which may account for its multidrug resistance, virulence, thermal tolerance, and osmotic-stress tolerance.

Polyenes

The polyenes attach to the ergosterol present in the fungal cell membrane forming pores which allows all internal content to be leaked to the exterior and therefore cause cell death [10,6]. However, *C. auris* amphotericin-resistant strains somehow were able to alter their sterol constitution of cell membrane on account of a point mutation in the FLO8 gene conferring resistance to amphotericin by forcing it out of the fungal cell even though this mechanism being not fully comprehended [10,6].

Echinocandins

This antifungal class takes action by inhibiting the β-1,3 glucan synthase, an important step in the formation of β-glucan, responsible for the fungal cell wall integrity. As an alternative, echinocandins are now becoming the first choice in treating *C. auris* infection before antifungal sensitivity testing due to how frequent the azoles resistance have become. Caspofungin has the best result regarding the amount of drug needed to inhibit the growth of *C. auris* [5]. Although mutations in any of the two existing hotspot regions in the FKS1 gene, responsible for encoding the synthesis of β-1,3 glucan of some strains of *C. auris,* have concerned specialists around the globe since it might also confer resistance to echinocandins [10,6].

Biofilm formation

C. auris' ability to form biofilms, especially on medical surfaces, is an imperative pathogenic factor related to its multidrug resistance. Essentially, in the early stages of the biofilm formation, the matrix itself can, both in length and in complex mannan-glucan constitution, guarantee resistance to the conventional drug therapy by decreasing the drug penetration among its layers working as a defense mechanism, known by efflux pumps [5,3]. The second factor includes the inability to inhibit ergosterol synthesis, which is an important component of fungal cell membranes, acquired by *C. auris* mutations in the ERG11 gene conferring resistance to azoles. Changes in the membrane level are considered responsible for its resistance to amphotericin. FSK1 gene mutations are enabling resistance to echinocandins as well. In addition, biofilms adherence allows *C. auris* to persist in numerous surfaces and also decrease the neutrophilic activity of the host [10,6].

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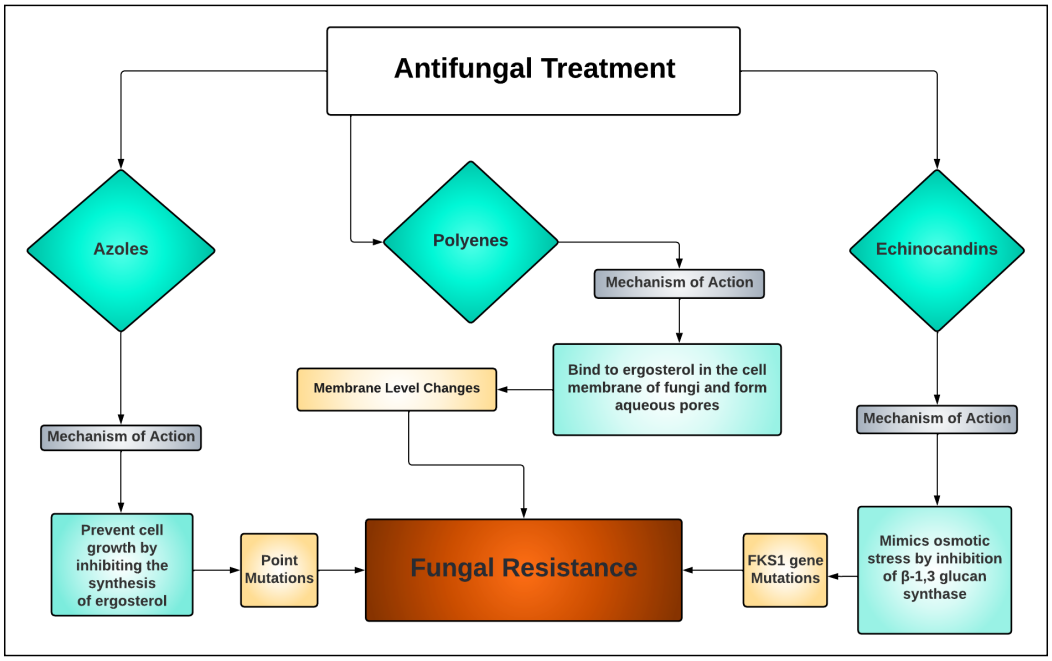

Figure 3: Available antifungal treatment and *Candida auris* resistance mechanism.

New Treatment Strategies

Ever since *C. auris* had been identified back in 2009 and its relevance as an emerging threat was consolidated worldwide, the necessity in developing new treatment strategies has become not only urgent but posed an unfathomable challenge to public health. It is fundamental to generate new diagnostic and treatment strategies to deal with such a virulent pathogen. A considerable amount of studies are being done with the sole purpose of finding alternatives to the scarce therapeutic options available. In this systematic review, we were able to sort out by authors and mechanism of action new promising approaches against *C. auris* as shown in the following table.

Table 1: New treatment strategies against *Candida auris* based on published studies up until October 2022.

Author	New Treatment Strategies	Pharmacological Class/ Classification	Mechanism of Action	Microbial Result	Ref.
Abdul Jalil et al. (2022)	Toyocamycin	Adenosine analogue	XBP1 inhibitor	Biofilm-inhibiting Effect	[24]
	Darapladib	Substituted pyrimidone	Inhibitor of Lipoprotein-associated Phospholipase A2 (lp-PLA2)		
de Oliveira et al. (2022)	Compound MMV1593537	Non-toxic fungicidal molecule	Affects cellular division	Control the growth of *C. auris*	[25]
Orofino et al. (2020)	Compound BM1	Macrocyclic antifungal Compound	Active against strains overexpressing Cdr1 and Cdr2 efflux pumps (azole-resistant Candida strains)	Overexpression efflux pumps	[26]

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Azie et al.(2021) Siebert et al. (2022)	Ibrexafungerp (SCY-078)	First-generation antifungal compound	Broad-spectrum fungicidal β-1,3-glucan synthase inhibitor	- Abnormalities in cell division (fused cells) - Thickening of the cell wall with disappearance of the cell membrane - Leakage of cytoplasmic matrix - Destruction of cytoplasmic organelles	[27] [28]
Chu et al.(2021)	SCY-247	Second-generation antifungal compound	Interferes with the synthesis of β-1,3-d-glucan	Potent antifungal activity even in low pH levels (Synthetic urine)	[29]
Hager et al. (2018) Arendrup et al. (2020)	Manogepix (APX001A)	Active moiety of the novel drug candidate fosmanogepix (APX001)	Inhibitor of glycosylphosphati-dylinositol (GPI) biosynthesis	Compromises: - Cell wall integrity biofilm formation - Germ tube formation - Produces severe fungal growth defects	[30] [31]
Wiederhold et al.(2020)	T-2307 Arylamidine	Investigational arylamidine	Selectively disrupts yeast mitochondrial function	Collapse of fungal mitochondrial membrane potential - Affects growth	[32]
Liu et al. (2022)	17-AAG (17-allylamino-17-demethoxy-geldamycin)	Synthetic variant of geldanamycin	Competitively bind to ATP/ADP binding sites on Hsp90	Reduce fungal resistance	[33]
Sun et al. (2017)	NSC319726	Thiosemicarbazone zinc chelator	Inhibitory effect on fungal ribosome biogenesis and the induction of oxidative stress.	Growth inhibition and fungicidal effect	[34]
Nagy et al. (2020)	Farnesol	Fungal quorum-sensing molecule	- Inhibits the transition of yeast to hyphae - Modulate drug efflux and the development of biofilms - Increases oxidative stress	Reduced the growth rate of *C. auris*	[35]
Barreto et al. (2020)	Miltefosine	Alkylphosphocholine drug	Detergent properties and ability to induce apoptosis	Inhibiting the biofilm formation and damaging preformed biofilms of *C. auris*	[36]
Gowri et al. (2020)	Sertraline	Selective serotonin reuptake inhibitor (Antidepressant)	Binds to sterol 14 ∂ demethylase	Inhibited *C. auris* yeast to hyphae conversion and further the inhibition of biofilm formation (71%)	[37]

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Simm et al. (2022)	Pyrvinium Pamoate	Antiparasitic drug	Disruption of iron homeostasis	Inhibitor of the Pathogen's membrane flexibility through metabolic reprogramming and mitochondrial dysfunction	[7]
Bugli et al. (2022)	Myr-B	Lipopeptides	- Cell wall perturbation - Inhibition of cell adhesion onto surfaces - Interaction with other targets inside fungal cells	Antibiofilm activity	[38]
Rather et al. (2022)	cathelicidin LL-37	Antimicrobial peptide	- Disruption of the yeast cell membrane through efflux of ATP and proteins -Interaction with cell wall components - Inhibition of the cell cycle	Inhibits DNA synthesis in yeast cells	[39]
Kovács et al. (2021)	NFAP2	cationic antifungal proteins	pore-forming effect in the cell membrane	Growth inhibition	[40]
Cleare et al. (2020)	NO nanoparticles	Nanoparticles	Disruption of fungal growth and morphogenesis	Eradicates planktonic *C. auris* growth and significantly reduces and disrupts biofilm growth	[41]
AlJindan et al. (2022)	AgNPs	Nanoparticles	Disruption of the cell membrane integrity, permeabilizing the cell wall/membrane and inducing apoptotic cell death	Inhibition of over 80% of Biofilm Formation	[2]
Kamli et al. (2021)	Ag - Fe NPs	Bimetallic nanoparticles	Modulation of crucial antioxidant enzymes	Generates oxidative stress and the arrest of the cell cycle in the G2/M phase, leading to programmed cell death	[42]
Fernandes et al. (2022)	EOs (cajeput, niaouli, tea tree and white thyme) + antifungals	Essential Oils	Not Applicable	Inhibition of the planktonic growth and completely inhibit *C. auris* biofilm formation	[43]
Zhang et al. (2020)	Turbinmicin	Type II polyketides	Targets Sec14 of the vesicular trafficking pathway	Reduced antifungal activity	[44]
Paniagua et al. (2021)	Lactobacillus *Casei shirota*	Living Organism	Production of lactic acid	- Growth inhibition - Some effect on the formation of early biofilm structures	[45]

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Kubiczek et al. (2020)	BSA/THPC hydrogel	Two-layer medical composite hydrogel	Selective cell capturing within the affinity layer of the gel followed by subsequent AMP-dependent inactivation within the therapeutic Fmoc-Met-OH gel layer	Reduces the loading of the pathogen *C. auris*	[46]
de Groot et al. (2021)	L-Mesitran Soft	Medical-grade honey	Multiple mechanisms such as: - Osmotic activity - ↓ pH - Formation of hydrogen peroxide Besides the presence of various phytochemicals and bee-added peptides	Reduced the growth	[47]

As shown previously, many new treatment strategies have been developed in order to suppress the urgent demand posed by this emergent pathogen. The following topics convey a few promising therapeutic strategies.

Antifungal activity

Ibrexafungerp

Formerly known as SCY-078, this novel antifungal was developed by ScyNexis, Inc. functioning as a triterpenoid glucan synthase inhibitor. Its development was fundamentally based on multidrug resistant species such as *Candida auris.* In phase 3 of clinical trials, this broad-spectrum antifungal agent shows fungicidal properties as well as activity against echinocandin resistant strains which possess the FKS1 mutations [48]. Besides, it has high tissue and organ penetration ergo being tested for invasive life-threatening candidemia regarding *C. auris* [27]. According to Azie et al. [27] in a Scynexis study, Ibrexafungerp was able to thicken the *C. auris*' cell wall allowing the leakage of all its internal content and causing its destruction. A second generation, a fungerp antifungal agent known as SCY-247 is being tested *in vitro* showing promising fungicidal results against several *C. auris*' strains [29].

APX001A

Hager et al. [30] tested various resistant *C. auris* strains both *in vitro* and *in vivo* with this prodrug form and assessed that it targets a fungal enzyme GWT1 crucial for the synthesis of fungal cell wall proteins and therefore it was able to damage cell wall integrity and then compromise the biofilm formation. Furthermore, the minimum concentration necessary to inhibit 90% of cell growth in this prodrug was relatively considered less then those in ibrexafungerp. Poses a promising strategy in fighting *C. auris* [13].

Agents with biofilm inhibition

Farnesol

Nagy et al. [35] showed *in vitro* and i*n vivo* results against *C. auris*' isolates significantly reducing the planktonic growth of it by causing disturbance in the membrane flexibility and integrity. As a fungal quorum-sensing molecule, it was also able to regulate the efflux pumps at the membrane level in the early stages of biofilm development acting on cell adherence and downregulation of the ERG11 gene. Therefore, by creating oxidative stress and weakening the biofilm formation in its early stages, combined therapy with triazoles may now reverse the inhibition of ergosterol synthesis and ergo remain effective [13].

Silver Nanoparticles (AgNP)

Nanoparticles have been studied with great results on antifungal activity and induced apoptosis in fungal cells [13]. AlJidan et al. [2] investigated the effect of silver nanoparticles on *C. auris* isolates working both as an antifungal and antibiofilm agent. According to the study, as *C. auris* is able to withstand high temperatures and inhospitable conditions, it also protects itself by forming a very well organized and structured biofilm. Antibiofilm activity is fundamental to control biofilm formation and colonization in patients. Therefore, the study evaluated the effects of AgNP in concentrations from 2,3 to 0,017 ppm were able to inhibit 80% of biofilm formation as dressings containing AgNP. Higher concentration inhibited more than 80% of biofilm formation thus further studies to debate on its toxicity are still ongoing. This exceptional study concludes that nanoparticles are becoming a new front facing nosocomial infections in order to prevent outbreaks within medical facilities.

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Antimicrobial peptides

NFAP2 Neosartorya fischeri antifungal protein 2

Kovács et al. [40] presented a novel member of small cysteine-rich and cationic antifungal protein from filamentous ascomycetes with potential approach on *Candida* biofilms. This ability was possible due to the combination with conventional antifungal therapy through synergy. Expressing a pore-forming effect, NFAP2 enhances and allows the action of conventional therapy drugs.

Repurposing drugs

Pyrvinium Pamoate

Simm et al. [7] established that by triggering metabolic dysfunction through the use of pyrvinium pamoate it represses fungal proliferation and enhances drug susceptibility. The study shows that fungal pathogens need metabolic adaptability due to the lack of macro and micronutrients from the host. As a defense mechanism from the macrophages called nutritional immunity, the host is able to sequester iron in order to reduce its availability to the fungal pathogens impeding its replication [7]. This adaptability triggered by encoded genes has been allowing access to the host's iron via siderophores transporters. The aim of the research was to induce metabolic stress using the antiparasitic drug pyrvinium pamoate due to its antifungal activity. This drug promotes multifaceted metabolic repression blocking the ability of the fungal pathogen to gain access to the micro and macronutrients. Pyrvinium pamoate disrupts iron homeostasis in *C. auris* therefore inhibiting its growth in a fungistatic manner, the study concluded. By allowing nutritional deprivation on *C. auris,* the synergism with antifungal conventional therapy enhances action against this emergent yeast, except fluconazole [7].

Miltefosine

Barreto et al. [36] shows this antiparasitic drug as a repurposed agent against both planktonic and biofilm formation of *C. auris* due to its significant antifungal activity and the ability to induce apoptosis in fungal cells. It has also been used to treat leishmaniasis and cutaneous metastases in breast cancer [23]. On the other hand, miltefosine's toxicity and side effects are reported as serious and drug encapsulation nanocarriers were developed to prevent its toxicity [23,49].

CONCLUSIONS

Candida auris infection has become a global emerging threat due to its multidrug resistance ability and easiness to spread throughout healthcare facilities around the world. Additionally, it can be not only extremely persistent on hospital surfaces such as bed rails, thermometers, windows and medication poles but also resistant to regularly used disinfectant agents, including quaternary ammonia compounds. Currently, it represents a treatment challenge in which advanced strategies are unavoidable and required in order to prevent another outbreak. Further research is needed focusing on biofilm formation and pathways to outwit this emergent pathogen as well as safer and efficient control measures curtailing the mortality rates.

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