RESISTANCE TO ANTI-FUNGAL AGENTS IN *Candida albicans*: BIBLIOMETRIC ANALYSIS OF SCIENTIFIC LITERATURE

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SUMMARY

One of the best indicators of the progress of research in a specific topic is the analysis of the production of scientific articles; bibliometrics is a useful discipline to analyze such information in a quantitative way. Infections produced by Candida albicans *are an important topic worldwide and, the mortality related to them has increased, particularly in immunocompromised patients. To document the state of the art of research in the topic of 'Mechanisms of resistance to* C. albicans *anti-fungal agents', based on a bibliometric study of the articles published for 16 years (2002-2018), a search for articles that described it in the Scopus database was carried out. The information was filtered by keywords and 79 documents were exported and later analyzed using the software VOSviewer®. The use of bibliometric indicators is a solid tool for the diagnosis of research on the resistance of* C. albicans *to anti-fungal agents.*

Introduction

Scientific information is disseminated through the publication of articles in specialized magazines; thus, the analysis of scientific publications is a measure of the progress of the production of knowledge (Basualdo *et al*., 2016). Publications on a given topic generally increase when the problem becomes a matter of public health or when it has been recently discovered; an example of this are infections caused by fungi, among which are the genus *Candida*. This genus is made up of 163 species, out of which approximately 10 cause infections in humans, *Candida albicans* being the most important. It is considered part of the human microbiota (Khademi *et al*., 2017) colonizing specifically the gastrointestinal and genitourinary tracts of healthy people, although in immunocompromised individuals or individuals with some predisposition factor, it is a possible opportunist pathogen, capable of causing infections of the mucosa and systemics (Hampe *et al*., 2017). This yeast is an aerobic microorganism, it reproduces asexually and is dimorphic, allowing it to present a free life morphology and a different one when parasitizing; this transition between the way of growth from yeast to hyphae is important for the development of its pathogenicity, as hyphae only reproduce during the invasion to tissue. In fungal taxonomy *C. albicans* is placed in the Phylum Ascomycota, order Saccharomycetales, Family *Saccharomycetaceae* (Quintana *et al*., 2017).

In recent years, the incidence of infections produced by *C. albicans* has increased considerably (Khademi *et al*., 2017). Such infections can be classified in two groups: 1) affections at the level of mucosae (oral, gastrointestinal, and vaginal) and, 2) systemic infections, which can be deadly in patients with a diminished immune system (Bhattacharya *et al*., 2016). Polyenes, echinocandins and azoles are used and anti-fungal agents to treat these infections (Kontoyiannis and Rusell, 2002; Bhattacharya *et al*., 2016); however, the development of resistance against antifungal agents, particularly azoles, has been widely documented as a problem in *Candida* sp. (de Oliveira Mima *et al*., 2010).

Bibliometric studies are a valuable tool to describe the information of regional, national, and international investigations and to analyze the impact these studies have on the generation of new knowledge. The aspects or elements that are usually used as a point of analysis in bibliometric investigation are the institutional affiliation or relation of the documents, the publication dates or time ranges, the main authors and coauthors, the journals and other sources of information mentioned in the documents and, keywords or descriptors (Boeris, 2011). The aim of the present document is to carry out a bibliometric analysis to help shed light on original investigations, both national and foreign, with the analysis of scientific articles by the

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RESISTENCIA A AGENTES ANIMICÓTICOS EN *Cándida albicans*: ANÁLISIS BIBLIOMÉTRICO DE LA LITERATURA CIENCTÍFICA

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RESUMEN

Uno de los mejores indicadores del progreso de las investigaciones en un campo específico es el análisis de la producción de artículos científicos. La bibliometría es una disciplina útil para analizar tal información de mamera cuantitativa. Las infecciones producidas por Cándida albicans *son un tópico de importancia a nivel mundial y la mortalidad relacionada con ellas ha ido en aumento, particularmente en pacientes inmunocomprometidos. A fin de documentar el estado del arte de las investigaciones en el tópico 'Mecanismos de resistencia a agentes antimicóticos contra* C. albicans*' con base en un estudio bibliométrico de los artículos publicados durante 16 años (2002-2018), se llevó a cabo una búsqueda de artículos en la base de datos Scopus. La información fue filtrada por palabras clave y 79 documentos fueron exportados y luego analizados utilizando el software* VOSviewer®*. El uso de indicadores bibliométricos es una herramienta sólida para el diagnóstico de investigaciones sobre la resistencia de* C. albicans *a los agentes antimicóticos.*

RESISTÊNCIA A FÁRMACOS ANIMICÓTICOS EM *Candida albicans*: ANÁLISE BIBLIOMÉTRICA DA LITERATURA CIENTÍFICA

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RESUMO

Um dos melhores indicadores de progresso das investigações em um campo específico é a análise da produção de artigos científicos. A bibliometria é uma disciplina útil para analisar essa informação de maneira quantitativa. As infecções produzidas por Candida albicans *são um tema de importância em nível mundial e a mortalidade associadas a elas vem aumentando, principalmente em pacientes imunocomprometidos. A fim de documentar o estado da arte das pesquisas sobre o tema 'Mecanismos de resistência a fármacos antimicóticos contra* C. albicans*' a partir de um estudo bibliométrico dos artigos publicados durante 16 anos (2002-2018), foi realizada uma busca de artículos na base de dados Scopus. A informação foi filtrada por palavras chave e 79 documentos foram exportados e posteriormente analisados utilizando o software* VOSviewer®*. A utilização de indicadores bibliométricos é uma ferramenta sólida para o diagnóstico de pesquisas sobre a resistência de* C. albicans *aos fármacos antimicóticos.*

application of quantitative and methods and mathematical statistical models, in order to obtain data that help provide knowledge in relation to the evolution of the topic of 'Mechanisms of resistance to antifungal agents in *Candida albicans*' (Camps, 2007).

Materials and Methods

Bibliometric analysis is a technique that helps perform a broad revision of the academic literature through the quantitative analysis of historical publications; this may reveal the latest advances, topics of importance for research, tendencies and innovative methods that enrich and complement them, and that act as a guide for new investigators (Okumus *et al*., 2018).

Antimicrobial resistance is not only a problem in bacteria; in recent years, an increase in resistant fungi has also been reported, *C. albicans* being one of the most important, since it is a topic that has become more and more frequent at an intra-hospital and community level, and that deserves the attention of health workers and regulating entities (Chowdhary *et al*., 2017).

Understanding resistance mechanisms and their prevalence is important to implement measures to prevent and cure the infections. A search for articles that described the resistance of *C. albicans* to antifungal agents was undertaken, using a group of keywords that cover basic aspects that refer to antimicrobial resistance by this yeast: '*Candida albicans*', 'antifungal agents' and 'resistance genes', with particular focus placed in the latter (Table I). The articles were gathered using the Scopus database, from which bibliographical references and citations were taken. The term '*Candida albicans*' was used as an initial search term; search criteria included the article title, author, abstract, keywords, etc. Speech marks were used to refine the search criteria and to filter the information required, giving the results more firmness. Likewise, topics and authors that were not relevant to the investigation were excluded. To obtain more precise information, the term 'resistance mechanisms' was included to perform a new filtering. A period of 16 years (2002-2018) was selected to have a wide timeframe, and thus perform a detailed search. Out of total of 408 results, 79 papers were considered adequate for revision due to their affinity with the investigation, and they were later exported to Office Excel (Microsoft®). The articles were exported to VOSviewer (version 1.6.8, Centre for Science and Technology Studies, Leiden University, The Netherlands) to analyze and observe relations between authors, countries, co-citations and terms. The exported database was used to create a two-dimensional pattern, in such a way that the distance between two elements reflects the similarity or relation of the articles in the most accurate way possible (Chen *et al*., 2010).

TABLE I
EVIDENCE OF RESISTANCE MECHANISMS IN *Candida albicans*

Gene studied	Main discovery	Methodology used	Country	Source
MDR1	The expression of efflux pumps increases; is a common way, therefore this human pathogen fungus becomes resistant to fluconazole.	PCR	China	Feng *et al*., (2018)
		RT-PCR	United States	Khademi *et al*., (2017)
		RT-PCR	Indonesia	Rosana *et al*., (2015)
		FASTPREP/Q-PCR	Poland	Golabek *et al*., (2015)
		PCR	United States	Lohberger *et al*., (2014)
		PCR	United States	Schubert *et al*., (2011)
		PCR	United Kingdom	Franz *et al*., (1998)
		RT-PCR	China	Zang *et al*., (2013)
		RT-PCR	Iran	Salari *et al*., (2016)
		PCR	United States	Schneider and Morschhauser (2015)
		PCR	United States	Perea *et al*., (2001)
		RT-PCR	United States	Dhamgaye *et al*., (2012)
		RT-PCR	Canada	Znaidi *et al*., (2008)
ERG3	Codifies for enxyme 5,6-desaturase, essential for the bionsynthesis of ergosterol29. Enough to confer in vitro resistance to fluconazole	PCR	United States	Luna-Tapia *et al*., (2018)
		RT-PCR	China	Liu *et al*., (2015)
		PCR	Germany	Martel *et al*., (2010)
		PCR		Dudiuk *et al*., (2015)
ERG11	This gene codifies for enzyme lanosterol 14 alpha demethylase that participates in the biosynthesis of ergosterol25	q-PCR	Czech Republic	Dižová *et al*., (2018)
		PCR	Iran	Khademi *et al*., (2017)
		PCR	China	Feng *et al*., (2017)
		PCR	India	Mane *et al*., (2012)
		RT-PCR	Berlin	Xu *et al*., (2015)
		RT-PCR	Indonesia	Rosana *et al*., (2015)
		FastPrep/q-PCR	Poland	Golabek *et al*., (2015)
		PCR	United States	Jensen *et al*., (2015)
		PCR	China	Wang *et al*., (2015)
		PCR	United States	Flowers *et al*., (2015)
		PCR	United States	Vasicek *et al*., (2014)
		PCR	Poland	Stzelczyk *et al*., (2013)
		PCR	China	Zhang *et al*., (2013)
		PCR	China	Vale-Silva *et al*., (2012)
		PCR	Turkey	Manastir *et al*., (2011)
		RT-PCR	Finland	Siikala *et al*., (2010)
		RT-PCR	China	Zhang *et al*., (2013)
		PCR	United States	Bhattacharya *et al*., (2016)
		RT-PCR	Iran	Salari *et al*., (2016)
		PCR	China	Zhang *et al*., (2015)
		PCR	United States	Schneider and Morschhauser (2015)
		PCR	United States	Perea *et al*., (2001)
		PCR	Brazil	Carvalho *et al*., (2013)
		PCR	Germany	Sasse *et al*., (2012)
		RT-PCR	United States	Dhamgaye *et al*., (2012)
		PCR	Germany	Martel *et al*., (2010)
		PCR	United Kingdom	MacCallum *et al*., (2010)
		RT-PCR	United States	Heilmann *et al*., (2010)
		RT-PCR	Canada	Znaidi *et al*., (2008)
		PCR	China	Zhang *et al*., (2013)
		PCR	France	Coste *et al*., (2007)
		RT-PCR	United States	Reis de Sá *et al*., (2017)
		URA- BLASTER	China	Zhao *et al*., (2013)
FLU1	The expression of efflux pumps increases, contributing resistance to azoles and cycloheximide	RT-PCR	China	Zhang *et al*., (2013)
		RT-PCR	Egypt	Mostafa and Awad (2015)

The documents that were excluded did not comply with the topic of interest 'Mechanisms of resistance to antifungal agents of *Candida albicans*'. For example, Prevalence of *C. albicans* in pregnant women (Mucci *et al*., 2017) or, Phenotypical and genotypical evaluation of the influence of *Lactobacillus* in *C. albicans* (Sarbu *et al*., 2016).

Results

Analysis of textual data (SCOPUS)

Figure 1 shows the growing tendency of research in this topic between the years 2002 to 2018. Ninety nine updated and pertinent documents were selected, showing that it is a topic that is being constantly updated and publishing. It can be observed that the number of annual publications reveals a steady increase in the years 2006 to 2011 and increased gradually between 2013 and 2015. The journals *Antimicrobial Agents and Chemotherapy and Eukaryotic Cell* have published the most on this topic, with 49 and 12 documents, respectively, for the last 16 years. In the first of them 16 out of 49 publications are recent (2015-2017), which shows it is an active source of investigations on 'Mechanisms of resistance to antifungal agents in *Candida albicans*'.

Figure 2a shows the publications and the indexes of the most productive authors, each one of which has at least three publications and a maximum of 13. The highest numbers correspond to D. Sanglard, J. Morschhäuser and R. Prasad. Regarding affiliation (Figure 2b) it was found that, in the documents analyzed, the Second Military Medical University is the one with the highest number of affiliations (13), followed by the Jawaharlal Nehru University (12) accounting for 24% of the total between the two of them. As to the distribution of documents by country (Figure 2c), it was found that the United States is the most productive country in this field (86 publications), followed by China (48), Germany, India, UK and Brazil, while Switzerland, France, Canada and Iran had less than 15 publications on the topic.

Analyses of textual data using VOSviwer®

Using this software for analysis helps better understand the data. As mentioned earlier, D. Sanglard is one of the main leaders in this topic of research; his papers are mainly co-authored by S.L. Kelly and J. Berman (Figure 3a). This first group is followed by that of J. Morschhäuser, co-authored by M. Raymond and P.D. Rogers. A high level of collaboration is shown between these researchers, allowing a higher evolution at a scientific level and increasing the quality of their studies. On the other hand, the analysis

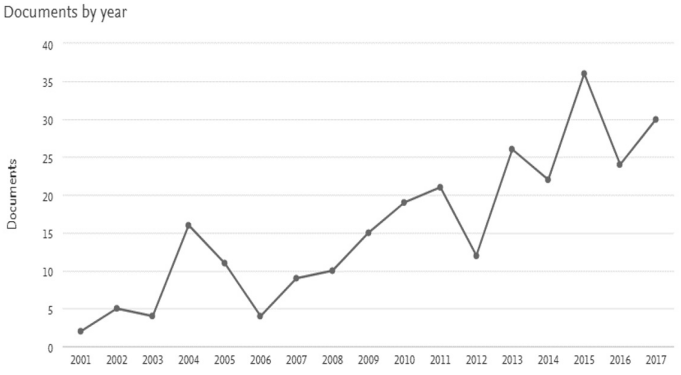

Figure 1. Number of documents on the topic per year, 2002 - 2018.

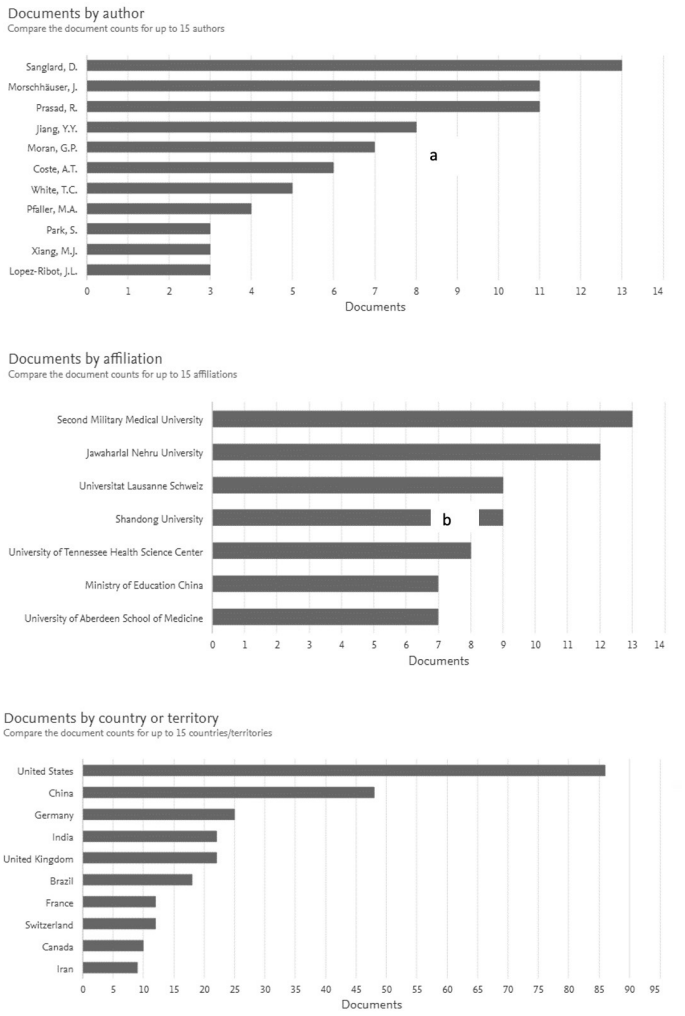

Figure 2. Main authors (a) affiliations (b) of the publications found c) Number of articles per country found on the resistance of *C. albicans* to antifungal agents.

of the countries in which the researchers publish (Figure 3b) shows a large interaction between the United States and China, followed by the United States and Germany, which are the main places that concentrate most of the citations of the studies on 'Mechanisms of resistance to antifungal agents in *Candida albicans*.' On the other hand, China is seen to interact and share studies with India and France.

Figure 3c shows that the most cited source is *Antimicrobial Agents and Chemo* and it presents co-citations with *Eukaryotic Cell and Journal of Antimicrobial Chemo*, generating the probability that these sources are related, due to their contents. Another relevant aspect is the citations of the publications; Figure 3d shows that Perea *et al*. (2001) and Coste *et al*. (2007) were cited with the greatest interaction, as did Guo *et al*. (2009), MacCallum *et al*. (2010), Mathé and Van Dijk (2013), and Jin *et al*. (2016).

Discussion

The present work attempts to offer a bibliometric description of the antifungal resistance to fluconazole in the past 17 years. The analysis showed that the publications on the topic have increased. The most active countries on the topic include the United States, China and Germany, although they are not the only ones, which indicates that the resistance of *Candida* sp. to

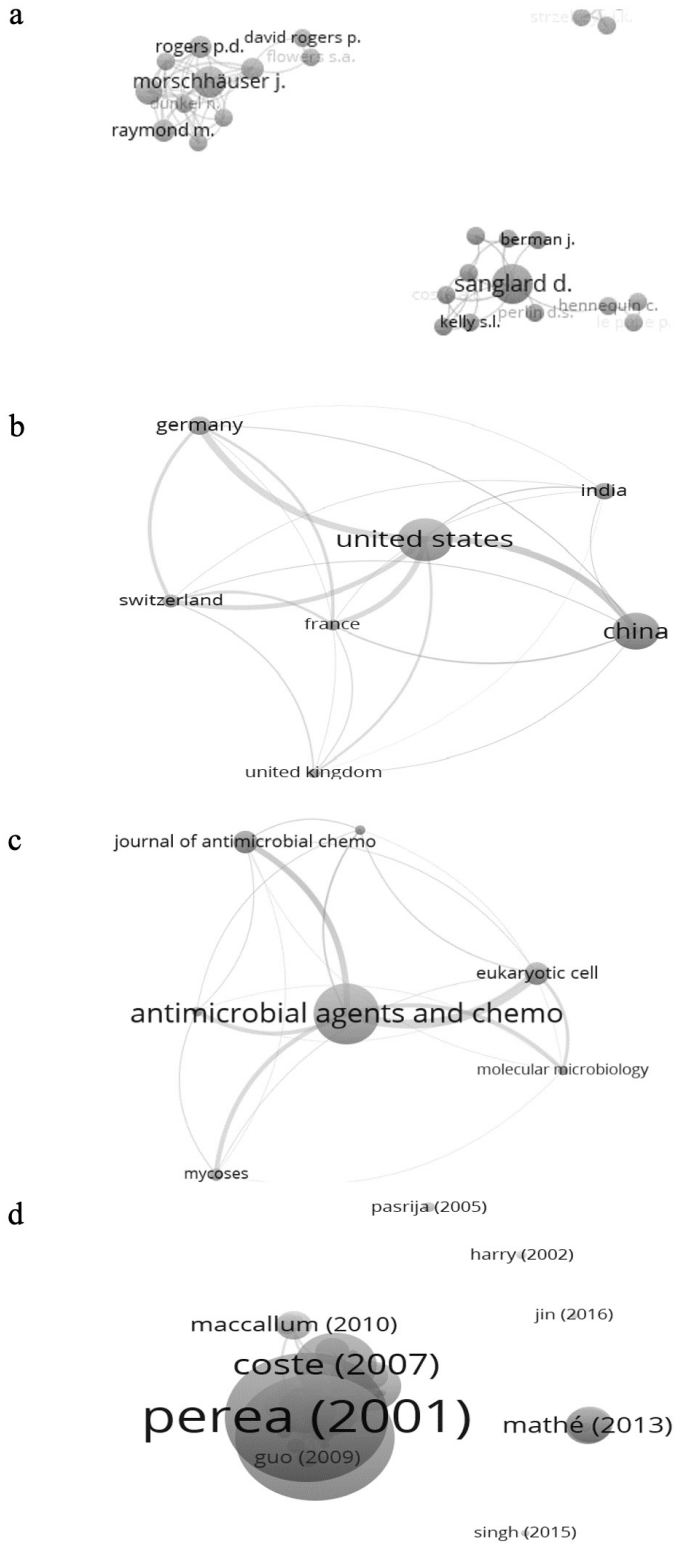

Figure 3. Bibliographic map showing the main authors of articles related to the resistance of *C. albicans* to fluconazole (a), citations per country (b), citations per journal (c) and, citations of documents per author (d).

antimicrobial agents is an important topic at a global level. Infections caused by fungi, mainly invasive ones in immunocompromised patients or patients that undergo transplants are a cause of death on the rise (Sweileh *et al*., 2017). The resistance of *Candida* sp. has been linked to the excess and inadequate use of antibiotics, which affects the microbiome and creates conditions that favor the yeast's growth.

Research requires the search for information and databases are tools for the search and recovery of information. Scopus is a database created in the year 2004 and it indexes over 16,000 peer-reviewed journals in all areas of knowledge, making it a solid database (Santa and Herrero-Solana, 2010; Basualdo *et al*., 2016). Therefore, this database was selected for the search of information in the present study. Bibliometric analyses of scientific information are an efficient tool for the evaluation of challenges, advances and perspectives of a specific topic (Khudzari *et al*., 2018). The efficiency of these analyses depends largely on the database used to search for information. In the case of Scopus, the search focuses on journals, which some authors see as inconvenient (Mongeon and Paul-Hus, 2016). However, for the area of the topic under study, the specific information is found in the type of documents under analysis. The information of books, reports and other types of documents is more frequent in the areas of humanities and the arts (Hicks and Wang, 2011). The tool used herein contributes to the advancement of research, since it can help identify the main contributors in a specific topic of science; the mapping provided by this analysis shows, in a graphic and simple manner, diverse aspects of the investigation (authors, countries, universities or research centers, journals, etc.) (Cobo *et al*., 2015).

The maps created using VOSViewer include the elements of interest, such as words, codes, authors and countries. In addition, these elements can be connected to analyze the relations between countries or authors (Sweileh *et al*., 2017; Khudzari *et al*., 2018) that carried out a bibliometric analysis on the fungal resistance of azoles. In their study, the latter also used the Vosviewer ® software and found an increase in the publications on the resistance to triazol, mainly in species of *Candida*. Fluconazole is the treatment of choice for *C. albicans*; however, the resistance to this and other antifungal agents has increased. The articles found show that some of the most important mechanisms are the use of exit flow pumps, biofilms, the synthesis of the enzyme lanosterol 14 alpha desmethylase and others. There are few published bibliometric studies on antifungal resistance; as mentioned, these analyses provide a good perspective on the current state of the topic in science, although an important limitation is that some journals are not indexed in Scopus and are not counted in the analysis. The use of bibliometric indicators is a solid tool for the analysis of the antifungal resistance of *C. albicans* and it provides a greater visibility of the investigation on this topic. Additionally, this article presents an analysis of the resistance to antifungal agents in *C. albicans*, including the resistance genes, the functioning of the resistance mechanism against fluconazole and other therapeutic agents.

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