

# Bibliometric analysis of bacterial resistance on periodontal disease

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## ARTICLE INFO

Received on: 07/11/2020  
Accepted on: 09/01/2021  
Available online: 05/04/2021

### Key words:

Bibliometric analysis,  
antibiotics, anti-infective,  
periodontal disease.

## ABSTRACT

Periodontitis is a disease that generates inflammation of the periodontal junction complex and is one of the main causes of oral morbidity in the world. The aim of this study was to analyze the relationship between periodontitis and antibiotic therapy in the last decades. Data collection was carried out using the Scopus database, and “antibiotic” and “periodontitis” were the terms used in the search during a time span of 1948–2020. VOSviewer 1.6.13 was used for data analysis and visualization. A total of 688 documents related to periodontal disease and antibiotic therapy were indexed in Scopus between 1953 and May 25, 2020. Studies related to this topic have been on the rise since the 1970s, and the main areas were (i) Medicine, (ii) Dentistry, and (iii) Immunology and Microbiology, where the studies were focused on infection, disease, microbiology, and treatment. Most used antibiotics for periodontal disease were metronidazole and amoxicillin, but *Porphyromonas gingivalis*, *Aggregatibacter actinomycetemcomitans*, and *Prevotella intermedia/nigrescens* exhibited resistance to these antibiotics probably due to their natural tolerance or excessive use. The countries that published the most studies on antimicrobial resistance in periodontics and had the strongest collaboration network were the United States, Germany, the United Kingdom, and Switzerland.

## INTRODUCTION

Periodontitis is a disease mediated by microorganisms that generates inflammation of the periodontal junction complex (Tonetti *et al.*, 2018) and is one of the main causes of tooth loss and oral morbidity in the world (Jin *et al.*, 2016). The onset and progression of periodontitis depend on dysbiotic ecological changes of the microbiome in response to nutrients from gingival inflammatory products and tissue decomposition that enrich some species and antibacterial mechanisms that attempt to contain microbial challenge within the gingival sulcus area by the spread of the bacterial biofilm along the root surface (Tonetti *et al.*, 2018). The main pathogens related to the development of this disease are *Aggregatibacter actinomycetemcomitans* and the so-called “red complex”: *Porphyromonas gingivalis*, *Treponema denticola*, and *Tannerella forsythia* (Haffajee and Socransky, 2005; Holt and

Ebersole, 2005). This disease and its relationship with antibiotics as adjuvant therapy has been of fundamental importance for the evolution of periodontology (McGowan *et al.*, 2018). However, the evidence regarding its effectiveness when antibiotics are administered systemically is not consistent. Therefore, localized antibiotic therapy has been directed to be used in maintenance or supportive periodontal therapy (Feres *et al.*, 2015). Periodontal therapy has evolved, and there is strong evidence about the clinical and microbiologic long-term results after the use of antibiotics as adjuvants for mechanical debridement therapy, especially in severe cases of periodontitis (Feres *et al.*, 2015), as well as the evolutionary evasion of microorganisms in recent times against antibiotic therapy (Feres *et al.*, 2015; Preus *et al.*, 2013). The use of antimicrobials as adjuncts to periodontal mechanical therapy in patients with periodontitis has been controversial and is often reserved for cases of exacerbation of periodontal lesions or in patients who do not respond immediately to conventional mechanical therapy or in those who have the risk of systemic compromise. However, due to the recent interest in the treatment of periodontitis, not only for dental reasons but due to the association of periodontitis with systemic diseases, periodontal treatment has acquired greater importance

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and the recognition of microbial specificity in severe periodontitis supports the use of therapy with antibiotics (Slots, 2020).

Antibiotic resistance is a phenomenon that can be explained from different population conditions, such as (i) geographic location, (ii) access to the production of certain antibiotics, (iii) knowledge of clinicians and adhesion of patients to pharmacological therapies, and (iv) type of microorganisms specific to each population. This phenomenon is a serious problem at the therapeutic level within the health sciences throughout the world; however, the knowledge on the causes and strategies that will be taken to face the problem is recent and limited. There are few disciplines that have advanced in this subject from the medical sciences (McGowan *et al.*, 2018).

Within dentistry as a discipline, periodontics is one the most advanced fields in the level of scientific evidence available for the analysis of resistance to antibiotics, which places it at a priority level to find trends in the behavior of antibiotics as adjuvant therapy and steps to be taken at a clinical, scientific, and public health level to try to minimize the phenomenon of antibiotic resistance in some regions of the world where the problem is still manageable (McGowan *et al.*, 2018; Preus *et al.*, 2013).

A bibliometric analysis allows a robust study of the bibliography from a conceptual, temporal, and network perspective that accounts for some evidence regarding the research questions that the scientific community is considering in a wide field of research (Ahmad *et al.*, 2020; Bar-Ilan, 2008; Gómez-ríos and Ramírez-malule, 2019). However, a bibliometric analysis of resistance bacteria on periodontal disease is still scarce. The aim of this study was to analyze the relationship between periodontitis and antibiotic therapy and its evolution over time.

## METHODS

### Database selection

In this study, the Scopus database was used as a tool to retrieve the most relevant documents related to resistance bacteria on periodontal disease. Data collection was acquired from Scopus on May 25, 2020, and comprised records obtained from a systematic search of documents matching the search terms in the fields of article title, abstract, and keywords. The search was refined to article and review as the document type. Thus, the resulting search was as follows:

- Search equation: (periodontal disease OR periodontal diseases OR abscess, periodontal OR abscesses, periodontal OR adult periodontitis OR adult periodontitides OR aggressive periodontitis OR chronic periodontitis OR chronic periodontitides) AND (antimicrobial drug resistance OR antibiotic resistance, bacterial OR antibiotic resistance, microbial).
- Timespan: 1948–2020; 688 articles and reviews were retrieved after removing duplicates.

### Data export and analysis

The information retrieved from the Scopus in the search was (i) citation information, (ii) bibliographical information, and (iii) abstract and keywords. Retrieved data were exported from

Scopus to Microsoft Excel. The software VOSviewer 1.6.13 was used for visualization and data analysis. Additionally, duplicated records were removed by using Mendeley software. In this study, the minimum number of occurrences of a keyword was set at five, and after removing the thesaurus terms, 52 of them met the threshold, which led to seven clusters.

### Bibliometric indicators

In the current study, the following bibliometric indicators were evaluated:

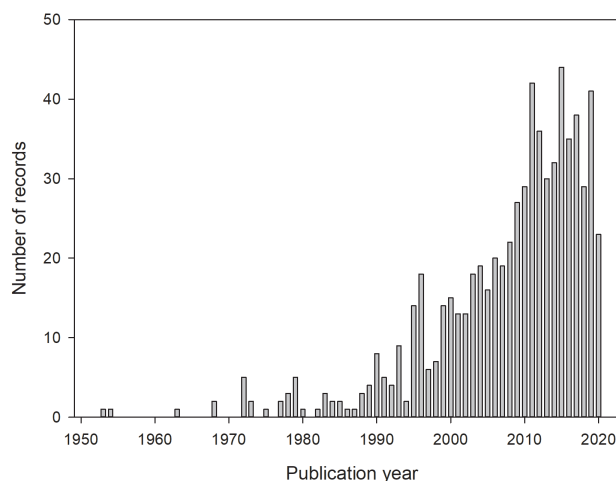
- Volume and growth of publications related to resistance bacteria on periodontal disease.
- Subject areas related to resistance bacteria on periodontal disease.
- Co-occurrence keyword network visualization.
- Co-occurrence keyword overlay visualization.
- Most active countries and institutions.

## RESULTS

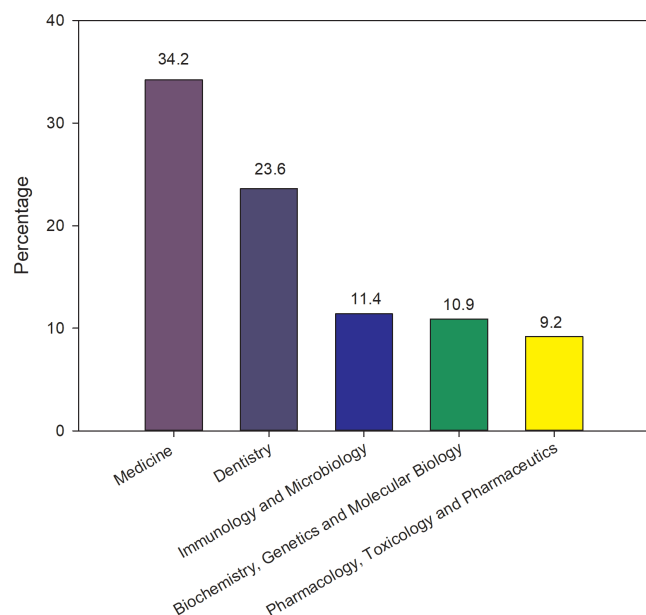
A total of 688 documents related to resistance bacteria on periodontal disease were indexed in the Scopus database between 1953 and May 25, 2020. Figure 1 shows the evolution of the number of publications in this field. It is evident how the number of publications per year has been growing over time in this discipline, having peaks of ascent marked in the years 1990, 2008, and 2014, where historically there have been findings of great value for periodontics (Fig. 1).

Areas of knowledge related to publications about resistance to antimicrobials in periodontal diseases are (i) Medicine, (ii) Dentistry, and (iii) Immunology and Microbiology, and a large volume of articles are published in medicine journals (Fig. 2).

When analyzing the co-occurrence of keywords network, four well-defined clusters resulted, corresponding to infection (yellow), disease (blue), microbiology (red), and treatment (purple, red, and green) (Fig. 3a).



**Figure 1.** Evolution of published studies related to antibiotic and periodontitis between 1948 and May 25, 2019.



**Figure 2.** Summary of publication grouped by areas on the field of resistance bacteria on periodontal disease studies between 1953 and May 25, 2020.

Regarding the time window of publications about bacterial resistance in periodontal diseases, it is observed how knowledge evolves over time and how the topics, in which researchers are concentrated in their research, change (Fig. 3b). From 2004 to more recent years such as 2015, it is noticed how at the beginning of the period they addressed issues related more to interventions, toward the middle of the period the research focuses more on the understanding of the disease and its associated factors. Afterwards (toward the end of the time window), it is seen how the different types of disease are analyzed and the most consistent therapeutic approaches with the different diagnoses were analyzed, also considering the endodontic-periodontal relationship between endodontic-periodontal lesions.

Table 1 shows the top 10 most presented keywords according to their frequency in the publications. Periodontal diagnosis in its variety of forms is the most frequent keyword, followed by words related to both the microbiota and the adjuvant antibiotic therapies.

Collaboration networks of countries with studies about resistance bacteria on periodontal disease are shown in Figure 4. The United States was the largest and most important node (Fig. 4a). Even though the United States was one of the countries that concentrated the studies in 2006, India, South Korea, Egypt, Saudi Arabia, and China were the leading countries between 2012 and 2014 (Fig. 4b). Besides, the United States, Germany, the United Kingdom, and Switzerland had the strongest collaboration network.

## DISCUSSION

The initial publications about antibiotic resistance and periodontal disease emerged in the late 1970s and early 1980s when anaerobic culture and techniques of determination of antibiotic susceptibility allowed elucidating the relationship

between microorganisms present in the subgingival plaque (Genco, 1981) and the onset and progression of periodontal disease were established (Feres *et al.*, 2015; Haffajee, 1994; Socransky *et al.*, 1998).

Around the year 1990, a first strong rise in publications related to antibiotic resistance of periodontopathic bacteria was presented, probably for two reasons: the publication of the first clinical consensus on periodontics follow-ups in the Workshop of the American Association of Periodontology (Periodontology, 1989) and in the following years the evidence of improvement in clinical markers such as clinical insertion levels as an indicator of success when nonsurgical root therapy was accompanied with systemic antibiotic therapy in patients with periodontitis (Aimetti *et al.*, 2012; Guerrero *et al.*, 2005; Preus *et al.*, 2013; Zandbergen *et al.*, 2013). Another peak of ascent in the publications was presented in 2008, and apparently, they are related to the evolution toward specific therapy with amoxicillin and metronidazole as drugs with greater effectiveness as adjuvants in periodontal therapy (Berglundh *et al.*, 1998; Guerrero *et al.*, 2005; Sgolastra *et al.*, 2012; Winkel *et al.*, 2001; Zandbergen *et al.*, 2013). A final peak occurs around the year 2014 where the use of advanced molecular analysis techniques allowed the drastic increase in publications that enrich the knowledge mainly aimed at understanding more precise aspects of the pathogenesis of the disease, advances in support diagnosis techniques, and studies of the effectiveness of clinical treatments (McGowan *et al.*, 2018).

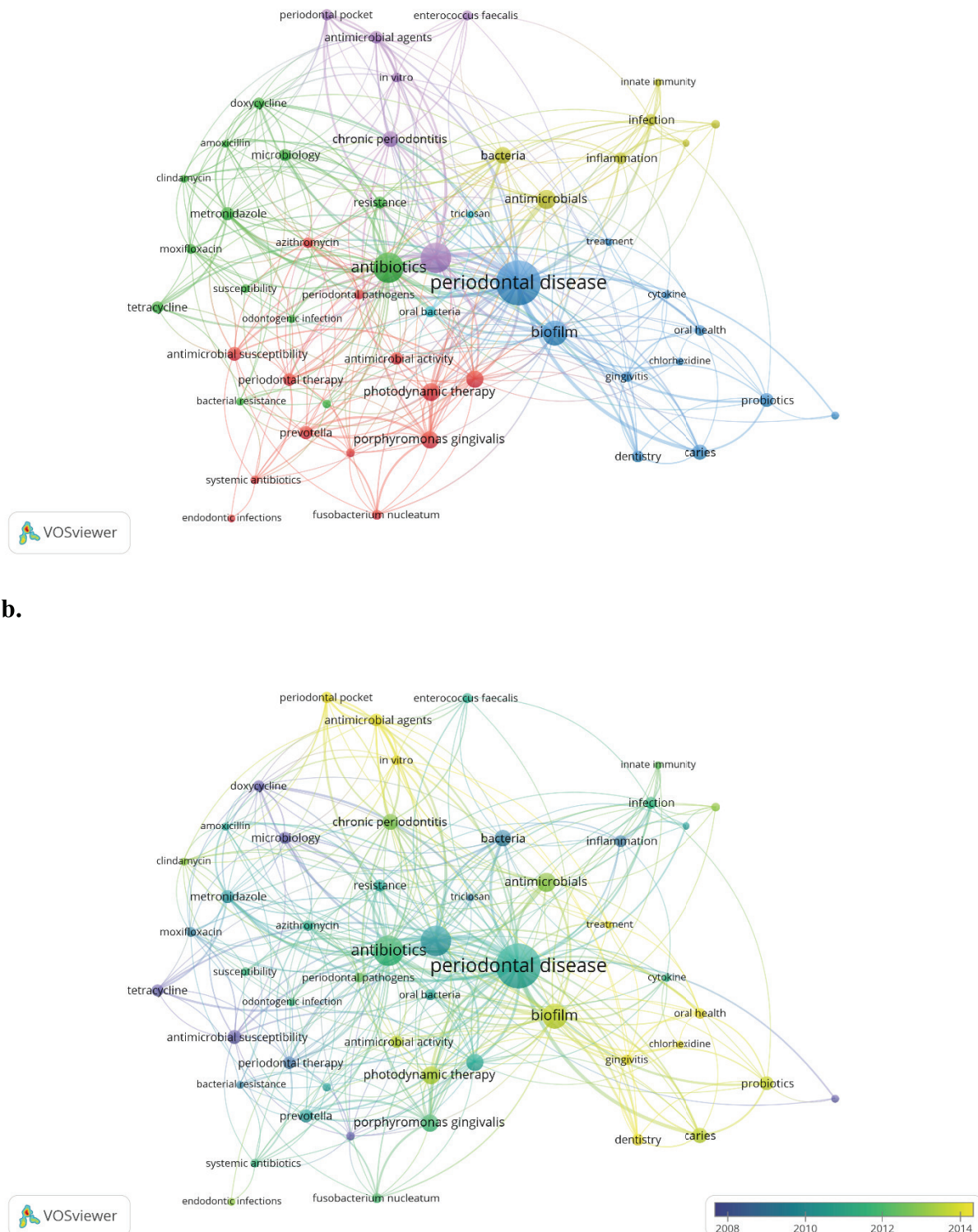
The analysis of the different areas in which the articles related to resistance bacteria on periodontal disease are published confirms the link between oral and systemic health and the relevance of the concept of periodontal medicine coined by Offenbacher (1996). This led to a large number of publications about the medical implications of periodontal infection at the systemic level. This also prompted research on the indiscriminate use of antibiotics as adjuncts to periodontal mechanical therapy, and it has been widely discussed as a topic of interest that links the basic with the clinical sciences in periodontology (Mahuli *et al.*, 2020).

The clusters of keywords network identified as infection, disease, microbiology and treatment show an idea of the perspectives from which the different problems surrounding this discipline and its clinical management are addressed and analyzed. Pathogenesis, diagnostics, prognosis, and treatment of periodontal diseases are topics addressed by the global workshops on periodontal diseases that are held regularly (Papapanou *et al.*, 2018).

The high occurrence of the term *P. gingivalis* found (Table 1) was expected, since the mentioned bacteria have been reported as a principal member of the red complex, a microbial cluster implicated in the etiology of periodontal disease (Haffajee, 1994; Haffajee and Socransky, 2005). Additionally, metronidazole and amoxicillin appeared as the main adjunct therapy to prevent or reduce the pathology progression (Berglundh *et al.*, 1998; McGowan *et al.*, 2018). Periodontal diseases associated with bacteria such as *P. gingivalis*, *A. actinomycetemcomitans*, and *Prevotella intermedia/nigrescens* exhibited variable susceptibility to antimicrobials, finding more resistance strains to metronidazole and amoxicillin (Ardila *et al.*, 2010; Jaramillo *et al.*, 2005).



**b.**



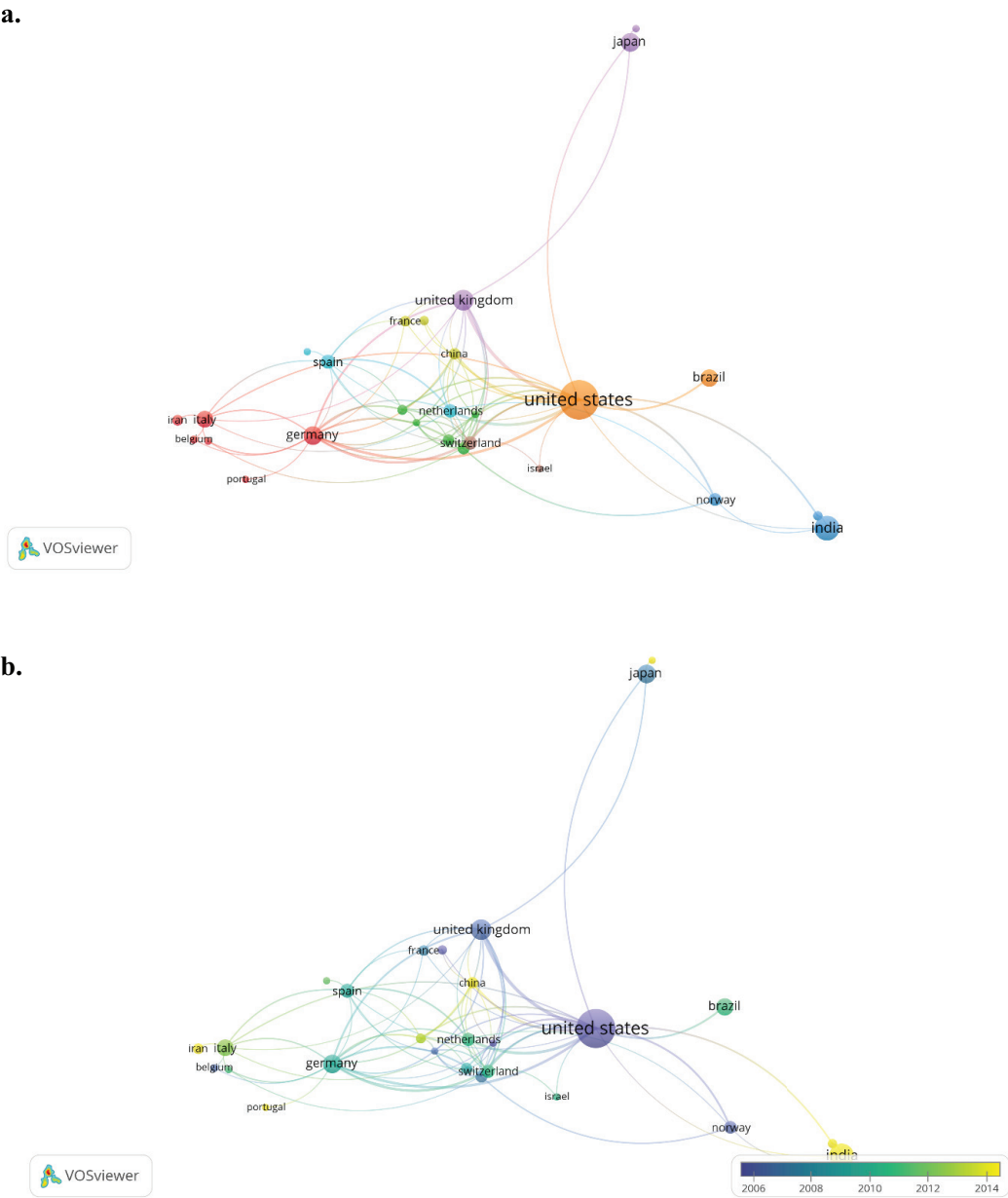
against periodontal pathogens such as *P. gingivalis* and *A. actinomycetemcomitans* (Peron *et al.*, 2019). The use of probiotics containing lactobacilli or streptococci to model the periodontal

**Table 1.** Top 10 author keywords of resistance bacteria on periodontal disease studies between 1953 and May 25, 2020.

Rank	Keywords	Occurrences
1	Periodontitis/periodontal disease/periodontal diseases	150
2	Antibiotic resistance/antimicrobial resistance/drug resistance	60
3	Antibiotics	52
4	Biofilm/biofilms	41
5	<i>P. gingivalis</i>	22
6	<i>A. actinomycetemcomitans</i> / <i>Actinobacillus actinomycetemcomitans</i>	22
7	Bacteria	20
8	Chronic periodontitis	18
9	Photodynamic therapy	16
10	Probiotics	14

microbiota in order to favor colonization by commensal bacteria has had positive effects on the control of the clinical parameters of periodontitis (Matsubara *et al.*, 2016).

Figure 4 shows an overview of the knowledge networks around the world in the investigation of periodontal disease. The United States is shown as a central object of research networks and publications on this subject. In South America, Brazil appears as the main contributor of research, but Chile and Colombia also appear as part of the network. There are also important research networks with several European countries such as Switzerland, Italy, Germany, and the United Kingdom. In terms of networks with the Asian continent, countries such as Japan, India, and China can be also observed with less participation.



**Figure 4.** Countries collaboration network of resistance bacteria on periodontal disease studies between 1953 and May 25, 2020. (a) Network visualization. (b) Overlay visualization. Countries contributing to a minimum number of both documents and citations of five.

## CONCLUSION

Studies related to bacterial resistance to periodontal disease have been on the rise continuously from the 1970s to the present time. In this sense, the main areas of this topic were (i) Medicine, (ii) Dentistry, and (iii) Immunology and Microbiology, where the studies were focused mainly on the following clusters: infection, disease, microbiology, and treatment. The antibiotics mostly used (as adjunct therapy) to prevent or reduce periodontal disease were metronidazole and amoxicillin but *P. gingivalis*, *A. actinomycetemcomitans*, and *P. intermedia/nigrescens* exhibited resistance to these antibiotics probably due to their excessive use. Additionally, the countries that published the most studies on antimicrobial resistance in periodontics and had the strongest collaboration network were the United States, Germany, the United Kingdom, and Switzerland.

## ETHICAL APPROVAL

This article does not contain any studies with human participants or animals performed by any of the authors.

## INFORMED CONSENT

For this type of study, formal consent is not required.

## AUTHORS' CONTRIBUTIONS

Natalia Aragón, Adriana Jaramillo-Echeverry, and Howard Ramírez-Malule contributed to conceptualization; Howard Ramírez-Malule contributed to methodology and supervision; Natalia Aragón and Adriana Jaramillo-Echeverry contributed to formal analysis and investigation, writing and preparation of the original draft, and writing, review, and editing.

## CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

## FUNDING

Funding information is not applicable. No funding was received.

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**How to cite this article:**

Aragón N, Jaramillo-Echeverry A, Ramirez-Malule H. Bibliometric analysis of bacterial resistance on periodontal disease. *J Appl Pharm Sci*, 2021; 11(04):118–124.