

Mapping the Landscape of Clinical Trials on Oral Biofilm: A Bibliometric Analysis

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ABSTRACT

Oral biofilms, complex communities of bacteria, contribute to the development of dental caries, periodontal disease, and other oral infections. Research on oral biofilms is crucial due to their significant impact on dental and overall health. This bibliometric analysis examines trends in clinical trials focused on oral biofilm, utilizing PubMed data from 1994 to 2024. The number of publications on this topic has steadily increased, reflecting ongoing research interest and activity. Notably, the leading authors in this field include Cury JA and Del Bel Cury AA, who have contributed significantly to the literature. Co-authorship analysis identified distinct clusters of collaboration. Clinical Oral Investigations has published the highest number of clinical trials on oral biofilm, followed by Caries Research and the Journal of Clinical Periodontology. The analysis also reveals that Brazil leads in scientific production, followed by the United States, Italy, and China, indicating a global research effort in understanding and managing oral biofilms. Keyword cooccurrence analysis identified several clusters focusing on various aspects of oral biofilm, including microbiology, treatment outcomes, and preventive measures. Over the years, research has evolved from pharmacological interventions to advanced methodologies like image processing and computer-assisted analysis. Notable trends include a focus on bacterial adhesion, dental plaque microbiology, and the efficacy of biofilm treatments. Recent studies have also explored novel agents such as probiotics and chlorhexidine, suggesting ongoing innovation in biofilm management strategies. Overall, this analysis underscores the dynamic nature of oral biofilm research, broadening the scope of topics and methodologies to enhance oral health outcomes through preventive and therapeutic approaches.

Keywords

Oral biofilm, Clinical trials, Bibliometric analysis, PubMed, Publication trends, Authorship characteristics, Collaboration networks, dental biofilm, scientometric analysis

INTRODUCTION

The oral cavity harbors a complex ecosystem of microorganisms, among which oral biofilms play a pivotal role. It forms when salivary glycoproteins create a pellicle layer on the teeth, which bacteria colonize, developing into structured microcolonies over time. Initial bacterial adhesion is reversible, primarily involving electrostatic and physical forces, with early colonizers like *Streptococcus* and *Actinomyces* binding to the pellicle and secreting extracellular polysaccharides (EPS) for stronger attachment. As the biofilm matures,

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coaggregation occurs, where later colonizers like *Fusobacterium nucleatum* adhere to early colonizers. The biofilm develops into a complex, multi-layered structure with channels for nutrient exchange and waste removal, ensuring sustainability.

Metabolic cooperation within the biofilm involves EPS, oxygen exchange, and pH regulation, which are essential for survival and nutrient access¹. This biofilm offers a protective environment for the bacteria, making them more resistant to antimicrobial treatments and the body's immune responses due to EPS. Eventually, clusters of bacteria can detach from the mature biofilm and spread to other areas of the mouth, perpetuating the cycle. Nutrient availability, saliva flow, and the host immune response influence this dynamic process. While oral biofilms are essential for maintaining oral health, dysbiosis within these communities can lead to various pathological conditions, including dental caries, periodontal diseases, and peri-implantitis. Bacterial species compete for limited space and nutrients in biofilms, each employing unique strategies to dominate. *Streptococcus mutans*, a key player in dental caries, inhibits several other *Streptococcus* species through acid production and mutacin excretion. *Streptococcus sanguinis*, beneficial in the oral ecosystem, counters *S. mutans* via hydrogen peroxide production, which inhibits glycolysis and protein synthesis in competitors. *Streptococcus gordonii* and *Streptococcus oralis* also inhibit *S. mutans* through hydrogen peroxide but are less effective than *S. sanguinis*. Other species like *Porphyromonas gingivalis* and *Fusobacterium nucleatum* engage in symbiotic relationships, aiding each other's growth, while *Lactobacillus* species produce acids and bacteriocins to outcompete others. Interactions in biofilms are complex, with antagonistic and cooperative relationships shaping the microbial community¹. Current methods include alkaline peroxides in denture cleaning tablets, which generate hydrogen peroxide and active oxygen to reduce biofilms. Antiplaque oral rinses, such as chlorhexidine gluconate and essential oils, are effective² but may have side effects, while herbal-based rinses offer natural alternatives. Investigational strategies involve bacteriophages^{3,4}, antimicrobial peptides^{5,6}, and quorum-sensing inhibitors⁷, each uniquely targeting biofilms. Advanced analytical methods, such as the

microwell plate assay, Calgary device, BioFlux system, confocal laser scanning microscopy, and atomic force microscopy, are crucial for studying biofilm growth and developing effective treatments⁸.

Understanding the dynamics of oral biofilms and their implications for oral health necessitates a comprehensive analysis of the scientific literature. Bibliometric analysis offers a systematic approach to scrutinizing the extensive body of research on this topic, providing insights into publication trends, influential authors, key research topics, and collaborations within clinical trials.

In this paper, we embark on a bibliometric journey to explore the landscape of clinical trials focused on oral biofilms. By employing bibliometric techniques, we aim to uncover patterns and trends that characterize the scientific endeavor in this domain. Such analysis sheds light on the current state of research and identifies potential avenues for future investigations and interventions in preventing and managing oral biofilm-related diseases.

MATERIALS AND METHODS

Database and Search Strategy

The bibliometric analysis was conducted using the PubMed database, a comprehensive repository of scientific literature spanning various disciplines. The search was performed on May 24, 2024, to retrieve relevant clinical trials on oral biofilms published in English. The search terms used were oral biofilms. The inclusion criteria for selecting studies were clinical trials published in English, focusing on oral biofilms. Exclusion criteria were established: publications other than clinical trials, such as review articles, editorials, and conference abstracts. All identified records were initially exported in a text file for further analysis. All the articles were screened manually based on their titles and abstracts to assess their relevance to the topic. Two independent reviewers performed the screening and selection process, with any disagreements resolved through discussion or consultation with a third reviewer if necessary. The study selection process is in a flow chart according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines⁹. This flowchart depicts the number of records identified, screened, assessed for eligibility, and included in the final analysis, along with the reasons for exclusion at each stage.

Bibliometric Analysis

Bibliometric analysis was conducted using several software tools, including Biblioshiny¹⁰, Vosviewer¹¹, Biorender¹², and Microsoft Excel. Data extraction from the selected studies was done using Biblioshiny software, which extracted the following information: title of the study, authors, journal name, publication year, study design, country of origin, and abstract. The bibliometric tools were utilized to examine various aspects of the literature, including publication trends, authorship characteristics, and collaboration networks. Descriptive statistics and graphical representations were used to summarize and visualize the findings.

Ethical Considerations

This bibliometric analysis used existing data from publicly available sources and did not involve human subjects. Therefore, ethical approval was not required for this study.

RESULTS

Search results- A total of 7260 results were initially identified. After applying the English language filter, 7082 results remained. From these, the distribution was as follows: 17 comments, 21 editorials, 32 observational studies, 98 case reports, 495 clinical trials, 1195 reviews, and 1 book (Figure 1). Upon manual inspection, 4 clinical trial protocols were excluded, leaving 491 clinical trials.

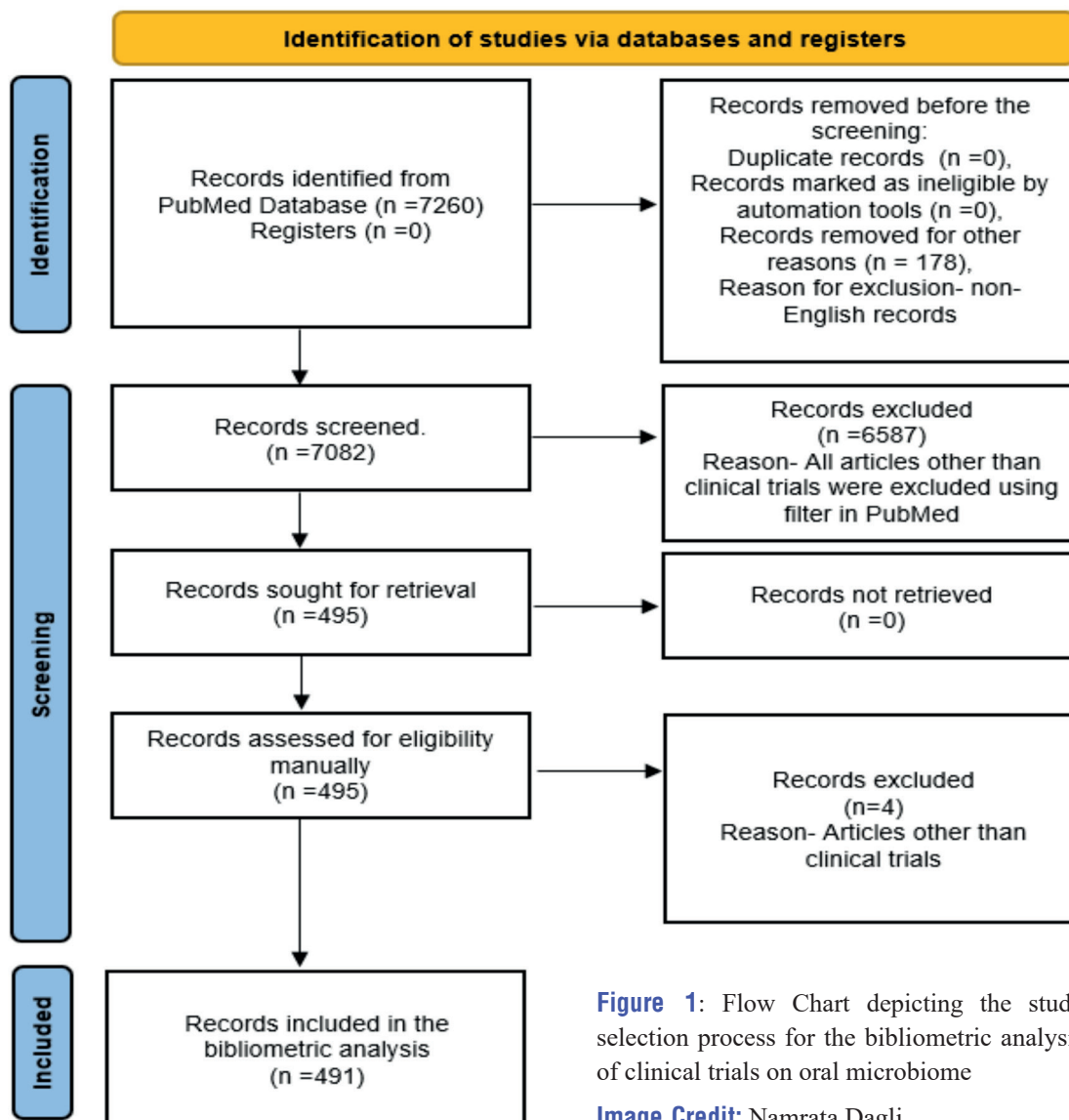


Figure 1: Flow Chart depicting the study selection process for the bibliometric analysis of clinical trials on oral microbiome

Image Credit: Namrata Dagli.

Main Information

The dataset spans from 1994 to 2024, encompassing 491 documents sourced from 147 journals, books, and other references. The annual growth rate of the papers is 9.45%, with the average age of the documents being 9.11 years. Each document references only one source on average. A total of 2042 Keywords were identified. The dataset includes contributions from 2313 authors, none of whom have single-authored documents. Collaboration is prevalent, with an average of 6.02 co-authors per document and 15.68% of the documents involving international co-authorships.

Publishing Trends

The number of clinical trials published in the PubMed database on oral biofilm has shown a marked increase over the years. Starting with a single publication each

year from 1994 to 1997, there was a brief period in 1998 where no articles were published. A gradual increase followed this in the number of articles. From 2004 onwards, the trend continued upward with 6 articles per year in 2004 and 2005, and 7 in 2006. A substantial surge occurred in 2007, with 16 published articles, which rose to 17 in 2008 and 2009. The number of publications fluctuated slightly in the following years but remained relatively high, peaking at 23 articles in 2011 and 31 in 2012. After a slight dip to 28 in 2013, the publications peaked at 40 in 2015. Although there was some variability from 2016 to 2024, the overall trend remained upward, with the number of articles consistently staying above 20 each year and reaching another peak of 35 in 2023. As of 2024, 15 articles have been published, reflecting ongoing research interest and activity in this area (Figure 2).

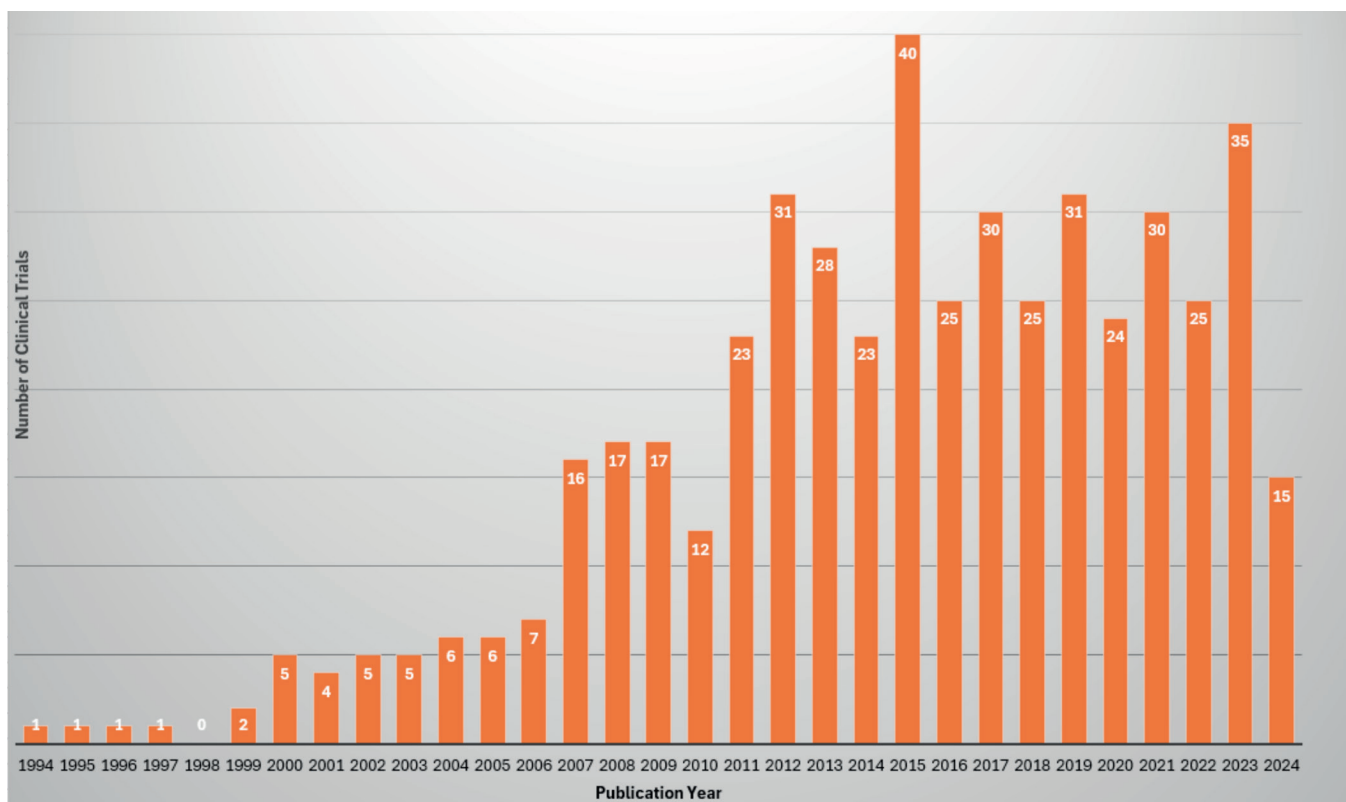


Figure 2: Annual scientific publications of clinical trials on oral biofilm.

Image Credit: Namrata Dagli.

Most relevant authors

Cury JA has been identified as the leading author in publishing clinical trials on oral biofilm, followed by

Del Bel Cury AA. The top ten authors have contributed 118 articles, accounting for 24.03% of the publications. The leading two authors alone have contributed 31.36% of the publications among the top ten (Figure 3).

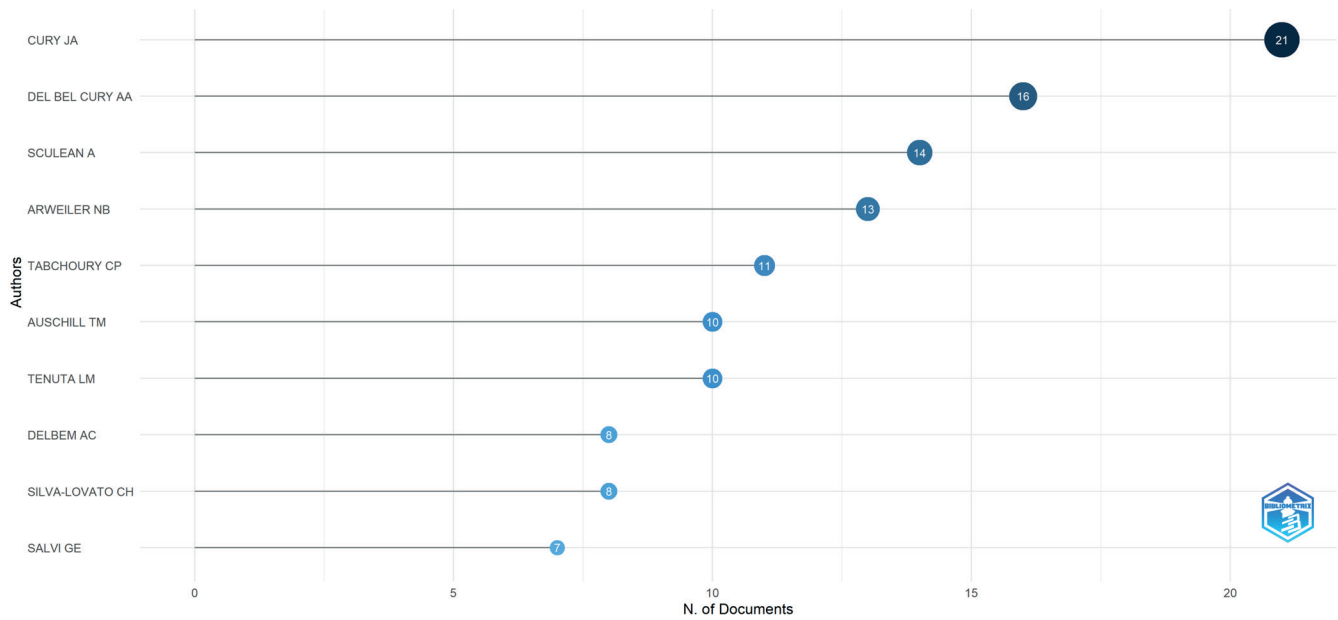


Figure 3: Most Relevant Authors based on the number of published clinical trials in PubMed.

Image Credit: Namrata Dagli

Co-authorship Analysis

The analysis by VOSviewer identified 2475 authors, of which 287 met the threshold of 2 publications. For each of the 287 authors, the total strength of coauthorship links was calculated, and the network visualization

was generated, which included the largest group of 53 connected items spread across 9 clusters with 139 links and 260 total link strength (TLS). (Figure 4) Sculean Anton has the highest TLS of 47, followed closely by Cury JA with a TLS of 45.

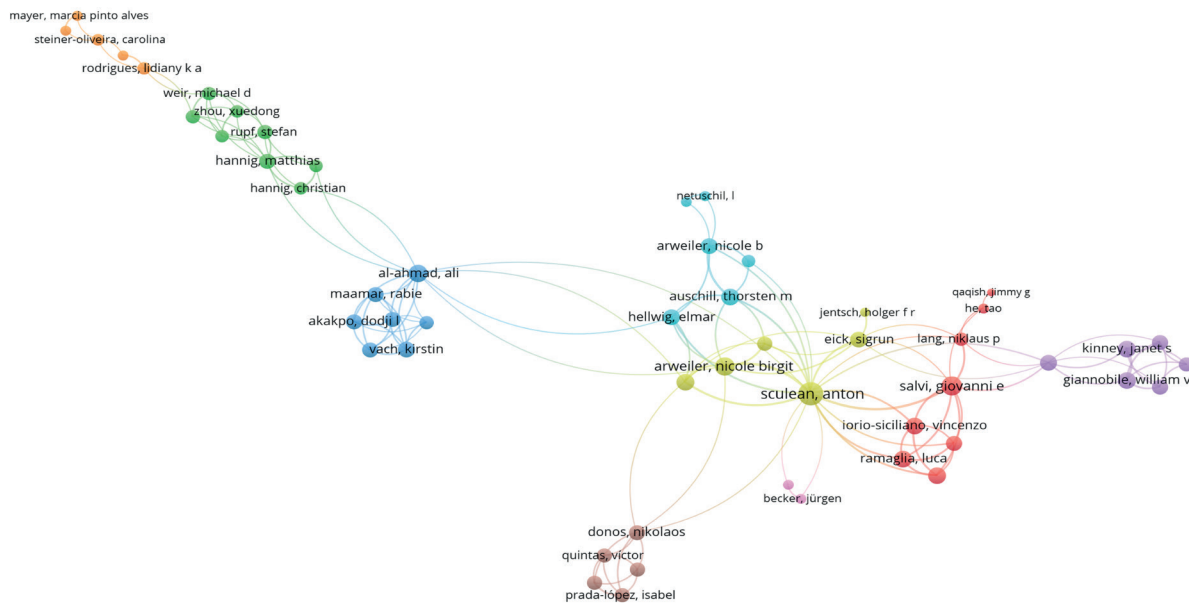


Figure 4: Co-authorship analysis of authors of clinical trials on oral biofilm

Image Credit: Namrata Dagli.

Temporal Analysis of Authors' Productivity

The dataset presents information on the frequency of clinical trials related to oral biofilm published in the PubMed database. The data spans several authors and years, detailing the frequency of publications (freq) each year. For example, Salvi GE has published one clinical trial in 2004, 2009, 2012, 2013, 2020, 2021, and 2023. Similarly, Silva-Lovato CH has multiple publications from 2007 to 2021, with some years having more than

one publication. Delbem AC and Tenuta LM have also published various publications over the years. Authors like Auschill TM, Tabchoury CP, Arweiler NB, Sculean A, Del Bel Cury AA, and Cury JA have contributed significantly over the years, with some years showing higher publication frequencies. This indicates a steady interest and ongoing research activity in oral biofilm among these authors within the PubMed database (Figure 5).

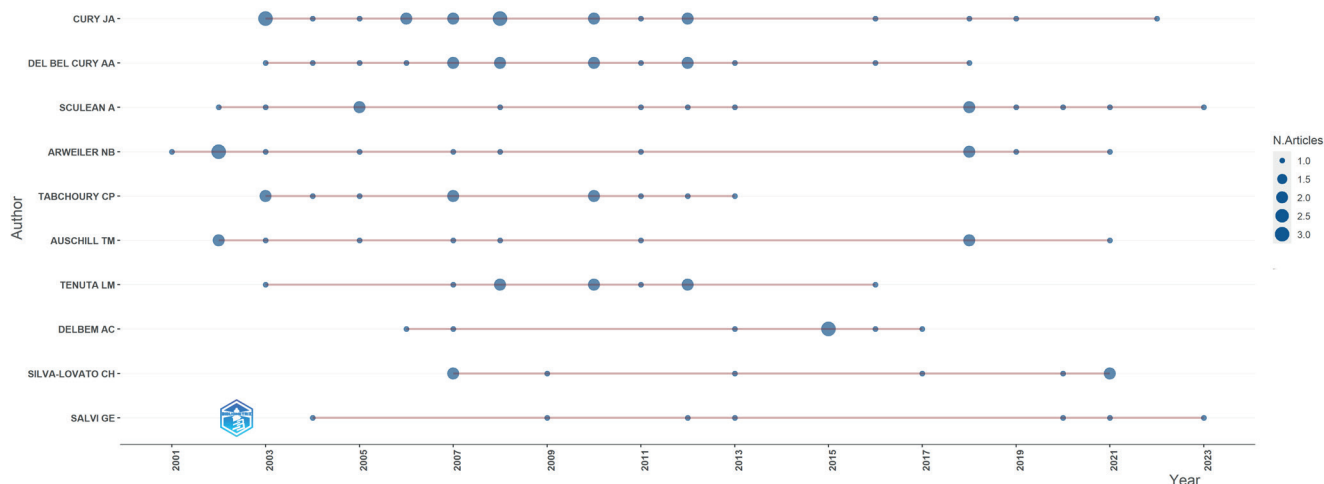


Figure 5: Temporal analysis of authors' productivity in publishing clinical trials on oral biofilm.

Image Credit: Namrata Dagli.

Most Relevant Journals

Clinical trials on oral biofilm have been extensively documented in various scientific journals. Among these, "Clinical Oral Investigations" leads with 47 articles, strongly emphasizing exploring the clinical implications and management strategies for oral biofilm. "Caries Research" follows with 27 articles, indicating significant interest in the role of biofilm in the development and prevention of dental caries. The "Journal of Clinical Periodontology" and the "Journal of Periodontology" contribute 23 and 22 articles, respectively, highlighting their focus on the periodontal aspects of biofilm, such as its impact on gum health and periodontal disease. The "International Journal of Dental Hygiene" has 19 articles underscoring the importance of biofilm control in maintaining oral hygiene.

Meanwhile, the "Journal of Dentistry" features 18 articles covering a broad spectrum of biofilm-related dental research. "The Journal of Clinical Dentistry" has 15 articles that suggest a practical approach to clinical

applications and treatments. "Brazilian Oral Research" and "Oral Health & Preventive Dentistry" each contribute 14 articles, showing a diverse geographic and preventive perspective on biofilm research. Lastly, the "Journal of Endodontics," with 13 articles, highlights the relevance of biofilm in endodontic infections and treatments. This distribution of articles across various journals indicates a comprehensive and multidisciplinary interest in oral biofilm research, encompassing clinical, preventive, and therapeutic dimensions (Figure 6).

Temporal Analysis of Journals' Production Over Time

Over the past three decades, clinical trials focusing on oral biofilm have significantly increased publications across several vital journals. In 1994, no clinical trials were published on this topic in the selected journals. The first such research was published in the Journal of Clinical Periodontology in 1996 with a single study. Subsequently, the Journal of Periodontology followed suit in 1997. The number of publications remained

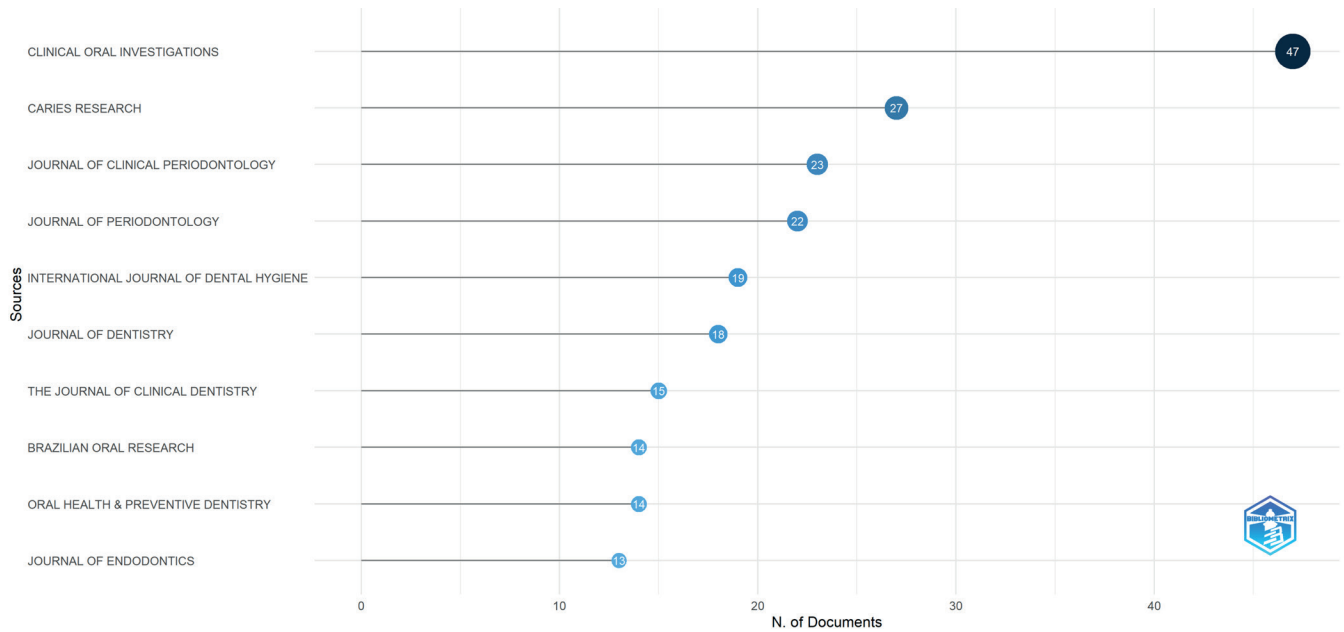


Figure 6: Most relevant journals based on the number of published clinical trials on oral biofilm in PubMed.

Image Credit: Namrata Dagli

relatively low and stable in these journals until the early 2000s.

From 2002 onwards, a gradual increase was noticed in the volume of clinical trials, with the Journal of Clinical Periodontology leading the way, reaching 5 publications in 2002. The Journal of Periodontology also began to show more activity around this time. By

2005, both journals had published few studies annually, with the Journal of Clinical Periodontology reaching 9 studies and the Journal of Periodontology publishing 3 studies. The upward trend continued through the 2010s, with notable increases across all journals. By 2013, the Journal of Clinical Periodontology reached 14 publications, while the Journal of Periodontology had

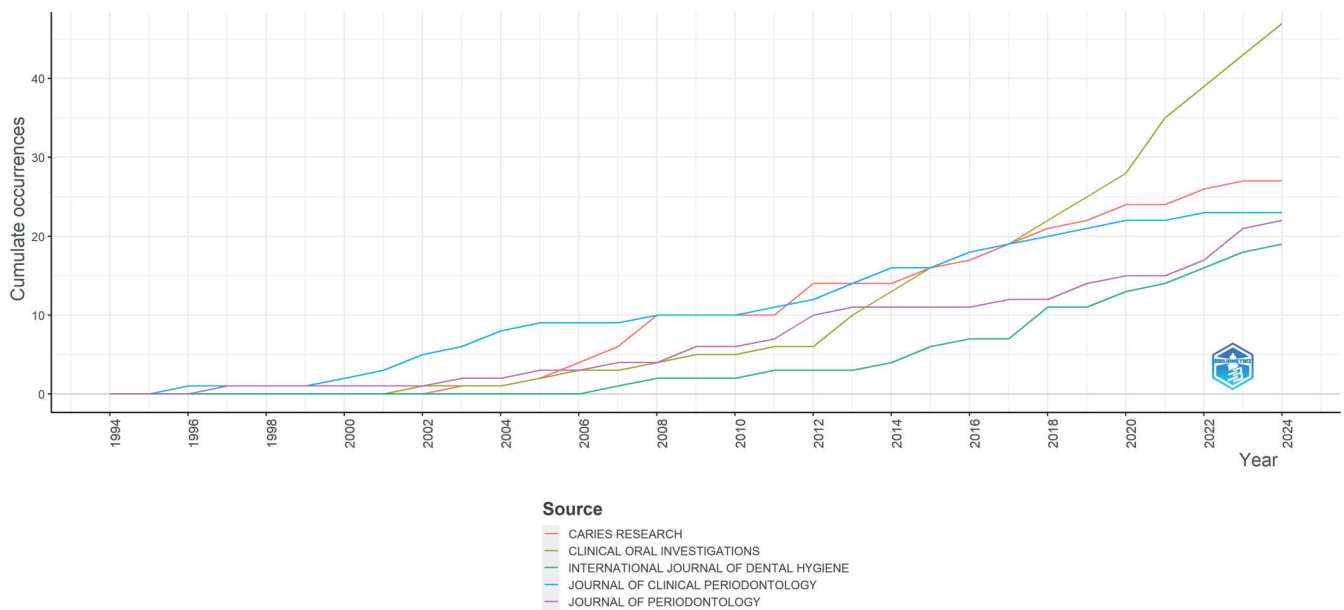


Figure 7: PubMed published clinical trials on oral biofilm over time.

Image Credit: Namrata Dagli.

11. Other journals, such as *Clinical Oral Investigations* and *Caries Research*, markedly increased publications. The 2020s have seen a dramatic rise in clinical trials published on oral biofilm. By 2024, *Clinical Oral Investigations* had reached 47 publications, *Caries Research* had 27, and the *Journal of Clinical Periodontology* maintained a steady output with 23 publications. The *Journal of Periodontology* and the *International Journal of Dental Hygiene* also increased, with 22 and 19 publications, respectively. This data highlights a growing recognition of the importance of oral biofilm research and its implications for dental health, as evidenced by the increasing number of clinical trials across these prominent journals (Figure 7).

Most Relevant Countries

Clinical trials published on PubMed focusing on oral biofilm span various countries, with Brazil leading

significantly with 530 studies. The United States is the second most prolific country, with 210 trials, reflecting its substantial contributions to this area of research. Italy and China also show considerable activity with 128 and 122 trials, respectively, highlighting their growing focus on oral health and related microbial studies. Germany contributes 113 trials, while Sweden adds 77, indicating a strong interest in European oral biofilm research. Canada and Australia, with 55 and 53 trials, respectively, are also active in this domain, emphasizing the global interest in understanding and managing oral biofilms. India and the Netherlands each contribute 48 trials, further diversifying the geographical landscape of this research field. This distribution underscores the widespread recognition of oral biofilm's significance in dental health and the collaborative international effort to advance knowledge and treatment strategies in this area (Figure 8).

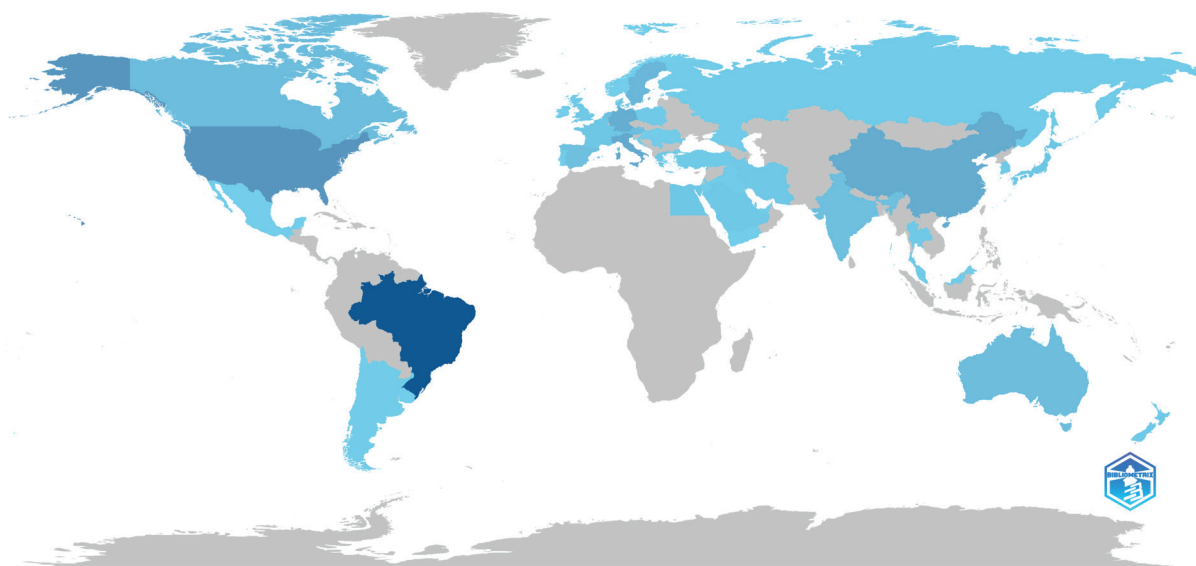


Figure 8: Scientific production of countries. **Image Credit:** Namrata Dagli.

Collaboration Frequency of Corresponding Author's Countries

The analysis of clinical trials on oral biofilm published in PubMed reveals distinct patterns across various countries. Brazil leads significantly with 125 articles, most of which are single-country publications (SCP) at 109, while multi-country publications (MCP) are 16. The United States follows with 48 articles, predominantly SCP (42) and 6 MCPs. Italy, with 24 articles, has 17 SCPs and 7 MCPs. Germany exhibits

a similar pattern, with 23 articles comprising 17 SCPs and 6 MCPs. China, with 19 articles, has 16 SCPs and 3 MCPs. Sweden, India, Canada, and the Netherlands have fewer articles, with Sweden producing 14 articles (11 SCPs and 3 MCPs) and India contributing 12 articles (9 SCPs and 3 MCPs). Canada has 11 articles, split into 7 SCPs and 4 MCPs. The Netherlands, with the least number of articles (7), includes 5 SCPs and 2 MCPs. The data reflects Brazil's dominance in the field, with varying degrees of international collaboration among other countries (Figure 9).

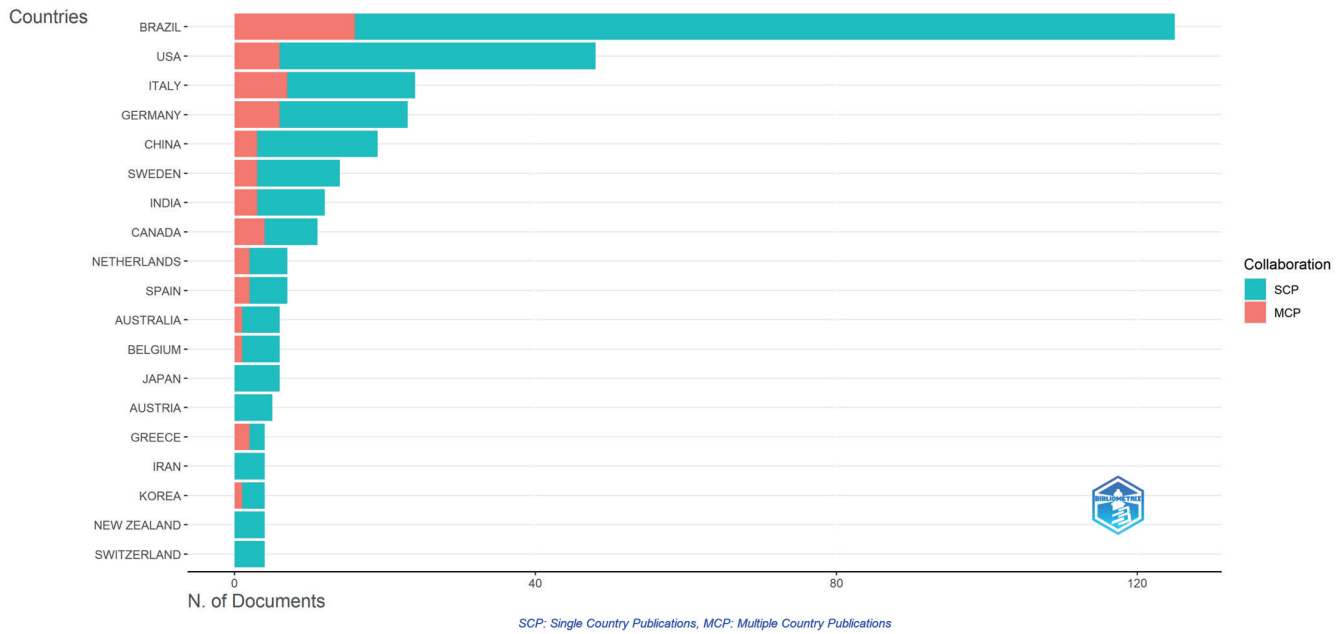


Figure 9: collaboration frequency of the most relevant countries
Image Credit: Namrata Dagli.

Temporal Analysis of Production of Countries

The number of published clinical trials on oral biofilm in PubMed has shown significant growth across several countries from 1994 to 2024. In the United States, the data starts in 1994 with no articles and shows a steady increase, reaching 210 articles by 2024. The most

notable jumps occurred after 2010, with articles rising sharply from 14 in 2010 to 180 in 2023, indicating an increasing focus on this topic. Italy’s publication count remains low and stable from 1994 until 2007, with minimal increases. However, from 2014 onwards, there is a marked rise, culminating in 128 articles by 2024, suggesting a growing research interest in oral biofilm

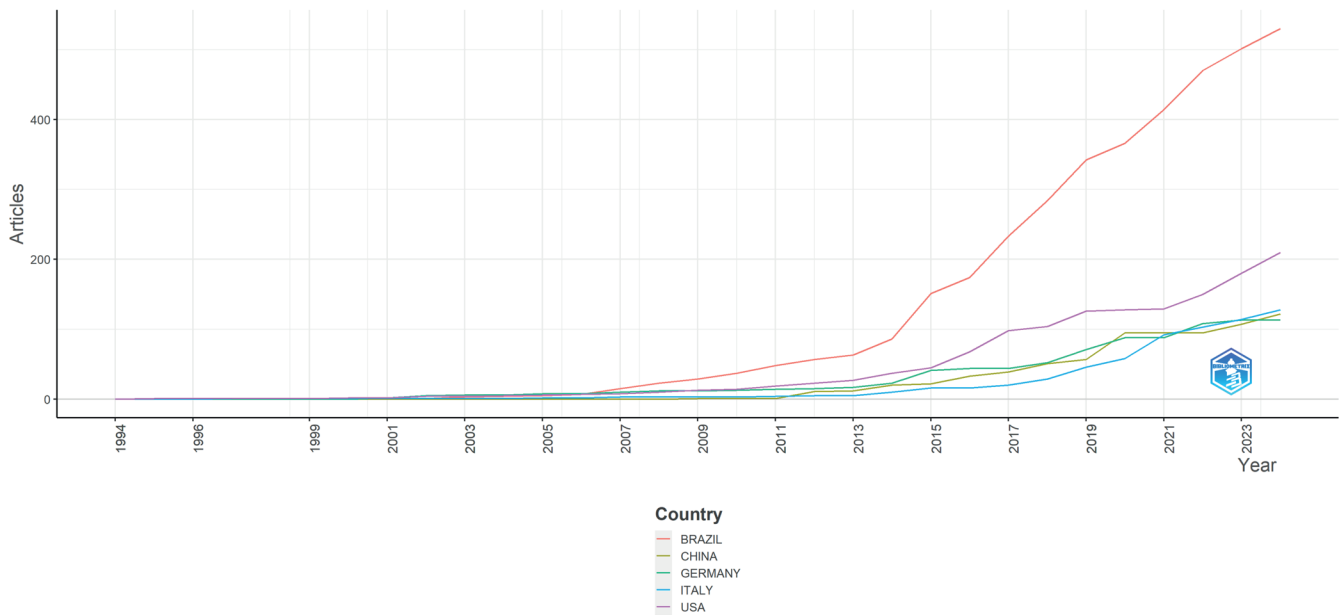


Figure 10: The scientific production of countries over time on oral biofilm. **Image Credit:** Namrata Dagli.

in recent years. Brazil exhibited a dramatic increase in publications, from no articles in 1994 to a significant rise in the early 2000s, and an exponential growth particularly noticeable after 2010. By 2024, Brazil will reach 530 articles, the highest among the countries listed, reflecting a robust expansion in research output. Germany has shown gradual growth since 2001, with a noticeable increase beginning in 2014. The number of publications will rise steadily to 113 by 2024, illustrating a consistent, though less dramatic, increase compared to Brazil. China's data began to appear in 2009, and the growth was relatively slow initially. However, starting in 2012, there has been a rapid rise in the number of publications, with a significant jump observed after 2015. China will reach 122 articles, indicating an accelerating interest in this research area

in the recent decade by 2024. Overall, the trend across all these countries indicates a significant and growing interest in the study of oral biofilm, with Brazil and the United States leading in the number of published clinical trials (Figure 10).

Cooccurrence Analysis of Keywords

VOSviewer analysis identified 1061 MeSH keywords, of which 120 were repeated at least 10 times. All these 120 items were included in generating network visualization. These keywords were spread across 6 clusters with 4248 links and 30519 Total link strength (Figure 11). The subject-specific Mesh keywords with the highest TLS value are biofilms, dental plaque, local anti-infective agents, dental plaque index, and chlorhexidine. The keywords in each cluster are listed in Table 1.

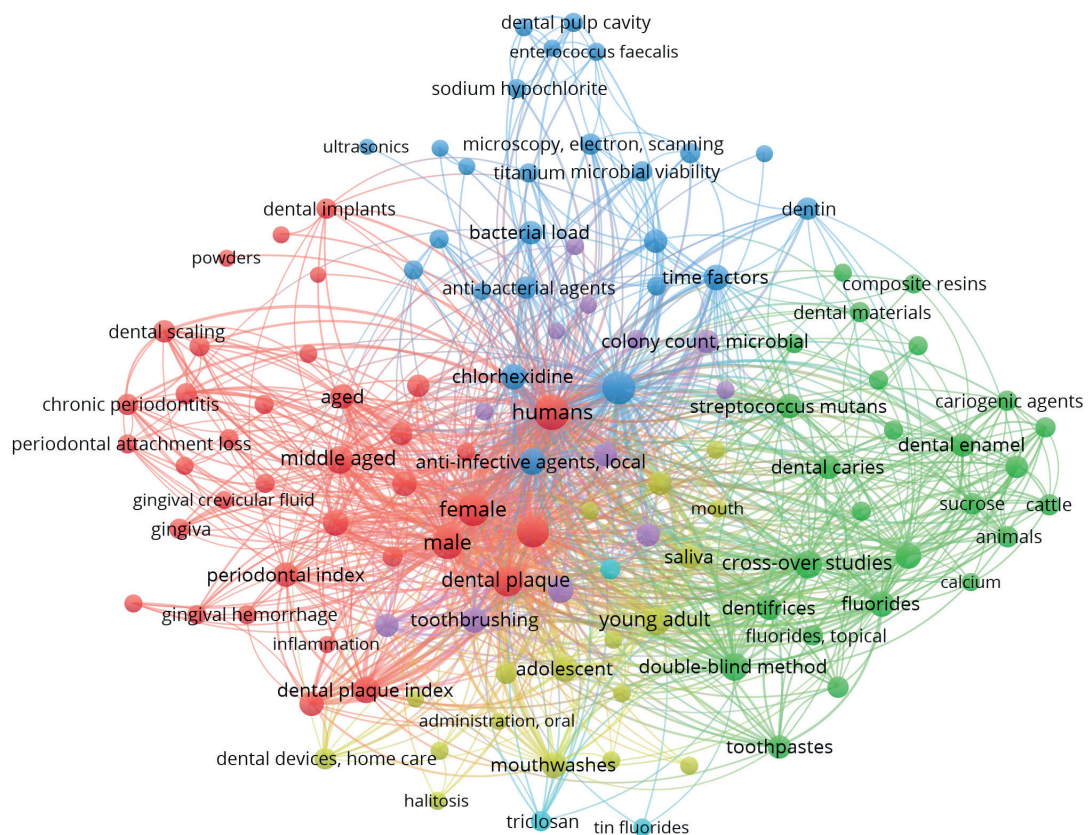


Figure 11: Cooccurrence analysis of the keywords used in the clinical trials on oral biofilm.

Image Credit: Namrata Dagli.

Table 1: MeSH keywords in each cluster identified in the cooccurrence analysis of keywords.

Serial No.	Clusters	Keywords
1	Cluster 1 (36 items)	adult, aged, <i>Aggregatibacter Actinomycetemcomitans</i> , bacteria, biomarkers, chronic periodontitis, combined modality therapy, dental implants, dental plaque, dental plaque index, dental polishing, dental scaling, female, follow-up studies, gels, gingiva, gingival crevicular fluid, gingival hemorrhage, gingivitis, humans, inflammation, male, middle-aged, peri-implantitis, periodontal attachment loss, periodontal diseases, periodontal index, periodontal pocket, periodontitis, pilot projects, <i>Porphyromonas gingivalis</i> , powders, prospective studies, root planning, treatment outcome, treponema denticola
2	Cluster 2 (26 items)	animals, calcium, cariogenic agents, cariostatic agents, cattle, composite resins, cross-over studies, dental caries, dental enamel, dental materials, dental restoration permanent, dentifrices, double-blind method, fluorides, topical fluorides, glass ionomer types of cement, hardness, hydrogen-ion concentration, <i>Lactobacillus</i> , resin types of cement, sodium fluoride, <i>Streptococcus</i> , <i>Streptococcus mutans</i> , sucrose, tooth demineralization, kinds of toothpaste
3	Cluster 3 (25 items)	anti-bacterial agents, anti-infective agents, local anti-infective agents, bacterial adhesion, bacterial load, biofilms, chlorhexidine, dental pulp cavity, dentin, enterococcus faecalis, equipment design, materials testing, microbial viability, confocal microscopy, electron scanning microscopy, molar, photochemotherapy, photosensitizing agents, root canal irrigants, root canal preparation, sodium hypochlorite, surface properties, time factors, titanium, ultrasonics
4	Cluster 4 (18 items)	administration oral, adolescent, cetylpyridinium chloride (CPC), child, child preschool, dental devices, home care, halitosis, microbiota, mouth, mouthwashes, orthodontic appliances, orthodontic brackets, placebos, plant extracts, probiotics, saliva, tongue, young adult
5	Cluster 5 (12 items)	aged 80 and over, analysis of variance, candida, colony count microbial, coloring agents, denture cleansers, denture complete, oral hygiene, single-blind method, statistics nonparametric, toothbrushing, water
6	Cluster 6 (3 items)	drug combinations, tin fluorides, triclosan

The keywords in cluster 1 suggest research in the context of clinical trials focused on various aspects of oral biofilm and periodontal health. These studies involve diverse human populations across different age groups and genders, as indicated by keywords such as “adult,” “aged,” “female,” “male,” and “middle-aged.” The research targets explicitly pathogenic bacteria associated with periodontal diseases, including *Aggregatibacter actinomycetemcomitans*, *Porphyromonas gingivalis*, and *Treponema denticola*. The studies address conditions like chronic periodontitis, gingivitis, periodontal diseases, and peri-implantitis, utilizing clinical measurements and indices such as biomarkers, dental plaque index, gingival crevicular fluid, gingival hemorrhage, periodontal attachment loss, periodontal index, and periodontal pocket to assess periodontal health and disease progression. Treatment modalities and procedures, including combined modality therapy, dental implants, dental plaque, dental polishing, dental scaling, gels, powders, and root planning, are explored to manage periodontal diseases and maintain oral health. The research involves various study designs and methodologies, such as follow-up studies, pilot projects, prospective studies, and evaluations of treatment outcomes, to determine the effectiveness of treatments and long-term results. Anatomical sites of interest, such as the gingiva, dental plaque, and periodontal pockets,

are focal points, emphasizing the inflammatory response associated with periodontal diseases. These studies aim to understand the etiology, diagnosis, treatment, and outcomes of periodontal diseases, highlighting the role of oral biofilm and bacteria.

Research involving these keywords in cluster 2 typically focuses on clinical trials investigating the prevention and treatment of dental caries and the management of oral biofilm. Studies using animals, including cattle, often serve as models for understanding the effects of various dental treatments and cariogenic agents, which promote caries’ development. Cariostatic agents, on the other hand, are investigated for their potential to inhibit caries formation. Materials like composite resins, glass ionomer types of cement, and resin types of cement are commonly evaluated for their effectiveness in dental restorations and their impact on dental enamel’s hardness and resistance to demineralization. Cross-over studies and double-blind methods ensure robust and unbiased results, often comparing treatments such as dentifrices, toothpaste, and topical fluorides like sodium fluoride. The role of hydrogen-ion concentration and the impact of dietary sugars, mainly sucrose, on oral health are also examined. The microbiological aspect focuses on cariogenic bacteria such as *Streptococcus mutans* and *Lactobacillus*, assessing how various agents affect their growth and biofilm formation. This research aims

to improve dental materials and preventive strategies to maintain oral health and combat tooth decay.

The keywords in cluster 3 indicate research on evaluating and developing effective treatments and interventions to combat bacterial infections in dental settings. This type of research investigates the efficacy of anti-bacterial and anti-infective agents, including local anti-infective agents, in reducing bacterial adhesion and bacterial load within biofilms. Biofilms, particularly those involving *Enterococcus faecalis*, are studied in various contexts, such as the dental pulp cavity and dentin. Key methods and materials are tested, such as chlorhexidine and sodium hypochlorite, which are common root canal irrigants used during root canal preparation. The impact of these agents on microbial viability is analyzed using advanced techniques like confocal microscopy and electron scanning microscopy. Furthermore, the research explores the role of equipment design and materials testing in improving treatment outcomes alongside the surface properties of dental materials, including titanium. The application of photochemotherapy and photosensitizing agents is another focal point, assessing their potential to enhance anti-bacterial effects. Additionally, the role of ultrasonics in root canal treatment and the significance of time factors in the effectiveness of various interventions are considered to optimize dental care procedures.

The keywords in cluster 4 suggest research evaluating various interventions and their effects on oral health across different age groups. These interventions include administering oral agents such as CPC and probiotics, which are investigated for their potential to alter the microbiota in the mouth, reduce halitosis, and improve overall oral hygiene. The studies likely involve diverse populations, including adolescents, children, preschool children, and young adults, to assess the effectiveness and safety of these treatments across various age demographics. Dental devices, orthodontic appliances, and orthodontic brackets are examined for their impact on biofilm formation. Additionally, the effect of saliva on biofilm formation on various oral surfaces, including the tongue, was studied. Home care practices, including mouthwashes and plant extracts, are evaluated for their efficacy in maintaining oral hygiene and preventing biofilm formation. Placebos may be used in these trials to establish the effectiveness of the tested active treatments.

The keywords in cluster 5 suggest that research should be focused on investigating the effectiveness of various oral hygiene interventions on biofilm and microbial colonies in elderly patients aged 80 and over, notably including denture cleansers and complete dentures, indicating a focus on denture wearers. *Candida* species and overall microbial colony counts are measured to evaluate the microbial load in the oral cavity. Coloring agents might be used to assess biofilm presence or distribution visually. Oral hygiene practices such as toothbrushing and using water as a cleansing agent are examined, potentially using a single-blind method to minimize bias. The study likely involves the use of analysis of variance (ANOVA) and nonparametric statistical methods to analyze data, ensuring robust and reliable results.

Keywords in cluster 6 typically focus on investigating the efficacy of various antimicrobial agents and their synergies in combating biofilm-related oral diseases. “Drug combinations” indicate studies that explore the synergistic or additive effects of using multiple antimicrobial agents simultaneously to enhance their overall effectiveness against oral biofilm. “Tin fluorides” refer to compounds used for their anti-cariogenic and antimicrobial properties, often assessed for their ability to reduce dental plaque and inhibit bacterial growth within the biofilm. “Triclosan” is an antimicrobial agent commonly studied for its effectiveness in reducing oral biofilm and preventing gingivitis. These clinical trials might indicate the comparative efficacy of these agents individually and in combination, aiming to identify the most effective treatment protocols for maintaining oral health and preventing biofilm-associated dental issues.

Trend Topic Analysis

Over the years, published clinical trials on oral biofilm in PubMed have revealed significant trends in keyword usage. Early research focused on the pharmacological and therapeutic applications of anti-infective agents and mouthwashes, with these topics frequently appearing in trials from the early 2000s (2000 to 2015). Image processing computer-assisted methods began appearing around 2004, while dental plaque research on drug therapy and microbiology grew momentum around 2005, reflecting a growing interest in these areas through the late 2000s and early 2010s.

Keywords related to bacterial adhesion, dental plaque

chemistry and microbiology, and cariostatic agents increased in frequency from 2004 onwards, indicating an expanding focus on preventive and therapeutic measures for oral biofilm management. Notably, the frequency of dental plaque microbiology and control studies peaked between 2004 and 2015, highlighting ongoing efforts to understand and mitigate plaque-related issues.

Between 2007 and 2015, there was a marked rise in research on sucrose adverse effects, titanium chemistry, microbial colony counts, toothbrushing instrumentation, and placebos in trials. The term ‘biofilms/drug effects’ was particularly prevalent, reflecting a significant area of study with a peak in the early 2010s.

From 2010 onwards, surface properties, bacterial load, and biofilm growth and development became prominent research areas. The keyword ‘biofilms’ showed an upward trend, with the highest frequency noted around 2019, signifying sustained interest in biofilm-related studies. Other notable terms include dental plaque microbiology and prevention, cattle in oral health studies, and dental home care devices, reflecting diverse

research interests.

From 2012 to 2022, the later years saw an increase in studies on gels, tooth demineralization prevention, the periodontal index, and dental implants, indicating a broadening scope of clinical trials. Keywords like ‘child, preschool,’ ‘dental plaque therapy,’ and ‘reproducibility of results’ also gained traction, underscoring the emphasis on pediatric oral health and methodological rigor.

Recent keywords from 2015 to 2023 include probiotics, powders, chlorhexidine, molar studies, fluoride pharmacology, microbiota, dental caries, and inflammation. These reflect evolving research directions towards novel therapeutic agents and a deeper understanding of the oral microbiome. The latest entries, such as dental plaque/drug therapy/prevention & control and gingivitis prevention & control/drug therapy, appearing around 2023 to 2024, indicate a current and ongoing focus on comprehensive strategies for managing oral biofilm and associated conditions (Figure 12).

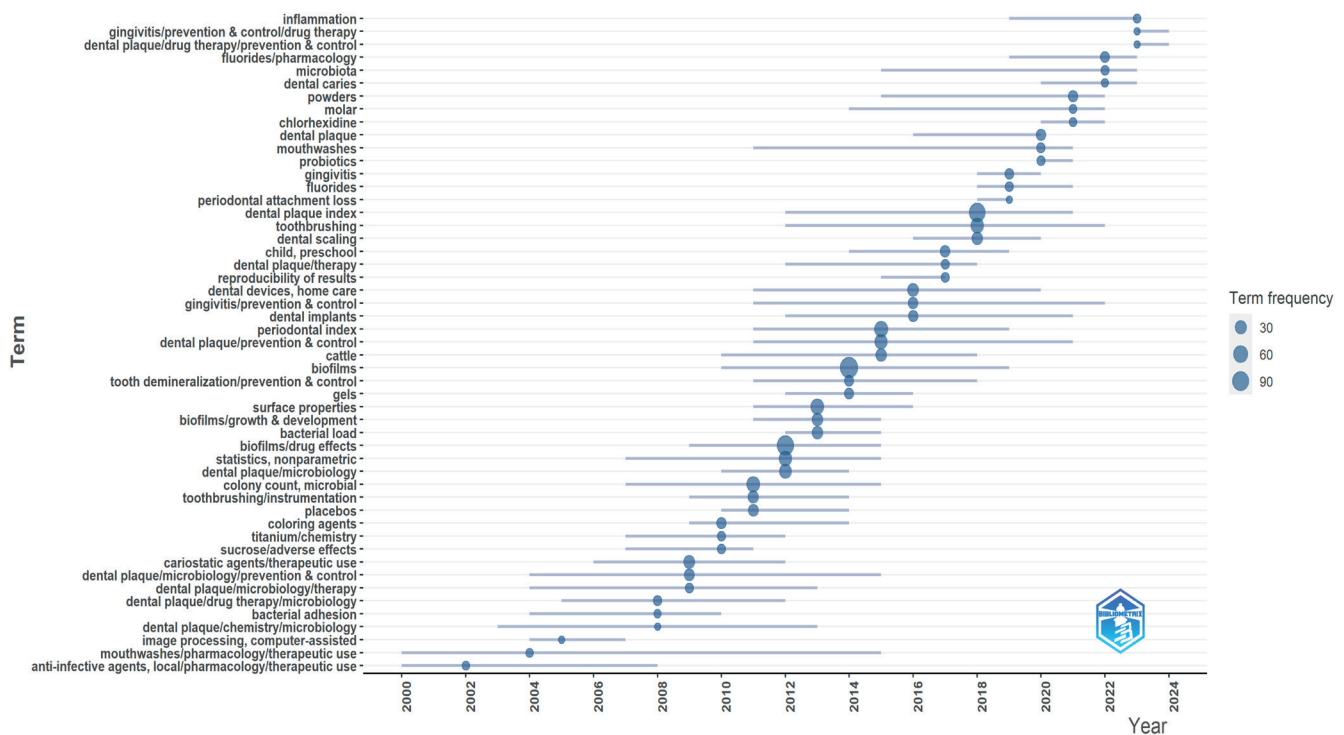


Figure 12: Analysis of topic trends. Image Credit: Namrata Dagli

DISCUSSION

The bibliometric analysis of clinical trials on oral biofilm reveals several key insights into the research trends, author contributions, and international collaboration within this field from 1994 to 2024. Initially, 7260 results were identified, and after filtering for the English language, 7082 remained. Following manual inspection, 491 clinical trials were included in the final dataset. This dataset spans three decades, showing an annual growth rate of 9.45% and an average document age of 9.11 years. The analysis highlights 2042 unique keywords and contributions from 2313 authors, indicating substantial collaboration, with an average of 6.02 co-authors per document and 15.68% of documents involving international co-authorships.

The publishing trends demonstrate a significant increase in clinical trials over the years. From the early 1990s, with minimal publications, there has been a steady rise, particularly from 2004 onwards. Notable peaks were observed in 2011, 2012, and 2015, reflecting heightened research activity. Despite some fluctuations, the overall trend remained upward, with 35 articles published in 2023 indicating sustained interest and ongoing research.

The analysis identifies Cury JA and Del Bel Cury AA as the leading authors, with the top ten contributing 24.03% of the total publications. A detailed coauthorship analysis using VOSviewer revealed 2475 authors, with a significant collaboration network comprising 53 connected items spread across nine clusters. Sculean Anton and Cury JA emerged as key authors with the highest total link strengths, highlighting their influential roles in collaborative research.

Journals such as “Clinical Oral Investigations,” “Caries Research,” and the “Journal of Clinical Periodontology” are prominent in publishing clinical trials on oral biofilm. The temporal analysis shows a marked increase in publications in these journals, especially from the early 2000s onwards, with “Clinical Oral Investigations” leading with 47 articles by 2024. This trend underscores the growing recognition of oral biofilm’s clinical implications and management strategies.

Geographically, Brazil leads with 530 studies, followed by the United States with 210 trials. Italy, China, and Germany contribute significantly, reflecting a global interest in oral biofilm research. The analysis of collaboration frequency indicates that most publications

are single-country efforts, although there is notable international collaboration, mainly from Brazil, the United States, and Italy.

In clinical trials on oral biofilm, research is categorized into several thematic areas based on keyword co-occurrence analysis. One primary focus is periodontal health, examining diverse human populations and targeting bacteria associated with periodontal diseases like *Aggregatibacter actinomycetemcomitans*, *Porphyromonas gingivalis*, and *Treponema denticola*. These studies investigate chronic periodontitis and gingivitis, utilizing clinical measurements and indices to assess disease progression and treatment outcomes. Another significant area is dental caries prevention and treatment, exploring the effects of cariogenic and cariostatic agents, various dental materials, and fluoride treatments, often using animal models and robust methodologies such as cross-over and double-blind studies. Anti-bacterial treatments in dental settings are a considerable research focus, evaluating the efficacy of agents like chlorhexidine and sodium hypochlorite in root canal therapy through advanced microscopy techniques and materials testing. Research on oral health interventions spans different age groups, assessing the effectiveness of oral agents such as CPC and probiotics and the impact of orthodontic appliances and home care practices on biofilm formation. Studies on oral hygiene in elderly patients particularly focus on denture wearers, measuring microbial load, and the effectiveness of denture cleansers. Additionally, research on drug combinations and antimicrobial agents explores the synergistic effects of multiple agents, including tin fluorides and triclosan, in reducing dental plaque and preventing gingivitis, aiming to identify effective treatment protocols for maintaining oral health.

Over time, research trends in oral biofilm clinical trials have evolved significantly. From 2000 to 2015, early studies concentrated on anti-infective agents, mouthwashes, and the drug therapy and microbiology of dental plaque, with image processing and computer-assisted methods gaining prominence around 2004. Starting in 2004, there was an increased focus on bacterial adhesion, dental plaque chemistry and microbiology, and cariostatic agents. Between 2007 and 2015, research expanded to include the adverse effects of sucrose, titanium chemistry, microbial colony counts, toothbrushing instrumentation, and the use of placebos

in trials, with the term ‘biofilms/drug effects’ peaking in the early 2010s. Post-2010, studies emphasized surface properties, bacterial load, and biofilm development, with the keyword ‘biofilms’ peaking around 2019. From 2015 to 2023, there was a surge in studies on probiotics, chlorhexidine, the oral microbiome, and dental caries, reflecting an ongoing focus on comprehensive biofilm management strategies and exploring novel therapeutic agents and methodologies to advance oral health.

Overall, this bibliometric analysis highlights the dynamic and collaborative nature of research on oral biofilm, with significant contributions from various authors and countries. Over time, the increasing number of publications underscores the growing recognition of the importance of understanding and managing oral biofilm in dental health. The extensive collaboration and diverse journal contributions reflect a multidisciplinary approach to advancing knowledge and treatment strategies in this crucial area of oral health research. However, there is still a need to explore novel therapeutic agents and methodologies, foster interdisciplinary approaches, conduct comparative effectiveness research, leverage digital and technological advancements, and develop standardized trial conduct and reporting protocols. We have summarized the findings of this study in [Figure 13](#).

A bibliometric analysis on the Web of Science database examined the international scientific literature on oral biofilms, spanning formation, bacterial adhesion, prevention, and treatment. Analyzing 921 articles from 1991 to 2015 across 274 journals, involving 2804 authors from 695 institutions across 59 countries, reveals significant global interest, particularly from the United States and the United Kingdom. Notably, the 17 most impactful articles, published between 1995 and 2009, demonstrated a diverse approach to understanding and addressing oral biofilms, exploring mechanisms to penetrate biofilm structures, inhibit bacterial adhesion, and reduce pathogenic activity, thereby offering potential avenues for improved prevention and treatment strategies ¹³.

Another bibliometric research in Scopus and Web of Sciences databases on periodontal disease biofilms shows a significant increase in studies, especially in 2016, 2020, and 2023, highlighting growing scientific interest. Key authors like Colombo APV and journals such as the *Journal of Periodontology* are influential. Despite advancements in biofilm pathogenesis, research

gaps remain, necessitating more precise analysis and innovative therapies. Emerging keywords like “subgingival biofilm” reflect current research trends, while established terms remain relevant. The shift from traditional to modern research themes has practical implications for oral health policies. Interdisciplinary collaboration has become crucial, fostering innovation and personalized therapies in periodontal disease management ¹⁴.

We could only identify those, as mentioned above, two bibliometric analyses on similar topics. However, many systematic reviews and narrative reviews were identified on the topic, covering several aspects such as the role of oral biofilm in the pathogenesis of oral, periodontal, and systemic disease, intraoral appliances for biofilm analysis, and various interventions to prevent biofilm formation ¹⁵⁻¹⁹.

LIMITATIONS OF THIS STUDY

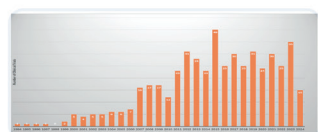
The bibliometric analysis of clinical trials on oral biofilm published in PubMed has several limitations. First, relying on MeSH keywords may not capture all relevant studies, as some pertinent research might be indexed under different or not indexed with MeSH terms. This can lead to an incomplete dataset and potential biases in the analysis. Second, the analysis is restricted to PubMed, excluding other significant databases like Web of Science, Scopus, and Embase, which might contain relevant studies, thereby limiting the comprehensiveness of the analysis.

Additionally, the temporal trends identified may be influenced by changes in indexing practices and the introduction of new MeSH terms over time rather than actual shifts in research focus. The clustering and network visualization techniques used, such as those in VOSviewer, are subject to the algorithm’s parameters and may not accurately reflect nuanced relationships between keywords. Furthermore, the analysis does not account for the quality or impact of the studies, focusing solely on keyword frequency and cooccurrence, which may overlook the significance of individual studies or emerging research areas with fewer publications.

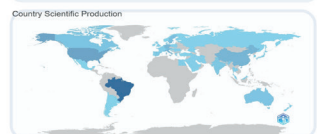
Another limitation is the potential for language bias, as PubMed primarily indexes English-language journals, which may exclude relevant research published in other languages. The study design and methodological quality of the included trials are not assessed, which could influence the interpretation of the findings and the

Key Findings

Bibliometric Analysis of clinical trials on oral biofilm



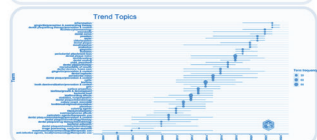
Publication Trends: A consistent rise is observed in publications over the years, peaking at 40 articles in 2015.



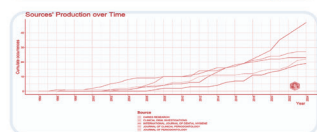
Scientific Production of Countries: Brazil leads with 530 studies, followed by the United States with 210 trials. Italy, China, and Germany also contribute significantly, reflecting a global interest in oral biofilm research.



Keyword Cooccurrence Analysis: The subject-specific Mesh keywords with the maximum cooccurrence are biofilms, dental plaque, local anti-infective agents, dental plaque index and chlorhexidine.



Topic-Trends Analysis: Research on oral biofilm has evolved from a focus on anti-infective agents and mouthwashes to exploring advanced topics such as biofilm growth, surface properties, and the oral microbiome, with recent studies emphasizing novel therapeutic agents and comprehensive management strategies.



Most Relevant Sources: Clinical Oral Investigations has published the highest number of clinical trials on oral biofilm, followed by Caries Research, and the Journal of Clinical Periodontology.

Softwares used:
VOSviewer & Biblioshiny

Figure 13: The key findings of the bibliometric analysis of clinical trials on oral biofilm.

Image Credit: Namrata Dagli.

perceived importance of specific research topics. These limitations highlight the need for a more comprehensive and methodologically rigorous approach to bibliometric analysis in future studies.

FUTURE STUDY RECOMMENDATIONS

Future research should continue exploring the synergistic effects of various antimicrobial agents, specifically combinations of tin fluorides, triclosan, and other novel agents, to enhance their efficacy in reducing dental plaque and preventing gingivitis. Longitudinal studies are needed to understand the long-term impact of different therapeutic interventions on periodontal health, including the sustained effectiveness of treatments in preventing disease progression and recurrence. Additionally, research should focus on developing and testing innovative dental materials with enhanced anti-biofilm properties, such as those that prevent bacterial

adhesion and biofilm formation or release antimicrobial agents over time.

Depending on individual risk factors and microbiome profiles, personalized treatment plans should be explored to develop more effective prevention and management strategies for oral biofilm-related diseases. Moreover, there is a need for more research on the impact of dietary habits and lifestyle factors on oral biofilm formation and dental health, including the effects of various diets, sugars, and nutritional supplements on the oral microbiome. Given their unique oral health challenges, targeted studies on pediatric and geriatric populations are essential. Research should focus on age-specific interventions, including developing safe and effective treatments for children and elderly patients with dentures.

Incorporating advanced imaging and diagnostic techniques, such as confocal microscopy and electron

scanning microscopy, in future research can provide a deeper understanding of biofilm structure and dynamics, helping to evaluate the effectiveness of various treatments at a microscopic level. Investigating the efficacy of different home care practices, including mouthwashes, probiotics, and plant extracts, in maintaining oral hygiene and preventing biofilm formation is also crucial. Research should evaluate the role of emerging technologies, such as smart toothbrushes and personalized dental care apps, in enhancing home care practices.

Further research is needed to understand the complex interactions within oral biofilms and their ecological dynamics, including the interactions between different microbial species and their response to various treatments. To ensure the generalizability of findings, future clinical trials should include diverse populations with varying demographics, geographic locations, and socio-economic backgrounds. Addressing these recommendations can lead to a more comprehensive understanding of oral biofilm and the development of more effective prevention and treatment strategies.

CONCLUSION

The field of clinical trials on oral biofilm has shown a substantial increase in research activity, as evidenced by a consistent rise in publications over the years. Starting from a minimal number of articles in the 1990s, there has been a significant surge in publications, peaking at 40 articles in 2015 and remaining robust with over 20 articles per year since then. Coauthorship analysis has revealed a collaboration network among many authors, with key figures like Sculean Anton and Cury JA having the highest total link strength. The research has been widely disseminated across various journals, with “Clinical Oral Investigations,” AND “Caries Research,” AND “Journal of Clinical Periodontology” leading in the number of articles published. This indicates a multidisciplinary interest in oral biofilm research, covering clinical, preventive, and therapeutic aspects. Countries such as Brazil, the United States, Italy, and China have been at the forefront of research in this field, with Brazil leading in the number of published clinical trials. International collaboration is evident, although Brazil predominantly publishes single-country studies. Keyword analysis has identified several clusters

focusing on different aspects of oral biofilm research, including periodontal health, dental caries prevention, antimicrobial agents, and oral hygiene interventions. These clusters reflect evolving research trends and emphasize the multidimensional nature of oral biofilm research. The bibliometric analysis highlights a growing global interest in understanding and managing oral biofilm, with significant contributions from researchers worldwide. The findings underscore ongoing efforts to advance knowledge and treatment strategies in this critical area of dental health. However, it is essential to explore novel therapeutic agents and methodologies, encourage interdisciplinary approaches, conduct comparative effectiveness research, utilize digital and technological advancements, and develop standardized protocols for the conduct and reporting of trials.

CONSENT FOR PUBLICATION

The author reviewed and approved the final version and has agreed to be accountable for all aspects of the work, including any accuracy or integrity issues.

DISCLOSURE

The author declares that they do not have any financial involvement or affiliations with any organization, association, or entity directly or indirectly related to the subject matter or materials presented in this editorial. This includes honoraria, expert testimony, employment, ownership of stocks or options, patents, or grants received or pending royalties.

DATA AVAILABILITY

Information is taken from freely available sources for this editorial.

AUTHORSHIP CONTRIBUTION

All authors contributed significantly to the work, whether in the conception, design, utilization, collection, analysis, and interpretation of data or all these areas. They also participated in the paper’s drafting, revision, or critical review, gave their final approval for the version that would be published, decided on the journal to which the article would be submitted, and made the responsible decision to be held accountable for all aspects of the work.

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