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Candida auris: a bibliometric analysis of the first ten years of research (2009–2018)

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ABSTRACT

Candida auris (*C. auris*) is an emerging multidrug resistant fungus considered as the cause of several nosocomial infections of bad prognosis. This study presents a bibliometric analysis of global scientific research on *C. auris* since it was isolated first in 2009. A systematic search was conducted in Scopus databases in the period of 2009–2018 and a total of 227 indexed documents were retrieved. A sharp increase in the number of studies related to drug and multidrug resistance of *C. auris* during 2016–2018 was observed, coinciding with an increase in the number of first-case and outbreak reports worldwide. The leading countries based on the number of publications were United States, India, and the United Kingdom. Nevertheless, Netherlands ranked first when (i) ratio between the number of citations and number of publications, (ii) ratio between the number of publications and gross domestic product (GDP), and (iii) ratio between the number of citations and GDP were used as indicators of productivity. Despite the recent emergence of the topic since the first-case report in 2009, recent research efforts have allowed identifying Ibrexafungerp (SCY-078) and Rezafungin (CD101) as possible candidates for facing the actual antifungal resistance of *C. auris*.

INTRODUCTION

Candida auris (*C. auris*) is an emerging multidrug resistant yeast species attributed as the cause of nosocomial invasive infections. The first clinical case of candidiasis caused by *C. auris* was reported in Japan in 2009 from a patient's external ear canal, and hence its name (*auris*, from latin: ear) (Satoh *et al*., 2009). Since this is the first report, the number of cases and outbreaks referring infection with *C. auris* have been increasing from year to year arising the alerts of national health institutions in several countries due to its bad prognosis, high mortality rate, and rapid spread, even under aseptic conditions in the healthcare settings. *C. auris* adds to the list of multidrug and antibiotics resistant infections, considered currently as one of the main public health global concerns (Gómez-Ríos and Ramírez-Malule, 2019). It has been widely reported that the invasive candidiasis caused by this yeast is resistant to the main antifungal antibiotics and it is usually incorrectly identified by the commercial biochemical methods available in the healthcare institutions (Forsberg *et al*., 2019; Spivak and Hanson, 2018). Therefore, the epidemiological features as the prevalence and incidence of infections are still difficult due to the lack of consistent information (Cortegiani *et al*., 2018; Snyder and Wright, 2019).

C. auris grows as yeast or pseudohyphae and it is a biofilm-forming strain. The reasons for the inability of *C. auris* to form hyphae are still unknown, although several hyphae-inhibiting metabolites and biofilm-forming metabolites have been identified as some of its secretion products (Semreen *et al*., 2019). The ability of this fungus to form biofilms is of special importance in the context of nosocomial diseases, since the presence of contaminated surfaces in healthcare settings contributes to the extensive transmission of infectious diseases. Pathogens embedded in dry surface biofilms, including *C. auris*, are able to persist on surfaces for weeks, even after rigorous surface decontamination procedures (Ledwoch and Maillard, 2018; Vickery, 2019).

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This pathogen fungus represents a serious global health threat due to its persistence in the healthcare settings and opportunistic ability to cause infection via colonization of skin and bloodstream with high mortality rates (around 60%), especially in hospitalized patients with concomitant conditions (recent surgery, invasive medical devices, or admission to intensive care facilities) or risk factors (early and elderly age, intensive use of antifungal antibiotics, or immunosuppression) (Snyder and Wright, 2019). Despite the issues in its identification, e.g., by using traditional phenotypic and molecular techniques, the number of first-case and outbreak reports is increasing, revealing the virulence of the organism; which it has been already detected in five continents in more than single-case patients (Jeffery-Smith *et al*., 2018; Kathuria *et al*., 2015; Snyder and Wright, 2019). Besides, one also can consider that better detection methods might actually the reason why more outbreaks are described. In this regard, confirmed outbreaks have been reported in Europa, America, and Asia (Calvo *et al*., 2016; Sana *et al*., 2019; Schelenz *et al*., 2016), multiple cases in 23 countries and single cases in at least 11 countries. Nevertheless, an undetermined number of cases might be misidentified as the phylogenetic related species *Candida haemulonii (C. haemulonii)* or other, hence retrospectively the number of cases and countries with emergent outbreaks of *C. auris* could be considerably higher (Cortegiani *et al*., 2018; Govender *et al*., 2018). *C. auris* has been not detected out from healthcare environments and the mechanisms explaining the rapid spread of this pathogen are not completely understood; moreover, omics techniques allowed to determine the simultaneous emergence of independent clonal populations on different areas (Cortegiani *et al*., 2018; Lockhart *et al*., 2017).

In addition to its difficult detection, treatment options are reduced due to its resistance to azole, polyenes, and echinocandins antifungal antibiotics, allowing it to cause widespread spectrum infections, and even death (Chowdhary *et al*., 2014; Khillan *et al*., 2014). Furthermore, *C. auris* exhibits resistance to some common disinfection agents such as the quaternary compounds and it is able to survive on dry and moist surfaces up to two weeks, showing a notable persistence in the healthcare environments after disinfection (Cortegiani *et al*., 2018; Ledwoch and Maillard, 2018; Spivak and Hanson, 2018; Vickery, 2019). Given the increasing interest on this pathogen yeast and the associated public health concerns, several reviews related to *C. auris* have been identified in the recent literature (Jeffery-Smith *et al*., 2018; Ku *et al*., 2018; Navalkele *et al*., 2017; Spivak and Hanson, 2018). However, a bibliometric analysis regarding the characteristics and impact of those studies is still missing. In this regard, bibliometric analysis constitutes a systematic tool for monitoring the research efforts on the field, offering to veterans and new scientists an overview of the scientific panorama concerning this emerging pathogen (Gómez-Ríos and Ramírez-Malule, 2019; Ramirez-Malule, 2018). In this contribution, a bibliometric analysis of the studies on *C. auris* published in the timespan from January 2009 to December 2018 is presented.

METHODS

Data search and collection were performed from Scopus database. In this study, the systematic search strategy included the terms in the title of the article, abstract, and keywords. Additionally, the 'document type' was not constrained. Thus, the resulting search was as follows:

(TITLE-ABS-KEY ("*Candida auris*") for general information search. The search was done on 11 May 2019.

TITLE-ABS-KEY (("*Candida auris*" OR "*C. auris*") AND ("resistance" OR "drug resistance" OR "multidrug resistance")) for specific drug resistance search. The search was done on 16 June 2019.

Timespan: 2009–2018.

The information retrieved from the Scopus database included: (i) citation information, (ii) bibliographical information, (iii) abstract and keywords, (iv) funding details, and (v) other information. The software VOSviewer 1.6.11 was used for visualization and data analysis (van Eck and Waltman, 2010).

RESULTS AND DISCUSSION

Evolution of research on *C. auris* between 2009 and 2018

In the period from January 2009 to December 2018, 227 documents were identified fulfilling the search criteria. Figure 1 shows the evolution of the number of publications per year. Notice that only nine documents were published between 2009 and 2014 and all of them consist in reports of identification and isolation from patients with candidemia in Japan (Satoh *et al*., 2009), Korea (Lee *et al*., 2011; Oh *et al*., 2010), India (Chowdhary *et al*., 2013; 2014; Khillan *et al*., 2014; Sarma *et al*., 2013), and South Africa (Magobo *et al*., 2014). However, a slight increase in the number of publications was observed between 2015 and 2016, but more important is the fact that the first reports of hospital outbreaks in Europe and America were published during these two years. Those outbreaks occurred in United Kingdom and Venezuela in 2015–2016 and 2012–2013, respectively (Calvo *et al*., 2016; Schelenz *et al*., 2016). The first reports of hospital outbreaks of *C. auris* in Europe and America are included in the list of the most cited documents (Table 1) evidencing its relevance in the field.

A sharp increase in indexed documents was observed in 2017 and 2018, probably triggered by the alerts of disease control organisms, better detection protocols in addition to surveillance programs. Additionally, during the last years the number of first-

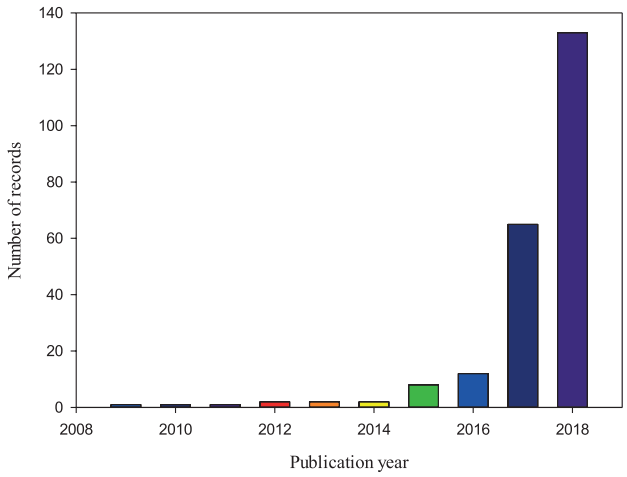

Figure 1. Evolution of number of publications related to *C. auris* between 2009 and 2018.

Table 1. Most cited documents in the global research regarding *C. auris*. Note: the results are based on Scopus reports.

Title	Authors	Year	Journal	Citations
Simultaneous emergence of multidrug-resistant *C. auris* on 3 continents confirmed by whole-genome sequencing and epidemiological analyses (Lockhart *et al*., 2017)	Lockhart SR, Etienne KA, Vallabhaneni S, Farooqi J, Chowdhary A, Govender NP, Colombo AL, Calvo B, Cuomo CA, Desjardins CA, Berkow EL, Castanheira M, Magobo RE, Jabeen K, Asghar RJ, Meis JF, Jackson B, Chiller T, Litvintseva AP	2017	Clinical Infectious Diseases 64(2), pp. 134–40	176
C. auris sp. nov., a novel ascomycetous yeast isolated from the external ear canal of an inpatient in a Japanese hospital (Satoh *et al*., 2009)	Satoh K, Makimura K, Hasumi Y, Nishiyama Y, Uchida K, Yamaguchi H	2009	Microbiology and Immunology 53(1), pp. 41–4	162
First hospital outbreak of the globally emerging *C. auris* in a European hospital (Schelenz *et al*., 2016)	Schelenz S, Hagen F, Rhodes JL, Abdolrasouli A, Chowdhary A, Hall A, Ryan L, Shackleton J, Trimlett R, Meis JF, Armstrong-James D, Fisher MC	2016	Antimicrobial Resistance and Infection Control 5(1), 35	134
Multidrug-resistant *C. auris* misidentified as *Candida haemulonii:* Characterization by matrix-assisted laser desorption ionization-time of flight mass spectrometry and DNA sequencing and its antifungal susceptibility profile variability by vitek 2, CLSI broth microdilution, and etest method (Kathuria *et al*., 2015)	Kathuria S, Singh PK, Sharma C, Prakash A, Masih A, Kumar A, Meis JF, Chowdhary A	2015	Journal of Clinical Microbiology 53(6), pp. 1823–30	132
First report of *C. auris* in America: Clinical and microbiological aspects of 18 episodes of candidemia (Calvo *et al*., 2016)	Calvo B, Melo ASA, Perozo-Mena A, Hernandez M, Francisco EC, Hagen F, Meis JF, Colombo AL	2016	Journal of Infection 73(4), pp. 369–74	116

case, multiple-case, and outbreaks reports increased significantly (Cortegiani *et al*., 2018; Osei Sekyere, 2018; Snyder and Wright, 2019). Interestingly, the notable increase of publications in the field during 2017 and 2018 evidences the accumulation of new knowledge about *C. auris*, which is also demonstrated by the emergence of a considerable number of review publications dealing with the topic in this period (Bidaud *et al*., 2018; Chowdhary *et al*., 2017; Cortegiani *et al*., 2018; de Cássia Orlandi Sardi *et al*., 2018; Forsberg *et al*., 2019; Jeffery-Smith *et al*., 2018; Navalkele *et al*., 2017; Osei Sekyere, 2018; Rossato and Colombo, 2018; Sears and Schwartz, 2017; Spivak and Hanson, 2018).

Table 1 presents the most cited research related to *C. auris* between 2009 and 2018 based on Scopus reports. Interestingly, the contribution with the highest impact in the field was an international collaboration between research centers of United States, Pakistan, India, South Africa, Brazil, Venezuela, and Netherlands (Lockhart *et al*., 2017). In that study, antifungal susceptibility test and Whole Genome Sequencing (WGS) methodologies were used to characterize 56 clinical isolates of *C. auris* from Africa, America, and Asia. The WGS results together with epidemiological observation confirmed the simultaneous emergence of different *C. auris* clonal populations on the three continents of the study (Lockhart *et al*., 2017). The analysis of the 56 isolates demonstrated that 93% of isolates were resistant to fluconazole, 54% to voriconazole, 35% to amphotericin B, and 41% were resistant to ≥ 2 antifungal classes; highlighting the global emergence of this multidrug resistance phenomenon (Lockhart *et al*., 2017).

Table 2 shows the top-5 sponsors funding researches related to the fungus *C. auris*. These sponsors were involved in 21.1% of all publications between 2009 and 2018. In this regard, pharmaceutical companies and disease control organisms clearly lead the sponsorship of research activities in this field.

In addition to sponsors, the knowledge generation activities led by the researchers are crucial to face the health concerns arisen from the emergence of *C. auris* and its multiresistant and invasive characteristics. Table 3 displays the most relevant authors, their affiliation, and the number of publications that were published in the period between 2009 and 2018, based on Scopus reports. Tables 1–3 provide relevant information for further identification of funding sources, networking, and collaboration opportunities with the leading institutions and researchers of this field.

Table 2. Top-5 sponsors funding researches related to *C. auris* between 2009 and 2018.

Rank	Sponsor	Publications
1	Astellas Pharma US/Astellas Pharma Canada (Astellas)/Astellas Pharma Global Development	12
2	National Institutes of Health/National Institute of Allergy and Infectious Diseases	11
3	Gilead Sciences	9
4	Pfizer	9
5	Merck	7

Figure 2 shows the areas of knowledge related to the studies of *C. auris* published between 2009 and 2018. In this regard, (i) *Medicine*, (ii) *Immunology and Microbiology*, and (iii) *Pharmacology, Toxicology and Pharmaceutics* contributed with 60.3%, 14.8%, and 10.9% of the indexed documents, respectively. *Medicine* was ranked first on this list since the most of publications consisted in cases and outbreaks reports, identification, and isolation of populations in hospitals of five continents (Ben-Ami *et al*., 2017; Borman *et al*., 2017; Calvo *et al*., 2016; Chowdhary *et al*., 2013; 2014; Emara *et al*., 2015; Satoh *et al*., 2009). The surveillance program of the Center for Disease Control and Prevention (CDC) updates monthly the new cases in the United States (https://www.cdc.gov/fungal/candida-auris/tracking-c-auris.html). Since its discovery in 2009, 725 cases (up to June 30, 2019) have been confirmed in the United States, most of them in the area of New York–New Jersey.

The leading countries in studies related to *C. auris* were United States, India, and the United Kingdom, which contributed

Table 3. Top-10 leading authors of studies related to *C. auris* between 2009 and 2018. Note: the results are based on Scopus reports.

Rank	Authors	Affiliation	Publications
1	Chowdhary A	Vallabhbhai Patel Chest Institute, New Delhi, India	27
2	Meis JF	Canisius Wihelmina Hospital (CWZ), Nijmegen, Netherlands	22
3	Lockhart SR	Centers for Disease Control and Prevention, Atlanta, United States	19
4	Berkow EL	Centers for Disease Control and Prevention, Atlanta, United States	17
5	Hagen F	Westerdijk Fungal Biodiversity Institute, Utrecht, Netherlands	10
6	Vallabhaneni S	Centers for Disease Control and Prevention, Atlanta, United States	10
7	Jackson BR	Centers for Disease Control and Prevention, Atlanta, United States	9
8	Litvintseva AP	National Center for Emerging and Zoonotic Infectious Diseases, Atlanta, United	9
9	Sharma C	Vallabhbhai Patel Chest Institute, New Delhi, India	9
10	Johnson EM	NHS Blood and Transplant, Bristol, United Kingdom	7

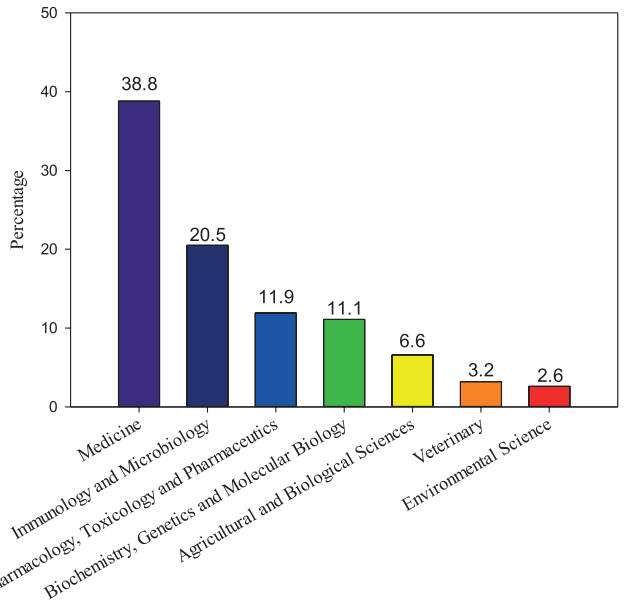

Figure 2. Evolution of number of publications related to *C. auris* between 2009 and 2018.

with 90, 45, and 32 documents, respectively (see Table 4). Those countries had also presented the largest number of detected cases up to date (Osei Sekyere, 2018). In this study, three additional indicators were considered to rank the impact of the research: (i) ratio between the number of citations and number of publications, (ii) ratio between the number of publications and gross domestic product (GDP), and (iii) ratio between the number of citations and GDP. In this regard, a redistribution of the top-10 leading countries was observed. Netherlands ranked first in all scenarios, evidencing the impact of the research performed in this country concerning *C. auris*. India and the United Kingdom were always within the top-5; in contrast, China occupied the last place. These findings are coincident with the information reported in Table 3, i.e., the most productive authors and the countries where their institutions are located. When productivity was stratified by calculating the ratio between either number of publications or number of citations and GDP, Colombia and Denmark were included in top-5. Colombia is the only Latin American country with a reported multicenter hospital-associated outbreak of *C. auris* occurred in 2016 (Armstrong *et al*., 2019; Escandón *et al*., 2018; 2019; Parra-Giraldo *et al*., 2018).

Figures 3 and 4 show the research-topic map of *C. auris* studies between 2009 and 2018. The network visualization contains 26 items grouped in four clusters (Figure 3). In this regard, the biggest node, which corresponds to the keyword with the highest occurrences, was *C. auris* (Figure 3 and Table 5). The first isolates of this fungus from patients were initially misidentified as *C. haemulonii*, and both are within the same cluster (the red one) (Kathuria *et al*., 2015). Here, it is clear the special interest on antifungal resistance and multidrug resistance of *C. auris*. In fact, *C. auris* has been reported to be resistant to fluconazole, amphotericin B, and to a lesser extent, to echinocandins (Lockhart *et al*., 2017). Lockhart *et al*., (2017) reported that 41 isolates from *C. auris* infection patients from Pakistan, India, South Africa, and Venezuela between 2012 and 2015, showed 93%, 35%, and 7% of resistance to fluconazole, amphotericin B, and echinocandins, respectively.

Figure 4 shows how the research topics moved from candidemia/outbreak/fungemia (end of 2016), passing by identification/candida/azoles/echinocandins (beginning of 2017), to infection control/invasive candidiasis/multidrug resistance/antifungal resistance (end of 2017). Future studies should be focused on cheminformatics and molecular applications for the design of either new or modified antifungal antibiotics as therapeutic alternative and control measures for future outbreaks of *C. auris* (Mas *et al*., 2019).

A total of 673 organizations were involved in 227 publications between 2009 and 2018. Seventeen organizations reached the threshold of three published articles but only thirteen of these institutions were interconnected. For a threshold of five published articles, only five of these institutions were interconnected. The collaboration between institutions seems to be highly specialized and centralized, probably due to the low diffusion of the methods and complexity of identification techniques, which can be rarely applied in the moment and place of the outbreaks, especially if those occur in non-developed countries. The incipient and specialized collaboration between organizations suggest that further and stronger alliances are needed to deal with this emerging pathogen by proposing methodologies for successful and fast diagnosis, epidemiologic surveillance, clinical management and pharmacologic alternatives to face the resistance phenomenon associated to *C. auris*.

C. auris: antifungal antibiotics and resistance mechanisms

Figures 5 and 6 help us to visualize the panorama of drug and multidrug resistance of *C. auris*. The number of studies related to drug and multidrug resistance of *C. auris* increased substantially during 2016–2018 (Figure 5). The keywords network analysis

Table 4. Top-10 leading countries of studies related to *C. auris* between 2009 and 2018.

Rank	Country	Publications	Citations	GDP*	Citations/Publications	Publications/GDP	Citations/GDP
1	United States	90	1446	19.4	16.1 (6)	4.6 (8)	74.5 (8)
2	India	45	1566	2.6	34.8 (3)	17.3 (4)	602.3 (2)
3	United Kingdom	32	607	2.6	19.0 (5)	12.3 (5)	233.5 (5)
4	Netherlands	27	1393	0.8	51.6 (1)	33.8 (1)	1741.3 (1)
5	France	14	130	2.6	9.3 (9)	5.4 (7)	50.0 (9)
6	Spain	13	261	1.3	20.1 (4)	10.0 (6)	200.8 (6)
7	Brazil	9	406	2.1	45.1 (2)	4.3 (9)	193.3 (7)
8	Colombia	9	128	0.3	14.2 (8)	30.0 (2)	426.7 (4)
9	Denmark	9	132	0.3	14.7 (7)	30.0 (3)	440.0 (3)
10	China	7	28	12.2	4.0 (10)	0.6 (10)	2.3 (10)

*Gross domestic product (GDP) 2017 in trillions of U.S. dollars. Source: The World Bank (The World Bank, 2018).

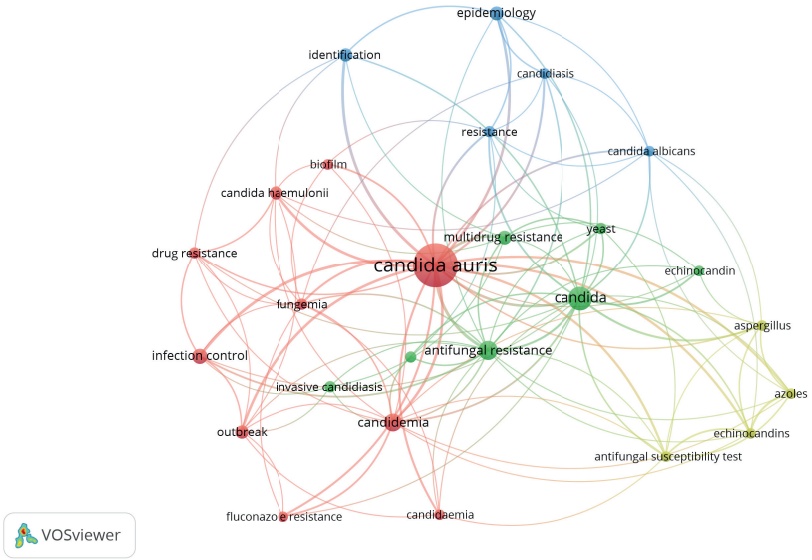

Figure 3. Network visualization of the research-topic map of studies related to *C. auris* between 2009 and 2018. Note: the minimum number of occurrences of a keyword is 5.

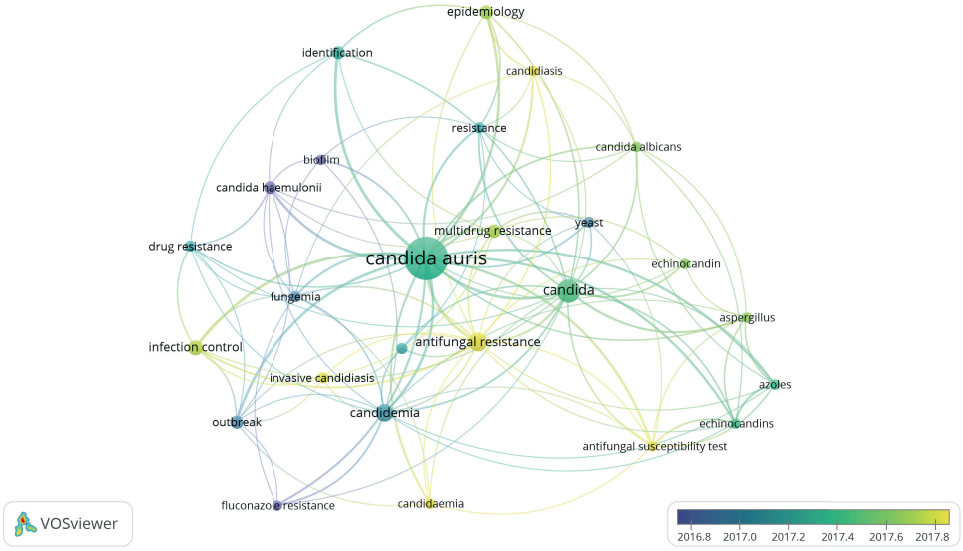

Figure 4. Overlay visualization of the research-topic map of studies related to *C. auris* between 2009 and 2018. Note: the minimum number of occurrences of a keyword is 5.

Table 5. Top-10 keywords of *C. auris* studies in the period of 2009–2018.

Rank	Keywords	Occurrences
1	*Candida auris*/*C. auris*	94
2	Candida	25
3	Antifungal resistance	16
4	Candidemia	14
5	Echinocandins/Echinocandin	10
6	Infection control	10
7	Epidemiology	9
8	Multidrug resistance	9
9	*Candida haemulonii*	8
10	Outbreak	8

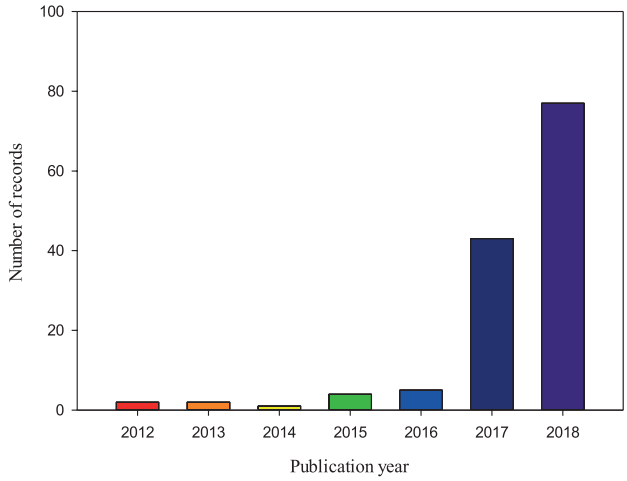

Figure 5. Evolution of number of publication of *C. auris* related to drug and multidrug resistance.

identified "*Candida auris*", "candida", "antifungal resistance", "fluconazole", and "multidrug resistance", as the nodes with more occurrences (Figure 6). Interestingly, around thirteen antifungal compounds used in the sensitivity tests of *C. auris* appears in the network, sharpening the problem of drug resistance.

Table 6 shows, in order of occurrences, the antifungal compounds tested on *C. auris*. These compounds are grouped in the antifungal classes of Azoles, Polyenes, Echinocandins, and Nucleoside analogs. A better knowledge of the mechanisms of antifungal inhibition and drug resistance in *C. auris* is required to propose pharmacological alternatives that help to the emergence of this multiresistant pathogen.

Currently, there is scarce knowledge about the physiology of *C. auris*; however, it shares similarities with other Candida species such as *C. haemulonii*, *C. pseudohaemulonii*, and *C. duobushaemulonii* that also causes bloodstream, invasive, and superficial infections with notable acquired drug resistance (Muñoz *et al*., 2018).

Most of the antifungals used against Candida species acts on components of fungi membrane and cell wall synthesis (Figure 7). Azole antifungals, such as imidazoles (clotrimazole, econazole, miconazole, ketonazole), triazoles (fluconazole, itraconazole, and voriconazole), and posaconazole are inhibitors of the Lanosterol 14-α-sterol demethylase enzyme, an enzyme involved in ergosterol biosynthesis, the main sterol of the fungus membrane (Krishnasamy *et al*., 2018). The disruption of this enzyme usually leads to the accumulation of toxic intermediates such as 14-α-methyl-3,6-diol, reducing the ergosterol content and affecting the membrane integrity. Polyenes such as nystatin, natamycin, and amphotericin B also act on the membrane, by binding to ergosterol and disrupting the fungal cell membrane resulting in pore formation. Echinocandins act on the cell wall of fungi, specifically inhibiting the 1,3-β-D-glucan synthase enzyme

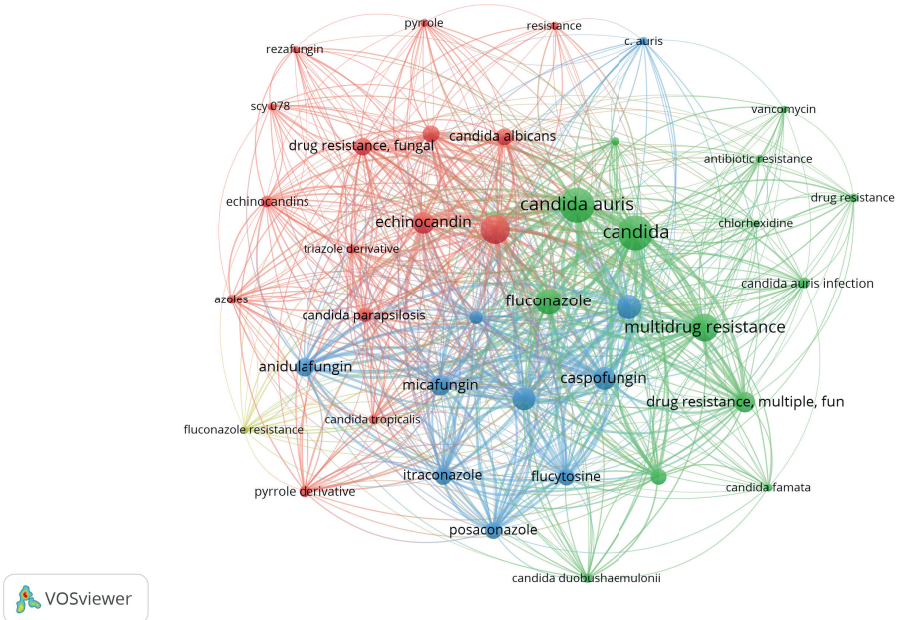

Figure 6. Research-topic map of studies of *C. auris* related to drug and multidrug resistance. Note: the minimum number of occurrences of a keyword is 5.

Table 6. Most studied antifungals in sensitivity tests against *C. auris*.

Drug Name	Antifungal Class	Action mode	Occurrences
Fluconazole	Azoles	Inhibitors of lanosterol 14-α-demethylase	64
Voriconazole			49
Itraconazole			30
Posaconazole			28
Isavuconazole			17
Amphotericin B	Polyenes	Bind to Ergosterol	58
Amphotericin B Lipid Complex			7
Caspofungin	Echinocandins	Inhibitor of (1,3)-β-D-glucan synthase	49
Micafungin			39
Anidulafungin			33
Rezafungin (CD101)		Inhibitor of 1,3-β-glucan synthase	5
Flucytosine	Nucleoside analogs	Inhibitors of DNA/RNA synthesis	27
Ibrexafungerp (SCY-078)	Akin to Echinocandins	Inhibitor of 1,3-β-glucansynthase	5

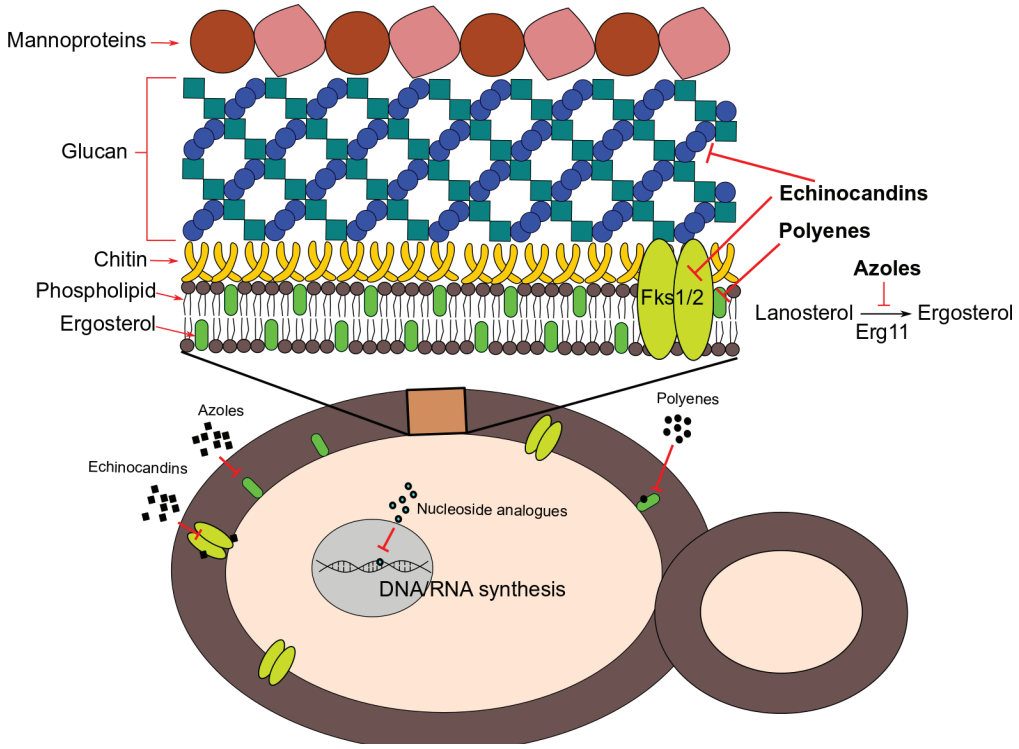

Figure 7. Scheme of action mechanisms of the antifungal classes tested in *C. auris*.

causing malformations on the fungal cell wall. Finally, nucleoside analogs as flucytocine affect replication and transcriptions by the inhibition of DNA and RNA synthesis.

Candida species, including *C. auris*, have developed resistance mechanisms against most of these classes of antifungals (Mas *et al*., 2019). Different Azole resistance mechanisms have been previously described for Candida species (Krishnasamy *et al*., 2018; Mishra *et al*., 2007; Morschhäuser 2002). Candida species can reduce the binding capacity between azoles and the enzyme 4-alpha-sterol demethylase due to alterations of the enzyme by mutations in ergosterol biosynthesis (ERG11) genes (Krishnasamy *et al*., 2018; White *et al*., 2002). In addition, it is known that those fungi can overexpress ERG11 genes in order to synthesize a higher amount of 14-α-sterol demethylase and therefore improving its survival (Krishnasamy *et al*., 2018; White *et al*., 2002). Likewise, the overexpression of efflux pump systems such as ATP-binding cassette (ABC) or major facilitator superfamily proteins diminishes the azole or drug concentration in the membrane of the fungi (Kanafani and Perfect, 2008; Krishnasamy *et al*., 2018).

Three mechanisms of antifungal resistance have been associated with polyenes (Peyron *et al*., 2002). As polyenes have a high affinity for ergosterol, some Candida species have developed resistance mechanisms by inhibiting the ergosterol biosynthesis

and replacing ergosterol by other biosynthetic precursors such as fecosterol, lanosterol, and episterol in the membrane (Peyron *et al*., 2002). Additionally, it has been demonstrated that some Candida species can change the permeability of the membrane to polyenes hence reducing its effect. Finally, resistance to amphotericin B has been associated with mutations in genes involved in ergosterol biosynthesis (ERG2 and ERG3) (Arikan and Rex 2010).

Resistance to echinocandins is known by triggering two resistance mechanisms (Beyda *et al*., 2012; Perlin, 2007). The first resistance mechanisms responsible for decreasing susceptibility to echinocandins are some specific mutations on genes encoding the subunits of 1,3 β-D-glucan synthase enzyme FKS (Glucan synthase genes) (Perlin, 2007). Furthermore, it has been shown that hotspot mutations on FKS1 and FKS2 genes induce the Minimum inhibitory concentration (MIC) in *C. albicans* and *C. glabrata* species (Katiyar *et al*., 2006; Park *et al*., 2005).

Finally, there exist two documented resistance mechanisms for nucleoside analogs like flucytosine (Vermes *et al*., 2000). The first one is the emergence of point mutations on cytosine deaminase gene (FCY1), purine-cytosine permease (FCY2), and uracil phosphoribosyl transferase (FUR1), which prevents transport and uptake of flucytosine. The second mechanism is the overexpression of pyrimidine biosynthesis generating a high demand of this antifungal to get elevated inhibitory effects. It is necessary to highlight that Candida species can grow by forming biofilms, which constitutes an additional diffusional and chemical barrier to all the existent antifungal drugs (Kean *et al*., 2018; Ledwoch and Maillard, 2018; Vickery, 2019).

Our bibliometric analysis showed new efforts to identify compounds with high antifungal activity (Table 6); specifically the inhibitor of glucan biosynthesis SCY-078 and the echinocandin CD101 (Larkin *et al*., 2017a; 2017b). Although those compounds are still in clinical development, they have shown high susceptibility on a panel of sixteen *C. auris* isolates, with MIC_{90} of around 1 mg/L for SCY-078 and an MIC_{50} of 0.125 µg/L for CD101 compound.

FUTURE PERSPECTIVES

C. auris outbreaks are of global concern because of its high rate of patient mortality (Calvo *et al*., 2016; Chowdhary *et al*., 2013). Up to June 30, 2019, CDC reported 725 confirmed and 30 probable clinical cases in twelve U.S. states and 1474 patients have been found to be colonized with *C. auris* in ten states with previously reported clinical cases. Furthermore, the CDC also recorded single and multiple cases of *C. auris* in several countries:

- Single cases of *C. auris*: Austria, Belgium, Chile, Iran, Malaysia, the Netherlands, Norway, Switzerland, Taiwan, and the United Arab Emirates.
- Multiples cases of *C. auris*: Australia, Canada, China, Colombia, France, Germany, India, Israel, Japan, Kenya, Kuwait, Oman, Pakistan, Panama, Russia, Saudi Arabia, Singapore, South Africa, South Korea, Spain, the United Kingdom, the United States, and Venezuela. Note: in some of these countries, the extensive transmission of *C. auris* has been documented in more than one hospital.

These data and our bibliometric analysis suggest that higher investment efforts from government institutions, pharmaceutical companies, universities, and research centers are urgent to design either new or modified drug combinations in addition to new, accurate, and faster identification techniques of *C. auris* aimed to control further outbreaks of candidemia especially in countries with lower income, where the sanitary conditions could enhance the spreading capacity of this pathogen.

CONCLUSION

A total of 227 articles related to *C. auris* between 2009 and 2018 were published with United States, India, and the United Kingdom as the research-leading countries in the field. Nevertheless, Netherlands ranked first when additional indicators were considered: (i) number of citations and (ii) GDP, showing the high impact of the research performed in this country. A significant increase in studies related to drug and multidrug resistance of *C. auris* during 2016–2018 was found. The incipient collaboration between institutions and the lack of knowledge regarding the physiology and drug-resistance mechanisms of *C. auris* demand further and stronger collaboration networks for dealing with this global health problem and improving the diagnostic and identification methodologies, as well as assure development and implementation of new antifungal antibiotics for treatment and outbreak control. Furthermore, the research was focused in the following areas: (i) *Medicine*, (ii) *Immunology and Microbiology*, and (iii) *Pharmacology, Toxicology and Pharmaceutics* with a participation of 60.3%, 14.8%, and 10.9% of the indexed documents, respectively. Finally, even though only ten years have passed since the first case and isolation of *C. auris* was reported, the knowledge of this pathogen in terms of genetics, transcriptomics, and antifungal resistance have increased faster than in previously discovered pathogens with considerably more researchers and institutions involved such as *Mycobacterium tuberculosis*.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

ETHICAL APPROVAL

Not required.

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