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Systemic Review

A Global Assessment of Antifungal Drug Resistance among *Candida* Species: A Meta-synthesis of Research Productivity and Scientific Report

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Keywords: Antifungal drug resistance; *Candida* species; non-albicans Candida; research advancement; global health

Abstract

Globally, the threat of microbial resistance to therapeutic drugs is increasing, with particular attention to certain microbes. *Candida* species are among the microbial groups eliciting serious antimycotic resistance concerns. Hence, this study provides scientific evidence of advances on antifungal drug resistance among *Candida* spp. Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, datasets were retrieved from the Web of Science and Scopus databases to analyze the available scientific evidence between January 2002 and February 2023. Three thousand, one hundred and ninety-nine (3,199) articles related to antifungal drug resistance among *Candida* spp. were published within the period, with an average citation/document of 27.77. An unprecedented increase in productivity occurred from 2016 and continued throughout the COVID-19 pandemic period to date, also in 2011 and 2019, peak periods were observed. The most active author was Pfaller MA, having the highest publications (n = 75; 2.34%) and a total citation of 7,575. The Antimicrobial Agents and Chemotherapy journal ranked first among the top-most sources with 268 (8.38%) articles. Most of the authors of these publications originate from the USA, with 536 (16.80%) articles and a total citation of 30,478. A robust collaborative network was noticed among authors, institutions, and countries in the developed nations, but lacking with authors in developing regions. Only the Republic of South Africa made the list of top 20 actively collaborating countries on the subject from African region. Also, the thematic landscape of research areas lacks important topics such as the discovery of novel drug targets and diagnostic tools. This article provides a comprehensive global overview of the up-to-date research on drug resistance among *Candida* spp. and associated diseases. It has underscored the need for further synergistic efforts worldwide to ensure global health.

Introduction

Concerns regarding microbial resistance to available therapeutic drugs continue to receive attention amongst diverse global investigators with a specific focus on bacteria and other microbial potential pathogens [1-4] mostly protozoans. However, little or poor related research attention and study reports have been recorded among the fungal members [5]. Such potential neglect still exists despite the estimations that global mortality rate of infections associated with mycotic strains (at ~1.5 million deaths per annum) are higher than that of malaria. The situation is complex by the high rate at which multidrug-resistant pathogenic fungi strains are emerging [6-9]. One group of human potential pathogenic fungi associated with such debilitating disease is the *Candida* species, which are implicated in superficial and invasive candidiasis, often as hospital-acquired infections [10,11].

Some of these hospital-related cases affect blood (candidemia), vagina (vulvo-vaginal candidiasis), skin (subcutaneous candidiasis) and other invasive and/or superficial candidiasis which are reported globally and annually. Candidemia, one of the mentioned cases, has been reported as one of the most prevalent bloodstream infections in the United States of America [12], with an estimated 25,000 cases each year [13]. An incidence of about 400,000 per annum globally [7], making it the most common invasive mycosis. Similarly, an average of about 138 million women worldwide have been reported to experience recurrent vulvo-vaginal candidiasis each year, while about 372 million women experience the condition in their lifetime. An estimated global prevalence of the disease has also been pegged at 3.9%, with annual productivity loss of 14.39 billion US dollars in the world's developed countries [14]. Such emerging reports have shown that candidal infections have been reported with high mortality rates ranging from 40% - 60% [10,15].

Historically, *Candida albicans* has been one primarily implicated potential pathogens of candidiasis, especially in immunocompromised people, as a result of surgery, the Human Immunodeficiency Virus (HIV) infection, organ transplantation, and the treatment of malignancy [16]. The yeast is a common/resident flora of the human skin and gut microbiota, from where it transits (as a commensal organism) to a potential pathogenic strain in other habitats [17]. In recent times, the incidence of other *Candida* species (non-*albicans*) in clinical systems is increasing in addition to multidrug resistance or multiple antifungal resistances (MAFR) indices. Species such as *C. tropicalis*, *C. glabrata* (syn. *Nakaseomyces glabrata)*, *C. parapsilosis, C. inconspicua, C. auris, C. guilliermondii,* and *C. krusei* (syn. *Pichia kudriavzevii*) are now associated with hospital-related infections, with increasing prevalence, severity, MAFR and management complications compared to *C. albicans*, especially due to the development of resistance against antimicrobials [10,18] agents. Notably, three non-*albicans* species (such as *C. auris, C. parapsilosis*, and *C. tropicalis*), in addition the *C. albicans*, have been listed in the recent WHO and CDC lists of fungal pathogens of medium and high priority, requiring serious public health action [13].

The incidence of drug resistance among fungal strains became of high interest, especially as there are limited classes of antimycotic agents available for treatments, compared to the array of antibiotics used for treating bacterial diseases. The few available antifungal agents were shown to belong to only three major classes, namely: polyenes (e.g., amphotericin B), azoles (e.g., itraconazole and fluconazole), and echinocandins (e.g., micafungin, anidulafungin, and caspofungin) [19]. The azoles typically interrupt the production of ergosterol, which is crucial for forming the fungal cell membrane. Polyenes act by binding to ergosterol in the fungal membrane, forming pores in the cell membrane, thereby creating large pores on the membrane and disrupting osmotic pressure in the cell. The echinocandins impair the cell wall formation by interfering with the β-1,3-D-glucan production[19]. Unfortunately, the abusive use and off-label application of these antifungal agents' has been attributed to the recent and worrisome emergence of resistance among fungi [20].

Drug resistance amongst *Candida* spp., like other organisms, could be traced to acquisition of resistance due to poor antifungal therapeutic stride [8,16,19,20] or intrinsic, as in the case of fluconazole-resistant *C. krusei* [20,21]. The unprecedented and unprofessional usage of the available antifungal agents to curtail the clinical mortality impact of invasive fungal infections and abating crop loss due to fungal infections in plants has been implicated as potential origin for generating positive selection pressure for resistant strains due to drug pressure. Also, the intrinsic fungal resistance attributes and other host-related factors have also contributed to the loss of efficiency of available antimycotic drugs, leading to the spread of drug resistance or MAFR among fungal pathogens and their associated diseases [6]. Furthermore, there is a need for accurate/appropriate early diagnosis, efficient surveillance/ monitoring strategy, and appropriate control/ management strategies to curb this development [11,22].

The paucity of data, as well as poor professional therapeutic application at the global level, has been identified as some of the significant setbacks in combating the menace of antifungal-resistant cases [13]. It was documented that very few countries have efficient surveillance processes for mycoses, hence, there is a need for more available statistics on their incidence, resistance, and economic burden of associated disease cases [13]. This important observation has prompted the process of incorporating antimicrobial resistance surveillance for invasive *Candida* (the first of its kind for fungal organisms) into the Global Antimicrobial Resistance Surveillance System (GLASS), which aims at promoting and strengthening standardized Antimicrobial Resistance (AMR) surveillance worldwide [13]. With the unprecedented rate of emergence of potential pathogenic fungi with multidrug resistance traits, especially those in the genus *Candida,* the scientific community and health professionals need to collaborate to address this critical threat to public and global health [8].

This study, therefore, aimed to appraise scientific studies on antifungal drug resistance among *Candida* spp. and how their associated infection reports have fared over the last two decades. This gives a clear picture of the recent research efforts to inform more proactive, robust, and efficient research and policy drives, against the emergence and spread of drug-resistant pathogenic members of the *Candida* genus. It would also assist researchers sensitization program, invigorate policymakers, and increase the interest of funding bodies to combat the menace of drug resistance among fungi and their associated infections while salvaging public and global health implications.

Methods and research design

Literature search strategy and data retrieval

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [23] were used to search the Web of Science (WoS) and Scopus databases for relevant papers on drug resistance in Candida spp. and associated infections. Title-specific search articles served as the primary search strategy using keywords. Only publications that included Candida species, their infections, and antimycotic or antifungal resistance in the title of the dataset were included in the marked list and exported in BibTeX (bib) and PlainTex, as shown in Figure 1, detailed in Figure 1.

Data processing and statistical analysis

The dataset variables were normalized and standardized using the bibliometrix and ScientoPy R-packages; duplicates were removed and saved in CSV files with R-studio 4.0.5. [4,24-26]. The main characteristics and productivity trend analyses by authors, sources/journals, countries, and yearly production were expressed by mean citations/articles and (co)-author indices such as articles/author, number of authors, number of appearances, single- and multi-authored articles, co-authors/article, and collaboration index of the consistent dataset, all performed in R. The most relevant performances involving entities, such as individuals/authors, journals, institutions, and countries, along with their H-index and citation rates, were reported. Descriptive statistics were utilized to examine the retrieved metadata, with results shown in ranges, percentages, and distribution/frequencies in tables and charts. The clustered metric and collaboration networks were computed and visualized using bipartite network tools (https://cran.r-project.org/web/packages/bibliometrix/vignettes/bibliometrix-vignette.html).

Results

Description of the retrieved data

Global research evolution landscape and publication performance: In an effort to accomplish the aim of this study, the applied search strategy identified 23,279 and 151 articles from the WoS and Scopus core databases, respectively, resulting in a total of 23,430 articles obtained for the survey period. However, after applying the exclusion criteria and removing irrelevant documents and duplicates, 3,199 articles (3,157 from WoS and 42 from Scopus) were included in the study (Figure 1).

The average citation per document was 27.77. Twenty-four authors published single-authored articles, within the survey period. The authors who reported related studies were 11,822, while co-authors per document indices recorded were 6.63. Also, a collaboration index of 3.36 was recorded (Table 1).

Furthermore, it was observed that there was a general increase in research outputs on drug resistance among *Candida* and their associated diseases from 2002 up to 2023 (Figure 2). However, it could be noted that there was a sharp increase in the number of publications between 2009 (n = 85, 2.66%) and 2011 (n = 143, 4.47%). Although there was a decrease in the number of publications in the following year (i.e., 2012) to 96, the steadily increasing trend resumed again in 2013 and attained a peak of 188 articles in 2015. A sharp decrease was again observed in 2016, however, a steady

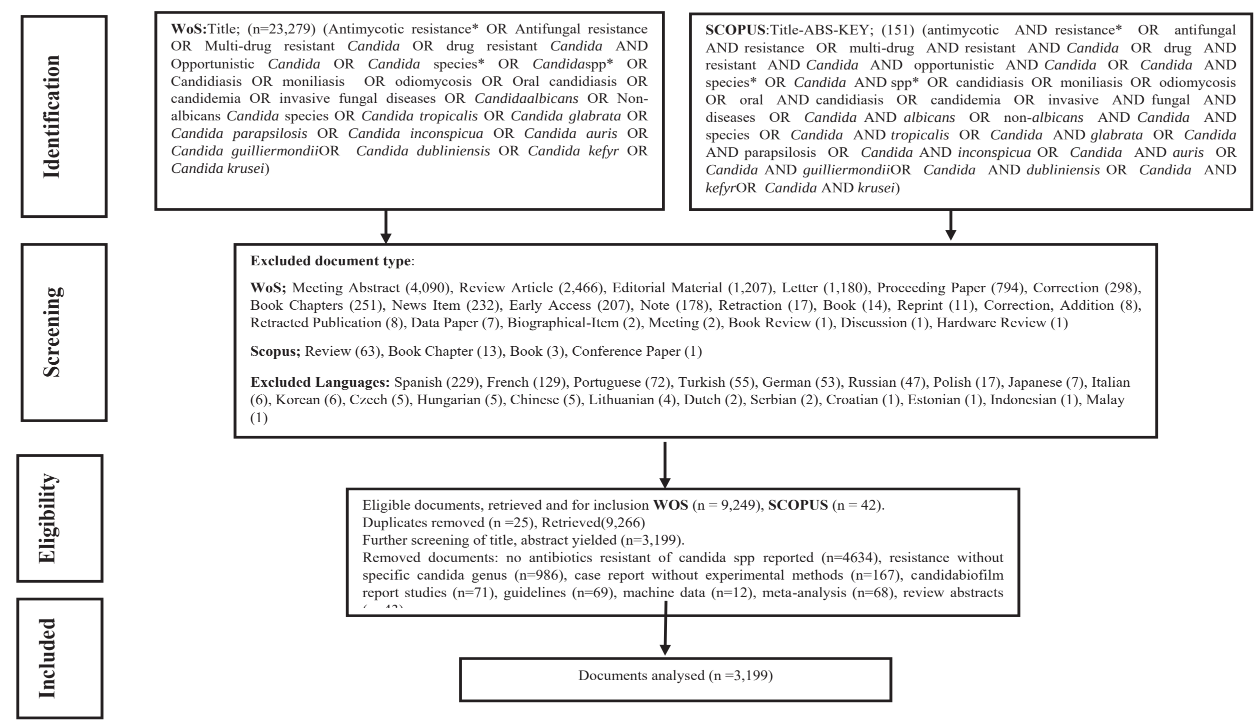

Figure 1: The method of finding, reviewing, and synthesizing published research articles on antifungal drug resistance in Candida species using PRISMA guidelines.

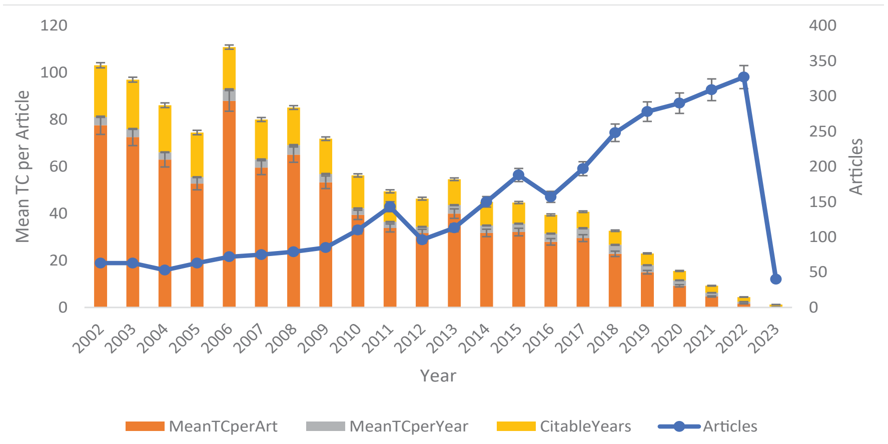

Figure 2: Research outputs on antifungal drug resistance in Candida spp and associated diseases.

Table 1: The main characteristics ofthe included dataset.

Description	Results
Timespan	2002:2023
Study Sources (Journals)	707
Number of articles	3199
Average years from publication	7.55
Average citations per document	27.77
References	49250
Document contents	
Keywords Plus (ID)	4113
Author's Keywords (DE)	4281
Authors	
Number of Authors	11822
Authors of single-authored documents	19
Authors collaboration	
Single-authored documents	24
International co-authorships %	23.98
Co-Authors per Documents	6.63
Collaboration Index	3.36

Table 2: Assessment of 20 most productive authors on antifungal drug resistance in *Candida* spp and associated diseases from 2002-2023.

Authors	Gender	Country	Number of articles	Percentage of total Articles	TC	H_ index	PY
Pfaller MA	M	USA	75	2.34	7575	54	2002
Diekema DJ	M	USA	46	1.44	5573	40	2002
Messer SA	M	USA	41	1.28	3786	35	2002
Perlin DS	M	USA	39	1.22	2548	25	2002
Castanheira M	F	USA	31	0.97	2029	26	2010
Guinea J	M	Spain	31	0.97	561	12	2008
Chen SC-A	F	Australia	30	0.94	1339	17	2008
Andes DR	M	USA	29	0.91	2553	25	2003
Liu X	M	China	28	0.88	468	14	2008
Peman J	M	Spain	28	0.88	936	13	2005
Meis JF	M	*Netherlands*	26	0.81	1467	14	2012
Quindos G	M	Spain	26	0.81	527	11	2002
Wang H	M	China	25	0.78	771	14	2011
Wang Y	M	China	25	0.78	226	10	2009
Chen Y	M	Taiwan	24	0.75	432	12	2006
Zhang J	M	China	24	0.75	451	8	2013
Colombo AL	M	Brazil	23	0.72	1496	18	2002
Li J	M	Switzerland	23	0.72	413	13	2008
Xu Y	M	China	23	0.72	375	10	2012
Li Y	M	China	22	0.69	291	8	2007

TC: Total Citation; PY: Publication Year; M: Male; F: Female

increase resumed in the following year (2017) through the 2020 COVID-19 pandemic year till 2022. Regarding the mean total citation per article and citable year, the opposite results were observed, as there was generally a steady decline from 2002 to date. This is reasonably expected since published articles gain citations with time (Figure 2).

Description of top influential publications and authors' productivity

Table 2 shows the top 20 most productive authors on the specific topic within the period. The author Pfaller MA ranked first with a total of 75(2.35%) articles and a total citation (TC) of 7,575, followed by Diekema DJ, who received 5,573 TC, though with about half (n = 46, 1.44%) of the publications of Pfaller MA. Messer SA and Perlin DS, with 41 (1.28%) and 39 (1.22%) publications, respectively, were the third and fourth most cited authors. The first five of the top-most authors hailed from the United States of America, while only two (10%) were female.

Table 3 shows the top-most cited papers on antimycotic/antifungal drug resistance among *Candida* species and their associated diseases. A publication by Mora-Duarte, et al.(2002) was the most cited article (975), with a TC per year of 44.32, followed by the publications by Garey, et al. (2006) and Panacek, et al. (2009) with TC of 860 and 665, respectively, in second and third positions. However, it could be noted that articles by Pfaller and his co-researchers featured prominently among the top 20 most cited papers, appearing thrice on the list.

Journal's productivity on antifungal resistance in Candida spp.

Table 4 shows the journal sources with the topmost impact on antimycotic/antifungal drug resistance among

Table 3: Twenty top-most cited papers on drug resistance in *Candida*spp.from 2002-2023.

Paper	Title	DOI	Total Citations	TC per Year
Mora-Duarte J, 2002, N Engl J Med	Comparison of caspofungin and amphotericin B for invasive candidiasis	10.1056/NEJMoa021585	975	44.32
Garey KW, 2006, Clin Infect Dis	Time to initiation of fluconazole therapy impacts mortality in patients with candidemia: a multi-institutional study.	10.1086/504810	860	47.78
Panacek A, 2009, Biomaterials	Antifungal activity of silver nanoparticles against Candida spp.	10.1016/j.biomaterials.2009.07.065	665	44.33
Pappas PG, 2003, Clin Infect Dis	A prospective observational study of candidemia: epidemiology, therapy, and influences on mortality in hospitalized adult and pediatric patients	10.1086/376906	627	29.86
Hajjeh RA, 2004, J Clin Microbiol	Incidence of bloodstream infections due to Candida species and in vitro susceptibilities of isolates collected from 1998 to 2000 in a population-based active surveillance program	10.1128/JCM.42.4.1519-1527.2004	506	25.30
Pappas PG, 2007, Clin Infect Dis	Micafungin versus caspofungin for treatment of candidemia and other forms of invasive candidiasis	10.1086/520980	482	28.35
Zelante T, 2007, Eur J Immunol 1	IL-23 and the Th17 pathway promote inflammation and impair antifungal immune resistance	10.1002/eji.200737409	445	26.18
Pfaller MA, 2010, J Clin Microbiol	Results from the ARTEMIS DISK Global Antifungal Surveillance Study, 1997 to 2007: a 10.5-Year Analysis of Susceptibilities of *Candida* Species to Fluconazole and Voriconazole as Determined by CLSI Standardized Disk Diffusion	10.1128/JCM.02117-09	440	31.43
Benjamin DK, 2006, Pediatrics	Neonatal candidiasis among extremely low birth weight infants: risk factors, mortality rates, and neurodevelopmental outcomes at 18 to 22 months	10.1542/peds.2004-2292	427	23.72
Schelenz S, 2016, Antimicrob Resist Infect Control	First hospital outbreak of the globally emerging Candida auris in a European hospital	10.1186/s13756-016-0132-5	412	51.50
Al-Fattani MA, 2006, J Med Microbiol	Biofilm matrix of *Candida albicans* and *Candida tropicalis*: chemical composition and role in drug resistance	10.1099/jmm.0.46569-0	367	20.39
Wells CA, 2008, J Immunol	The macrophage-inducible C-type lectin, mincle, is an essential component of the innate immune response to Candida albicans	10.4049/jimmunol.180.11.7404	323	20.19
Kathuria S, 2015, J Clin Microbiol	Multidrug-Resistant *Candida 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	10.1128/JCM.00367-15	312	34.67
Diekema DJ, 2002, J Clin Microbiol	Epidemiology of Candidemia: 3-Year Results from the Emerging Infections and the Epidemiology of Iowa Organisms Study	10.1128/JCM.40.4.1298-1302.2002	309	14.05
Pfaller MA, 2004, Clin Microbiol Infect	Twelve years of fluconazole in clinical practice: global trends in species distribution and fluconazole susceptibility of bloodstream isolates of *Candida*	10.1111/j.1470-9465.2004.t01-1-00844.x	296	14.80
Pfaller MA, 2019, Open Forum Infect Dis	Twenty Years of the SENTRY Antifungal Surveillance Program: Results for *Candida* Species From 1997–2016	10.1093/ofid/ofy358	265	17.67
Silva S, 2009, Med Mycol	Biofilms of non-*Candida albicans Candida* species: quantification, structure and matrix composition	10.3109/13693780802549594	261	12.43
Sanglard D, 2003, Antimicrob Agents Chemother	*Candida albicans* Mutations in the Ergosterol Biosynthetic Pathway and Resistance to Several Antifungal Agents	10.1128/AAC.47.8.2404-2412.2003	261	43.50
Chowdhary A, 2018, J AntimicrobChemother	A multicentre study of antifungal susceptibility patterns among 350 *Candida auris* isolates (2009–17) in India: role of the *ERG11* and *FKS1* genes in azole and echinocandin resistance	10.1093/jac/dkx480	261	43.50
Cleveland AA, 2012, Clin Infect Dis	Changes in incidence and antifungal drug resistance in candidemia: results from population-based laboratory surveillance in Atlanta and Baltimore, 2008–2011	10.1093/cid/cis697	260	21.67

TC: Total Citations

Candida species and their associated diseases. Among the top 20 journals, the journal Antimicrobial Agents and Chemotherapy recorded the highest number of articles, totaling 268 (8.38%), followed by the Medical Mycology journal and Journal of Clinical Microbiology in second and third positions with a total number of articles equal to 125 (3.91%) and 121 (3.78%) respectively.

Details of most active and cited countries

The United States of America took the lead among the top 20 most active and cited countries with the highest number of articles [*n* = 536 (16.80%)], a TC of 30,478, and an average article citation (AAC) of 56.90. Brazil was the second most productive country, with 369 (11.50%) published articles within the period; and, the articles received the second most TC of 6,765 (AAC=18.30), while China came third in publication numbers but fifth in TC after Italy and India that came third and fourth respectively (Table 5). Although there were significant collaborations between authors from different countries (inter-country collaboration), most research outputs were single-country publications (SCP). For instance, out of the 536 publications by the United States of America, 420 (78.34%) were SCP, while only 116 (21.66%) articles were multiple-country publications (MCP). Brazil and China also had a similar trend (Table 5).

Table 4: Top impact sources on drug resistance in *Candida* spp. From 2002-2023.

Source	No. of Articles	Percentage (%)
Antimicrobial Agents and Chemotherapy	268	8.38
Medical Mycology	125	3.91
Journal of Clinical Microbiology	121	3.78
Mycoses	82	2.56
Frontiers in Microbiology	78	2.44
Mycopathologia	76	2.38
Journal of Antimicrobial Chemotherapy	72	2.25
Journal of Fungi	62	1.94
PLOS One	58	1.81
Journal De Mycologie Medicale	46	1.44
Diagnostic Microbiology and Infectious Disease	45	1.41
Journal of Medical Microbiology	35	1.09
International Journal of Antimicrobial Agents	34	1.06
BMC Infectious Diseases	33	1.03
Clinical Microbiology and Infection	32	1.00
European Journal of Clinical Microbiology and Infectious Diseases	31	0.97
Jundishapur Journal of Microbiology	30	0.94
FEMS Yeast Research	25	0.78
Clinical Infectious Diseases	22	0.69
Scientific Reports	22	0.69

Table 5: Country impact on drug resistance in *Candida* spp. and associated diseases.

Corresponding author's country						Most cited countries		
Country	No. of Articles	% of total article	SCP	MCP	MCP_Ratio	Country	TC	AAC
USA	536	16.80	420	116	0.216	USA	30478	47.45
Brazil	369	11.50	301	68	0.184	Brazil	6765	19
China	316	9.90	264	52	0.165	Italy	5691	14.72
India	207	6.50	163	44	0.213	India	5393	29.43
Spain	156	4.90	113	43	0.276	China	4608	26.12
Italy	145	4.50	103	42	0.29	Spain	4365	18.76
Iran	129	4.00	109	20	0.155	United Kingdom	3071	37.22
Turkey	127	4.00	113	14	0.11	France	2876	88.51
Japan	98	3.10	85	13	0.133	Portugal	1928	37.51
France	79	2.50	66	13	0.165	Switzerland	1755	32.07
Portugal	66	2.10	45	21	0.318	Germany	1706	15.18
Korea	54	1.70	52	2	0.037	Australia	1578	29.84
Germany	50	1.60	25	25	0.5	Czech Republic	1479	23.6
Poland	46	1.40	41	5	0.109	Iran	1361	27.58
United Kingdom	46	1.40	26	20	0.435	Korea	1253	12.71
Saudi Arabia	45	1.40	27	18	0.4	Turkey	1237	43.36
Australia	39	1.20	24	15	0.385	Japan	1001	27.11
Mexico	35	1.10	26	9	0.257	Canada	878	9.29
South Africa	33	1.00	20	13	0.394	Netherlands	730	30.78
Switzerland	32	1.00	16	16	0.5	Denmark	663	35.21

TC: Total Citations; SCP: Single-Country Publication (intra-country collaboration); MCP: Multiple-Country Publications (inter-country collaboration); AAC: Average Article Citations

Collaboration and networking by researchers, institutions, and countries

Figures 3a-c below show collaborations between authors, institutions, and countries on research related to antifungal drug resistance in *Candida* spp. and their infections. Each author (Figure 3a), institution (Figure 3b), and country (Figure 3c) is represented by a circle, with the size of each circle indicating the total number of publications, connected with interlinked lines indicating co-publications. The thickness of the line also indicates the strength of the collaboration. Though very dense network lines connect the authors in Figure 3a, only author Pfaller MA has very robust collaboration with other authors (especially Diekema DJ, Messers SA, and Castanheira M) among the topmost authors analyzed in this study in terms of research outputs. Equally, the institutional network analysis result also showed dense network lines; however, there is more robust intra-country institutional collaboration as evidenced by the strong institutional collaboration among US universities regarding research outputs. Figure 3c depicts active collaboration among countries, especially in North and, Southern America, Europe, and Asia. The United States of America has the most outstanding collaborative efforts with other countries, including Brazil, the United Kingdom, Spain, and China, while only South Africa featured on the list out of 53 African countries.

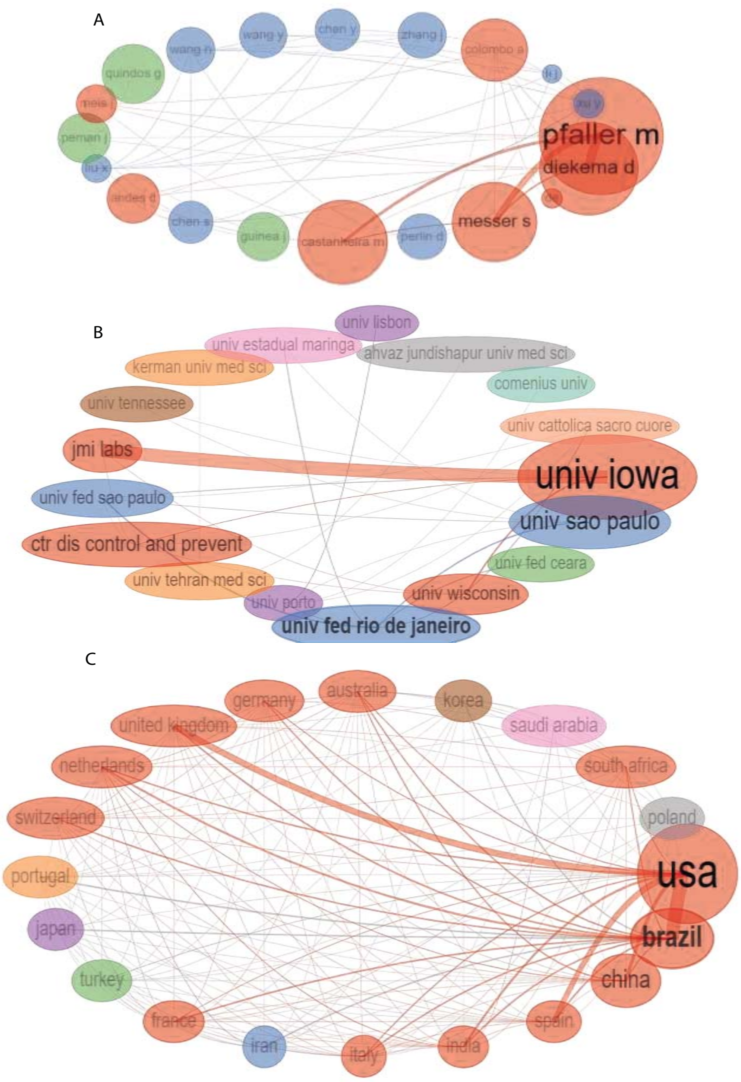

Figure 3: The collaboration network analyses. (a)Authors' collaboration network, (b) Institutional collaboration network, (c) Countries' collaboration network.

Table 6 shows the list of 20 most frequently used keywords in research related to antifungal drug resistance in *Candida* spp., out of 4,113 and 4281 for Keywords-plus (ID) and Author keywords (DE), respectively. The ID and DE have eight keywords in common: *Candida albicans*, bloodstream infections/candidemia, fluconazole, susceptibility, resistance, amphotericin-B, antifungal susceptibility, and antifungal agents. The first five among the top 20 keywords listed under the ID include Albicans (*n* = 906; 22.03%), epidemiology (*n* = 678; 16.48%), fluconazole (*n* = 564; 13.71%), susceptibility (*n* = 445; 10.82%), and resistance (*n* = 444, 10.80%). At the same time, the 5top DE include *Candida* (*n* = 478; 11.17%), *Candida albicans* (*n* = 392; 9.16%), Candidemia (*n* = 277; 6.47%), Candidiasis (217; 5.07%), and Antifungal (199; 4.65%). Twelve keywords were unique to the Keywords-plus, out of which related words such as epidemiology, risk factors, and surveillance co-exist. Also, twelve keywords were unique to the author keywords; however, it featured prominently the *Candida* genus and its different species which have shown antifungal drug resistance globally, including *Candida glabrata, Candida auris,* and *Candida tropicalis.*

Figure 4 shows the conceptual landscape of the various thematic areas in the top twenty articles on antifungal drug resistance and associated diseases among *Candida* spp. The analysis of the thematic areas showed they were distributed in 3 main clusters with different colors. The primary research focus in the blue cluster consists of themes related to epidemiology/surveillance of diseases associated with *Candida* spp., including candidiasis, invasive candidiasis, candidemia, risk factors, mortality, diagnosis, critically ill patients, and management/therapy. The red cluster features prominent themes on determining in vitro antifungal activity of various types of mycotic agents, including fluconazole, voriconazole, caspofungin, and amphotericin B. It also features the determination of virulence and resistance in the yeast

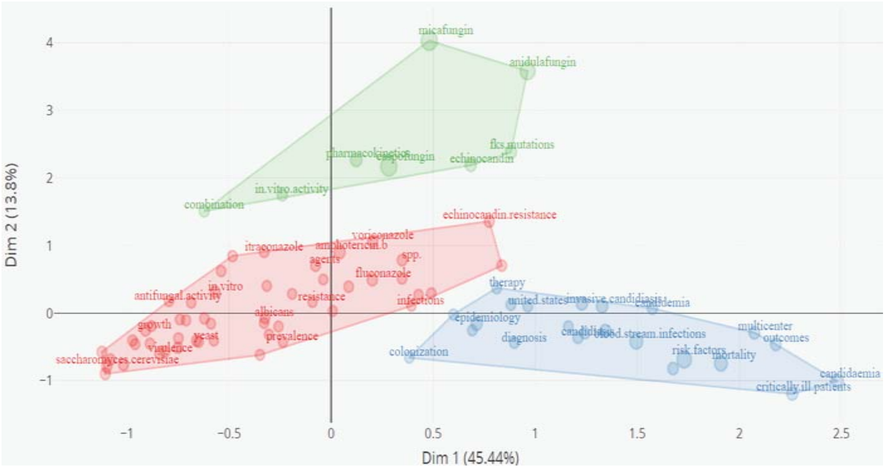

Figure 4: Thematic areas and conceptual landscapes by multiple correspondence analysis(MCA) of top 20 articles on antifungal drug resistance and associated diseases among *Candida* species.

Table 6: Top 20 keywords on drug resistance in *Candida* spp. and associated diseases.

Keywords plus (ID)			Author keywords (DE)		
Words	Frequency	%	Words	Frequency	%
Albicans	906	22.03	*Candida*	478	11.17
Epidemiology	678	16.48	*Candida albicans*	392	9.16
Fluconazole	564	13.71	Candidemia	277	6.47
Susceptibility	445	10.82	Candidiasis	217	5.07
Resistance	444	10.80	Antifungal	199	4.65
Amphotericin-B	319	7.76	Fluconazole	198	4.63
Infections	311	7.56	*Candida*spp	187	4.37
Surveillance	278	6.76	*Candida glabrata*	179	4.18
Blood-stream infections	264	6.42	*Candida auris*	173	4.04
Identification	258	6.27	Biofilm	168	3.92
In-vitro	258	6.27	Antifungal susceptibility	121	2.83
Risk-factors	250	6.08	Resistance	117	2.73
Invasive candidiasis	249	6.05	Vulvovaginal candidiasis	115	2.69
Antifungal susceptibility	225	5.47	*Candida* species	113	2.64
Mechanisms	188	4.57	Antifungal activity	109	2.55
Management	187	4.55	Antifungal resistance	104	2.43
Caspofungin	184	4.47	Susceptibility	90	2.10
Agents	164	3.99	Amphotericin b	87	2.03
Therapy	162	3.94	Antifungal agents	87	2.03
Mortality	154	3.74	*Candida tropicalis*	84	1.96

organisms. Lastly, the third cluster in green consists mainly of themes about the in-vitro activities and pharmacokinetics of echinocandins and its different types/derivatives, including caspofungin, micafungin, and anidulafungin. The main thematic areas of the study did not reveal other pertinent themes related to searching for novel antifungal small molecule inhibitors, new antifungal peptides, and natural/semi-synthetic chemical compounds that could be used to combat the scourge of drug/multidrug-resistant *Candida* species. Furthermore, research areas that deal with the determination of novel drug targets, in-vivo assessment, or clinical trials of novel antifungal agents still need to be included, as well as the development of novel diagnostic techniques.

Discussion

This scientometric study was carried out to provide an overview of the global research landscape on antifungal resistance in *Candida* spp. and their associated infections, based on data retrieved from WoS and Scopus data bases for over two decades (spanning January 2002-February 2023). There has been a relatively consistent increase in publication output in this area over the last twenty years (an almost perfectly linear increase, as shown in Figure 2). However, some notable peaks depicting sharp increases in publication output could be identified during the period. This finding is comparable to the recent results by Rojas-Rodríguez, et al. [27], which reveal research output on antifungal resistance of only *C. albicans* to fluconazole in the past seventeen years. This further underscores the importance of drug resistance in *Candida* organisms to the global scientific community, as they are fast becoming formidable opportunistic pathogens of susceptible human populations globally [28].

The notable sharp increase in the number of research publications between 2009 and 2011 may be attributed to the emergence of drug-resistant strains of *C. albicans and C. glabrata* [13] as well as the identification of another pathogenic drug-resistant species of *Candida*(i.e., *C. auris*) in the year 2009 in Japan [29]. Since its discovery, *C. auris* has become a global challenge, spreading to every continent [28,30]. The global increase in the incidence of drug-resistant strains of *Candida* spp., especially the spread of *C. auris* to other places like North America [31], Europe [32], and South Africa [33] around 2012 to 2017, could have also contributed to the noticeable upsurge in published articles in 2015. Although there was a noticeable decline in number of articles published in 2016, the further worldwide spread of the pathogen within five years spanning 2017-2021, to countries such as India, Pakistan, South Africa, Norway, Japan, Korea, Kuwait, Kenya, Israel, Canada, Venezuela, Spain, Germany, and many other countries, as observed by Kaur, et al. (2021), likely contributed to the steady increase in published articles recorded for the period, coupled with the aggravating co-infection incidences of COVID-19 with various *Candida* spp., causing COVID-19-associated candidiasis (CAC) [34-36]. This noticeable response of researchers to the emerging multidrug-resistant infectious agents in the *Candida* genus is commendable. It is an effort in the right direction as the world strives to attain Sustainable Development Goals, one of which is health for all (SDG3), although more is yet to be done regarding pathogenic fungi [13].

Looking at the list of the 20 most productive authors globally on the topic under evaluation, the authors from the United States of America are taking the lead. The majority of the leading authors in the field are from the country. As in other fields of scientific research, the most productive publications are associated with authors from the United States of America and other developed countries in the global north. These findings further confirm the active roles that the world's developed countries are playing in the fight against infectious diseases, considering their high level of commitment to research, unlike those in developing regions such as Africa [37]. However, many factors have been identified that contribute to the research divide as observed between the global North and the global South [38].

Nevertheless, as the world has become a global village, where the transmission of an infectious agent could occur spontaneously, as was experienced in the case of recent COVID-19, there is a need for every region of the world to be carried along to ensure an all-encompassing global health. International collaboration will go a long way to help the world's low and middle-income countries (LMIC) and overcome the resource and expertise deficit [39]. Most of the time, it is not that researchers in developing countries are folding their arms; however, the paucity of funds contributes majorly to their inability to showcase their research findings. For example, many quality research findings from developing regions that could have contributed to global data usually go unnoticed. This may be due to financial constraints limiting access to high-ranking journals that could help them gain visibility due to the high cost of publishing faced after much struggle to conduct such research amidst the paucity of funds [40].

The need for publishing quality research findings in high-impact journals must be considered. It may also help to ensure wider visibility and enhance the dissemination of research findings, which would support stakeholders in policy-making. The recent escalating emergence of multidrug-resistant strains of *Candida* spp. has further necessitated the need for all-encompassing efforts by all stakeholders in the knowledge industry, including publishing companies, to support the initiative of the WHO in bridging the knowledge gap in antimicrobial resistance surveillance, especially in fungal organisms. An example of this effort includes further calls for reduced article processing charges in open access (OA) journals. Such a reduction will significantly help promote data sharing and make quick access to important information possible, as experienced during the COVID-19 pandemic [41,42]. It has been asserted that only 10 to 15% of the amount charged to the authors as APC is required as running costs for publishing an article. Hence, publishers, as part of their corporate contribution to humanity, could lower their profit margin to make, especially, health-related research publications more visible by charging the lowest APC as possible [42]. Such a gesture will go a long way to complement the step taken by the WHO in incorporating antimicrobial resistance surveillance for pathogenic *Candida* spp. into the GLASS [13].

Notably, in this study, only two (10%) out of the twenty leading authors are female (Table 2), namely Castanheira Mariana of JMI Laboratories Incorporated, North Liberty, United States, and Sharon Chen, an Australian infectious disease expert, and also the Director, Centre for Infectious Diseases and Microbiology Laboratory Services, Westmead Hospital, Australia. It has been asserted strongly in a recent study that women are less recognized for their scientific contributions on patents and publications than their male counterparts, and such disparities could lead to difficulties in attracting women to the field of science and retaining senior female scientists [43]. Though the number of female researchers among the top twenty most prominent authors was examined in this study, the low percentage could still be explained based on the recent findings of Ross, et al. [43]. It further reiterates the need to encourage women scientists in terms of access to funding, among many other incentives. This will go a long way to ensure gender equality and women's empowerment as entrenched in Sustainable Development Goal 5 (SDG 5) by 2030.

Although a collaborative network exists between researchers, their institutions, and countries regarding research on the antifungal resistance in *Candida* spp. and their associated diseases globally, greater collaboration is required, especially between researchers in developed and developing countries [41,44]. For example, in this study, only South Africa out of the 57 African countries made the list of the top 20 actively collaborating countries on research focusing on antifungal resistance in *Candida*. This is not surprising, as it has been asserted that almost all African countries lack an effective surveillance system for mycotic infections except for South Africa. Also, it has been identified that only the country has a national mycology reference laboratory in the whole of the continent [44]. In a recent study, logistics has been identified as one of the most prevalent barriers to international collaborations among scientists, in addition to political and cultural barriers [45]. Infrastructural deficits due to lack of inadequate funding need to be addressed headlong by political players, policy makers, and funding agencies to facilitate international collaboration among scientists in developed and developing countries, to achieve the goal of health for all. The call for such a formidable collaboration becomes highly imperative as a global health problem requires global stakeholders' collective involvement in solving it [46], as it was experienced during the COVID-19 pandemic [39].

The evaluation of the prominent thematic areas and keywords in the field of antifungal resistance in *Candida* spp. showed the robustness of research efforts in many areas of importance. However, from our observation, contributions to some notable areas are urgently needed. These include research areas determining novel drug targets, in vivo assessment, and clinical trials of novel antifungal agents. Although there have been many frantic efforts by scientists in combing new antifungal agents, both from synthetic and natural products in recent years [47,48], a poor approval of novel antifungal drugs for human use has been rare [5]. Many novel antimycotic drugs, such as VT-119 and Nikkomycin, with different mechanisms and targets compared to those in use, are in different stages of clinical development, requiring significant funding of dedicated research to make them available [5,49]. The need to facilitate programs that specifically provide funding for anti-mycological research has become highly imperative to further promote the development of efficient antifungal drugs that could be used in combating resistant fungal strains and reduce mortality due to their infections [5]. Furthermore, the need for new, fast, and efficient diagnostic techniques that will facilitate an early diagnosis of *Candida*-related infection must be addressed to forestall their misdiagnosis and prevent incorrect therapeutic interventions (WHO, 2019).

In conclusion, this study evaluated scientometric research progress on antimycotic/antifungal drug resistance among *Candida* species and their associated diseases from 2002 to date. A steady and seemingly linear increase in published documents was observed on the subject under discussion within the period of the survey. Authors in the world's developed regions, their institutions and countries have significantly contributed to advancing research on antifungal resistance in *Candida* spp. and their associated diseases. However, this study has revealed the need for appropriate research attention on fungal and antimycotic resistance or MAFR, more inter-country collaboration, especially between the developed countries and the low and middle-income countries of the world, to ensure formidable efforts in combating the emergence of drug-resistance among *Candida* organisms. As the whole world has become a global village, the spread of infectious agent and their associated diseases has become highly sporadic, as experienced recently in the case of COVID-19. Therefore, no region is truly safe if others remain vulnerable to infectious diseases. This further reiterates the need for global synergistic efforts in research towards fighting the drug resistance menace in *Candida* organisms and many others. Also, the need for more efforts to unravel novel drug targets and develop new antifungal drugs with greater efficiency in treating multidrug-resistant strains of *Candida* organisms must be given utmost attention. Therefore, there is a need for future research to focus on developing novel diagnostic methods for the early detection of novel *Candida* spp. and their antifungal resistance traits among infected patients. This will help the implementation of appropriate control/management options to safeguard global health.

Limitations of the study

The study is limited by excluding articles published in other languages and articles that do not conform to topic-specific search codes/algorithms. The removal of non-English language format, public health system/government intervention newsletters, and other unrelated/unassociated articles which may focus on fungi other than *Candida* spp. and their antifungal resistance search terms, and the database employed for retrieval of details. Furthermore, other documents published on *Candida* in combination with bacteria, viruses, and other groups of organisms were excluded. However, we are assured of the quality of the research, with the extensive search of the ISI WoS and Scopus databases, using keywords that enable the synthesis of past and present studies for future preparedness.

Author contributions

Kayode Olayinka Afolabi and Hope Onohuean: Conceptualization; Hope Onohuean: Methodology, Software, Data curation; Kayode Olayinka Afolabi and Bright E Igere: Writing- Original draft preparation; Kayode Olayinka Afolabi, Bright E. Igere, Maryam Bello-Akinosho, Hope Onohuean, and Carolina Pohl-Albertyn: Writing- Reviewing and Editing. All authors read and approved the final manuscript.

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