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Biofilms in wound healing: A bibliometric and visualised study

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Abstract

Bibliometric analyses are often used as a means of visualising the knowledge base and associated trends and patterns in a target scientific field based on a quantitative review of the corresponding literature. In this study, we explore the current status of research pertaining to biofilms in wound healing and elucidate trends in this research space. Through this process, we gain insight into findings from papers indexed in the Web of Science Core Collection. These references were then analysed and plotted using Microsoft Excel 2019, VOSviewer, and CiteSpace V. The results provide a fresh perspective regarding global trends and hotspots in biofilm-related wound healing research. These findings also offer a foundation that researchers can use to identify active hotspots of scientific interest to guide further research endeavours.

KEYWORDS

bibliometric, biofilms, global trends, materials science biomaterials, microbiology, wound healing

Key Messages

- in this study, we primarily explore the current status of research pertaining to biofilms in the context of wound healing, thereby elucidating the trends in this research space
- this analysis suggests that particular attention should be paid to emerging research hotspots in this field associated with topics including antibacterial treatment, nanoparticles, *Pseudomonas aeruginosa*, silver nanoparticles cytotoxicity, etc.
- the overall publication output in this field has steadily increased year on year and has increased exponentially since 2010, with a marked

Peiting Li and Xiaofei Tong contributed equally to this study.

Jianda Zhou and Wei Wu had the same contribution to this article.

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improvement in the quality of publications. It is expected that biofilms will remain a hot topic of research for wound healing in the next few years

1 | BACKGROUND

Biofilms are bacterial communities enmeshed in extracellular polysaccharides and other polymers that are attached to a biological or inert surface. The establishment of these liquid-impregnated biofilms can adversely impact wound healing, contributing to the global healthcare burden associated with chronic wounds that do not heal properly.[1,2] These biofilms shield the bacteria present therein, protecting them from host immunity such that the bacteria are better able to thrive in chronic wound sites as compared to free bacteria. White blood cells are unable to effectively penetrate the biofilm interior or phagocytose the bacteria therein or produce reactive oxygen species capable of destroying these microbes,[3] compromising normal wound healing. The exopolymer characteristics of biofilms can also disrupt other facets of host innate immunity including complement fixation and the activation of an inflammatory response, further preventing phagocytic uptake of these microbes.

Biofilms are highly heterogeneous structures that vary substantially as a function of the microorganisms that compose them.[4] An estimated 60% of chronic wounds present with biofilms that can stimulate chronic unproductive inflammation,[2] inducing further tissue damage while failing to eliminate the pathogens triggering this deleterious response. Resultant changes in inflammatory gene expression can also promote the leakage of plasma from nearby capillaries, providing a source of nutrients to support microbial growth.[5] These biofilms can further spur oxidative stress and degrade key cytokines and receptors through the production of proteases, altering the composition of the host cytoskeleton while inhibiting apoptosis and mitosis, contributing to wound bed senescence.[4]

Detecting and diagnosing biofilms in the context of chronic wound infection relies on both successful biofilm localization and the identification of the causative pathogens present therein.[6] Diagnostic approaches can consist of molecular, microbiological, and morphological assays,[7] and no gold-standard approach to biofilm diagnosis in the context of chronic wound healing is available.[8] Biofilms incorporation is also associated with a reduction in bacterial metabolic activity, thus protecting them from antimicrobial drugs that function in metabolically active cells.[9] The exopolymer matrix also serves as a mechanical barrier to shield bacteria from these drugs and from host immune cells.[10] Notably, within biofilms, bacteria are able to exchange antimicrobial resistance genes in the form of plasmids, increasing their resistance to treatment and overall heterogeneity among chronic wound sites. Certain biofilms may exhibit concentration gradient effects that further constrain the efficacy of antibiotic and antiseptic compounds, whereas others may be largely eradicated by initial treatment such that only a small subset of cells are able to persist and re-establish the biofilm upon removal of therapeutic treatment. Biofilms may also evolve in response to antibacterial treatment by adopting a thicker mucoid phenotype.[4]

The ability of biofilms to delay wound healing has been a focus of growing research interest, leading to the establishment of wound care strategies in which a multipronged approach is employed to remove biofilms from wound beds and to improve the restoration of epithelial integrity.[11] At present, however, efforts to accurately define the composition and locations of biofilms at wound surfaces are often ineffective, increasing the need for more invasive and costly surgical or pharmacological treatments in order to improve patient outcomes. The specific mechanisms that govern the ability of biofilms to shape wound healing remain to be fully clarified, underscoring a need to remain up to date regarding emerging research in this field to aid efforts to guide their clinical treatment.

Bibliometric analyses are often used as a means of visualising the knowledge base and associated trends and patterns in a given scientific field based on a quantitative review of the corresponding literature.[12] Such analyses offer objective metrics by which research results can be assessed.[13] Despite growing research interest pertaining to the role of biofilms in the context of wound healing, no bibliometric analyses on this topic have been conducted to date. As such, a summary of the current status of this field is critical as a means of highlighting research trends and associated keywords. The present bibliometric analysis was thus conceived to explore the current status of research pertaining to biofilms and wound healing and

to elucidate trends in this research space, providing a foundation that researchers can use to identify active hotspots of scientific interest to guide further research endeavours.

2 | METHODS

2.1 | Search strategies

All data used for the present study were downloaded from the Science Citation Index-Expanded database of the Web of Science Core Collection (WoSCC) on 1 January 2022. The literature search was conducted using the following search terminology: TS = ('biofilm' or 'biofilms') and TS = ('wound' or 'lesion' or 'vulnus' or 'skin') and TS = ('healing' or 'regeneration' or 'repair' or 'reconstruction'). Only those studies and review articles published from 2000 to 2021 in English were included in this analysis. Overall, 1340 relevant studies were identified for inclusion in this analysis (Figure 1). For each publication, key information including the title, year of publication, authors' names, nationality, affiliation, journal, keywords, and abstract were downloaded from the WoS database in a TXT file that was subsequently imported into Microsoft Excel for analysis. All downloads were performed on a single day to avoid the impact of WoS database updates on the resultant analysis.

2.2 | Data collection and analysis

Two authors (L.P. and T.X.) independently identified studies from the WoSCC and extracted key data of interest including annual publication output, country/region, institutions, journals, authors, citation frequency, and the Hirsch index (H-index). The H-index is a number that summarises the productivity and prominence of a given author, institution, or region, corresponding to the publication of H papers that were cited a minimum of H times, providing a better means of gauging scientific impact. The Impact Factor (IF) value for each journal was obtained from Journal Citation Reports (JCR) 2021 along with corresponding quartiles. Inconsistencies were resolved through discussion and consensus. All data were then imported into Microsoft Office 365 (Washington), VOSviewer (Leiden University, Leiden, the Netherlands), and CiteSpace V (Drexel University, Pennsylvania) for subsequent bibliometric analyses.

Annual publication output, total/mean IF, H-index values, total numbers of citations per article, and total

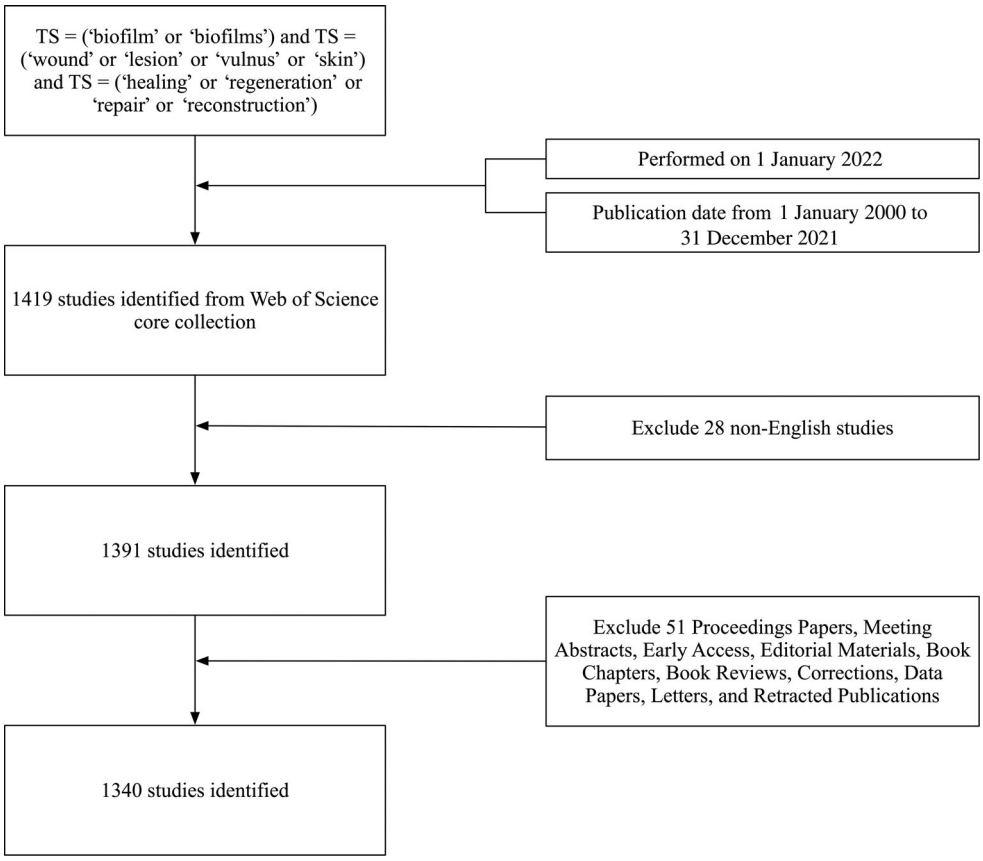

FIGURE 1 The search strategy used for the present bibliometric analysis. Searches of the Web of Science database were conducted with the following approach: TS = ('biofilm' or 'biofilms') and TS = ('wound' or 'lesion' or 'vulnus' or 'skin') and TS = ('healing' or 'regeneration' or 'repair' or 'reconstruction'). Studies published from 1 January 2000 to 31 December 2021 were eligible for inclusion. Of the 1419 studies identified through this initial search, 28 non-English studies were excluded, with 1340 of the remaining 1391 studies ultimately being included in the following analyses following the removal of 51 studies that did not meet with selected inclusion criteria. TS, topic search

numbers of citations per country/region were plotted and analysed using Microsoft Excel 2021. VOSviewer[14] was employed as a tool to generate network visualisation maps and to comprehensively examine collaborative interactions between authors, institutions, and countries/regions for highly co-cited articles. This software was also used to classify those keywords exhibiting high frequencies of co-occurrence into multiple clusters. Co-occurrence analyses were further used to summarise trends and research hotspots in this field, with 'author keywords' being selected as the unit of analysis in this approach. CiteSpace V was employed as a tool for co-citation analyses of journals, references, and clusters, enabling the construction of a co-cited reference timeline highlighting the rise and persistence of certain clusters within this research field. This program was also used to highlight those keywords associated with a burst in research output and to visually map all relevant items pertaining to this topic, with such citation bursts being integral to identifying emerging trends within a given research space.[12] The 'years per slice' and 'top N per slice' values were respectively set to 1 and 50, yielding a network map extracted from the top 50 most cited papers, with each slice consisting of a 1-year period.

3 | RESULTS

3.1 | Publication output and temporal trends

In total, 1340 studies (1122 articles, 218 reviews) met the inclusion criteria for this analysis. Overall publication output rose steadily prior to 2010 and increased sharply in subsequent years to 249 publications in 2021—over 9-fold more than in 2010 when 25 were published (Figure 2A). While 249 articles were published to date in 2021, this does not correspond to the total number of annual publications. Based on these trends, the number of studies forecast to be published in 2022 in this field is 275.

3.2 | Contribution of countries/regions and an analysis of international cooperation

Overall, the included studies were associated with 2034 institutions and 89 countries/regions (see Table, Supplemental Digital Contents 1 and 2). The USA was the source of the largest number of studies and the most cited papers, with 422(31.493%) publications and 14 988 citations, followed by China (170 papers, 3882 citations), England (133 papers, 3984 citations), India (96 papers, 1193 citations), and Germany (86 papers, 2085 citations). The number of studies published in China has gradually risen and is approaching the publication output of the USA in this research space. The overall national output of the 10 most productive countries/regions is summarised in Table 1 and Figure 2B.

A cluster analysis revealed that 35 countries/regions were represented over 10 times, and these were grouped into 7 clusters based on the number of co-authored articles (Figure 3 and see Table, Supplemental Digital Content 3). The first cluster included China, India, Japan, South Korea, and Singapore. The second cluster included England, Italy, Sweden, and Wales. The third included France, Spain, Belgium, Portugal, and Poland. The fourth cluster included Germany, Switzerland, Russia, and Austria. The fifth cluster included the USA, Canada, and Taiwan. The sixth cluster included the Netherlands and Turkey. The seventh cluster included Australia. The first

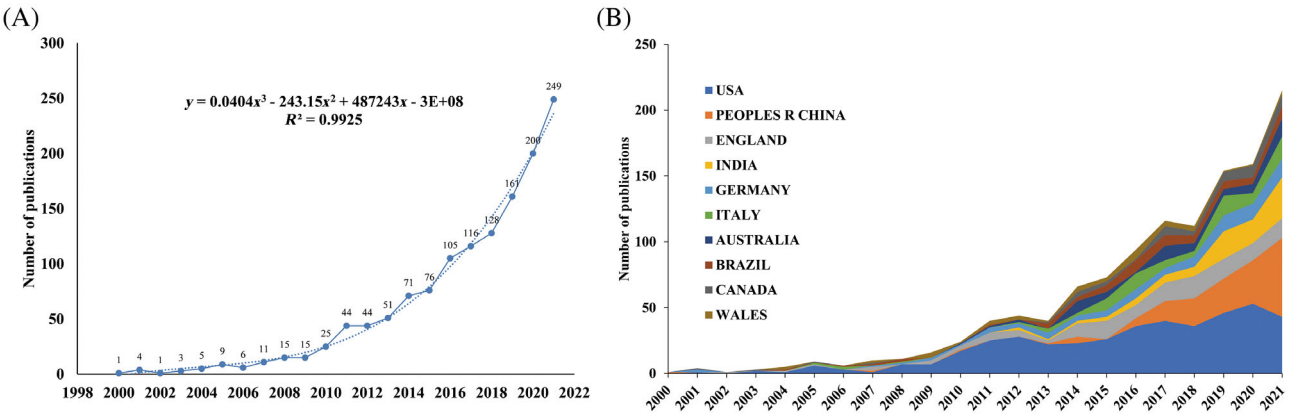

FIGURE 2 Trends in the number of publications and analysis of country/regions in biofilms in wound healing research. (A) The annual worldwide publication output. (B) Growth trends in the publication output from the top 10 countries

TABLE 1 The top 10 countries/regions and institutions with the greatest numbers of relevant publications

Rank	Country/region	Documents	Citations	Rank	Institution	Documents	Citations
1	USA	422	14 988	1	University of Copenhagen	36	1992
2	Peoples R China	170	3882	2	State University System of Florida	33	1056
3	England	133	3984	3	University of Florida	29	991
4	India	96	1193	4	University of California System	26	591
5	Germany	86	2085	5	Chinese Academy of Sciences	24	1326
6	Italy	81	1661	6	Montana State University Bozeman	20	1399
7	Australia	62	2047	7	Montana State University System	20	1399
8	Brazil	61	897	8	Harvard University	19	1105
9	Canada	48	962	9	Ohio State University	19	795
10	Wales	43	2390	10	Texas Tech University System	19	719

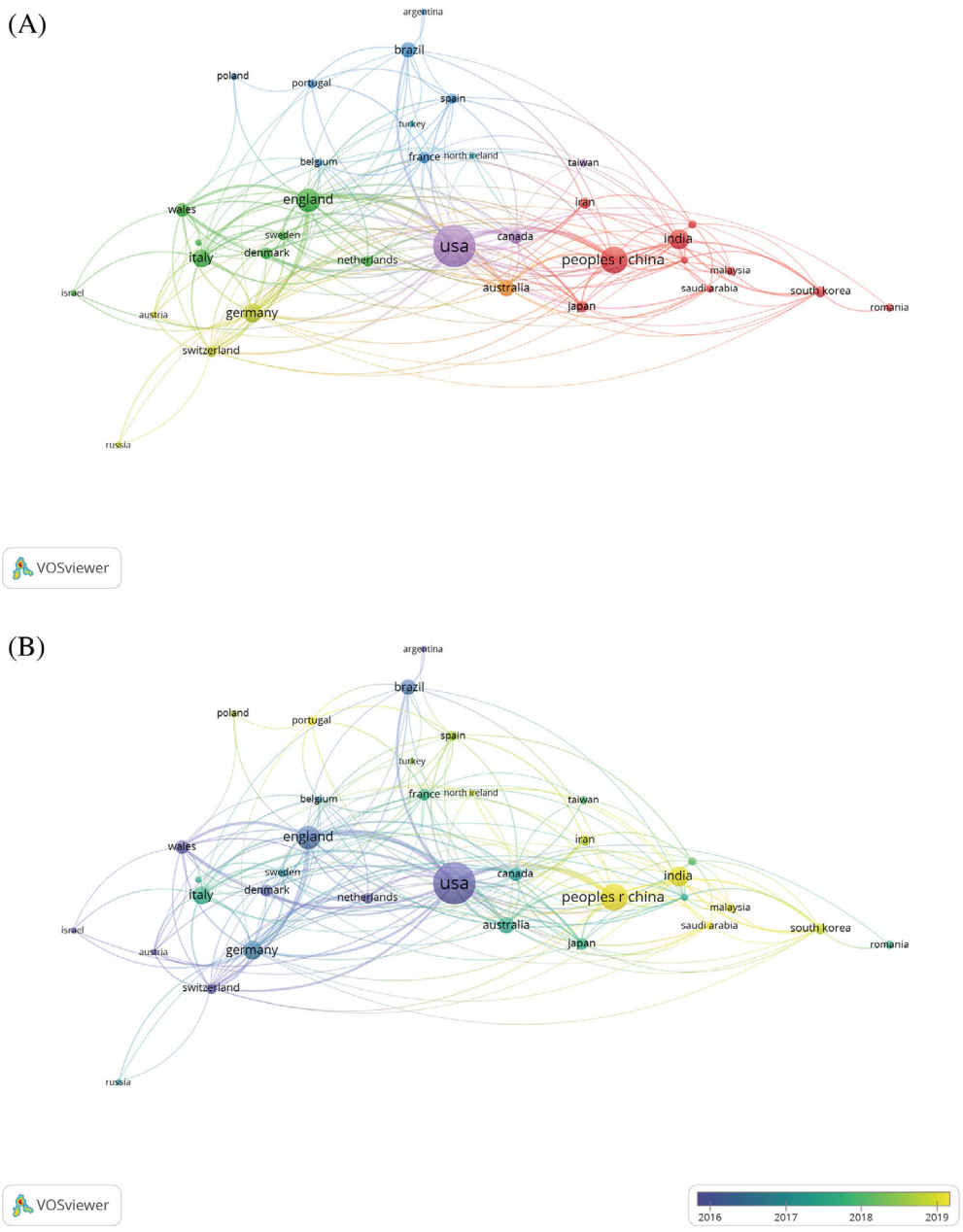

FIGURE 3 Cluster analysis of countries and regions represented over 10 times. (A) A visualisation map was generated in which 35 countries/regions were grouped into 7 collaborative clusters, with each cluster having a specific colour. Nodes correspond to countries, with node size being proportional to the number of publications. Links indicate collaborations, with the distance and thickness of these links being related to the strength of that collaboration. (B) Node colour corresponds to the average year of publication in the indicated countries/regions, ranging from blue (earlier) to yellow (more recent)

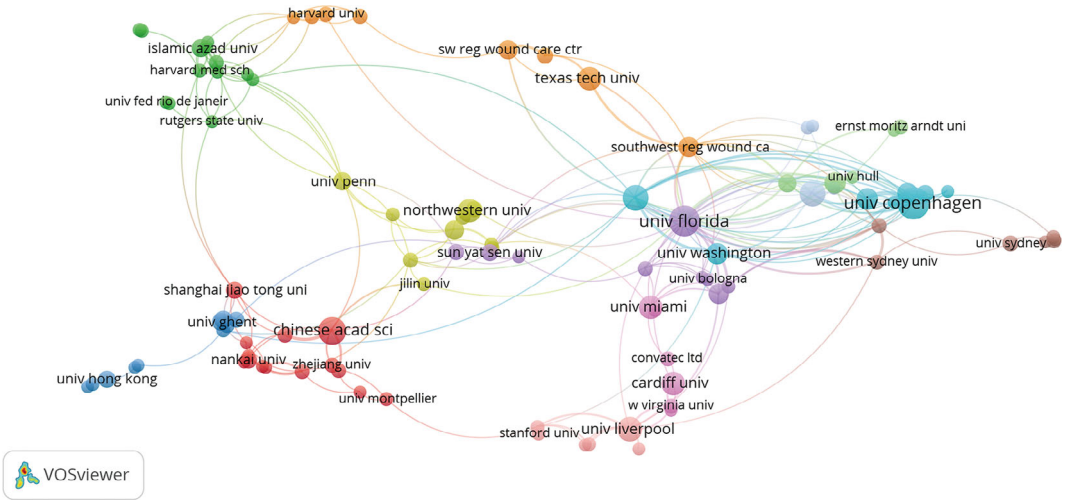

FIGURE 4 Institutional cluster map. Publications from 101 institutions were used to construct a collaboration map consisting of 12 collaborative clusters (with each cluster being composed of nodes of a specific colour). Nodes correspond to a given institution, while node size corresponds to the number of publications, links correspond to collaborative relationships, and the thickness and distance of links between nodes correspond to the strength of that collaborative relationship

cluster exhibited the strongest connections, indicating that China, the USA, South Korea, England, and Japan engage in the greatest amount of collaborative research. Overall bilateral collaborative research between China and the USA was found to be limited, with studies from the latter largely ranging from clinical studies to basic medical science, whereas Chinese studies were focused on topics such as nanoscience/nanotechnology, multidisciplinary materials science, surgery, and biomedical engineering. Further strengthing of international cooperation and collaboration may further help to advance this research field.

3.3 | Institutional contributions

The 10 institutions that have contributed most substantially to this field are compiled in Table 1 and include the University of Copenhagen (36, 2.687%), State University System of Florida (33, 2.463%), University of Florida (29, 2.164%), University of California System (26, 1.94%), and Chinese Academy of Sciences (24, 1.791%). We then used VOSviewer to conduct a co-authorship analysis focused on institutions in an effort to elucidate collaborative relationships (Figure 4 and see Table, Supplemental Digital Content 4). In this analysis, 101 institutions exhibited >5 occurrences, forming a co-authorship network that was separated into 12 clusters for which the representative institutions were the Chinese Academy of Sciences, University of Massachusetts, University of Bern, Iowa University, University of Florida, Tech University Denmark, Massachusetts Institute of Technology, Ingham Inst Appl Med Res, Cardiff University, Scapa Healthcare, University of Huddersfield, and Ohio State University. Among these institutions, the Chinese Academy of Sciences, Nankai University, Shanghai Jiao Tong University, and the University of Pennsylvania exhibited the closest cooperative relationships.

3.4 | Leading journals in this field

The 1340 identified publications associated with research focused on biofilms and wound healing were published in 538 total journals (see Table, Supplemental Digital Content 5), with the top 10 most represented journals being shown in Table 2. The greatest number of studies in this field were published in the *Journal of Wound Care* (63 publications, 4.701%), which exhibited an IF of 1.798 in 2020, followed by the *International Wound Journal* (49 publications, 3.657%), and *Wound Repair and Regeneration* (44 publications, 3.284%).

Among journals with an IF >10, the article 'Biofilms in Chronic Wounds: Pathogenesis and Diagnosis' published by Wu et al. in *Trends in Biotechnology* ranked most highly (IF = 19.536), followed by 'Multifunctional Modification of SIS Membrane with Chimeric Peptides to Promote Its Antibacterial, Osteogenic, and Healing-Promoting Abilities for Applying to GBR' published by Mu et al (IF = 18.808) and 'Ultra-Conformable Ionic Skin with Multi-Modal Sensing, Broad-Spectrum Antimicrobial and Regenerative Capabilities for Smart and Expedited Wound Care' published by Lin et al (IF = 18.808; Table 3).

TABLE 2 The top 10 journals and authors with the greatest numbers of relevant publications

Rank	Journals	Country	IF 2021	Documents	Citations	Rank	Authors	Documents	Citations
1	Journal of Wound Care	UK	2.072	63	1269	1	Percival SL	35	1901
2	International Wound Journal	UK	3.315	49	1264	2	Bjarnsholt T	20	1787
3	Wound Repair and Regeneration	USA	3.617	44	2863	3	Schultz G	19	823
4	Wounds A Compendium of Clinical Research and Practice	USA	1.546	26	414	4	Wolcott RD	16	1500
5	Plos One	USA	3.24	25	1279	5	Leung KP	14	557
6	Advances in Wound Care	USA	4.73	22	694	6	James GA	13	1163
7	ACS Applied Materials Interfaces	USA	9.229	18	285	7	Galiano RD	12	673
8	Frontiers in Microbiology	CHE	5.64	18	265	8	Mustoe TA	11	673
9	International Journal of Biological Macromolecules	NLD	6.953	17	225	9	Roy S	11	259
10	Plastic and Reconstructive Surgery	USA	4.73	16	573	10	Bowler PG	10	281

TABLE 3 The top 10 authors with the highest-impact publications

Rank	Publication year	Author	Title	Publication title	DOI	IF	JCR
1	2021	Rodrigo-Navarro, Aleixandre; Sankaran, Shrikrishnan; Dalby, Matthew J.; del Campo, Aranzazu; Salmeron-Sanchez, Manuel	Engineered living biomaterials	Nature Reviews Materials	10/gnsxkm	66.308	1
2	2019	Lu, X.; Keidar, M.; Laroussi, M.; Choi, E.; Szili, E. J.; Ostrikov, K.	Transcutaneous plasma stress: From soft-matter models to living tissues	Materials Science & Engineering Reports	10.1016/j.mser.2019.04.002	36.214	1
3	2019	Buch, Pranali J.; Chai, Yunrong; Goluch, Edgar D.	Treating Polymicrobial Infections in Chronic Diabetic Wounds	Clinical Microbiology Reviews	10.1128/CMR.00091-18	26.132	1
4	2021	Chang, Mayland; Nguyen, Trung T.	Strategy for Treatment of Infected Diabetic Foot Ulcers	Accounts of Chemical Research	10.1021/acs.accounts.0c00864	22.384	1

(Continues)

TABLE 3 (Continued)

Rank	Publication year	Author	Title	Publication title	DOI	IF	JCR
5	2018	Chen, Zhaowei; Wang, Zhenzhen; Ren, Jinsong; Qu, Xiaogang	Enzyme Mimicry for Combating Bacteria and Biofilms	Accounts of Chemical Research	10.1021/acs.accounts.8b00011	22.384	1
6	2019	Kalan, Lindsay R.; Meise, Jacquelyn S.; Loesche, Michael A.; Horwinski, Joseph; Soaita, Ioana; Chen, Xiaoxuan; Uberoi, Aayushi; Gardner, Sue E.; Grice, Elizabeth A.	Strain- and Species-Level Variation in the Microbiome of Diabetic Wounds Is Associated with Clinical Outcomes and Therapeutic Efficacy	Cell Host & Microbe	10.1016/j.chom.2019.03.006	21.023	1
7	2019	MacLeod, Amanda S.	Bad 'Staph' in the Wound Environment of Diabetic Foot Ulcers	Cell Host & Microbe	10/gn726s	7	Galiano RD
8	2012	Reid, Ian R.; Cornish, Jillian	Epidemiology and pathogenesis of osteonecrosis of the jaw	Nature Reviews Rheumatology	10/fqppt6	8	Mustoe TA
9	2019	Wu, Yuan-Kun; Cheng, Nai-Chen; Cheng, Chao-Min	Biofilms in Chronic Wounds: Pathogenesis and Diagnosis	Trends in Biotechnology	225	9	Roy S
10	2018	Machala, Zdenko; Pavlovich, Matthew J.	A New Phase in Applied Biology	Trends in Biotechnology	573	10	Bowler PG

3.5 | Publication distributions by author

In total, 6527 authors were found to have contributed to the identified research output in this field (see Table, Supplemental Digital Content 6), with the 10 most productive of these authors being compiled in Table 2. Percival SL ranked first among these authors with 35 publications, followed by Bjarnsholt T (20 articles), Schultz G (19 articles), Wolcott RD (16 articles), Leung KP (14 articles), and Galiano RD (13 articles). Percival SL additionally exhibited the greatest number of citations in this analysis (1901). Just 9 authors were found to have published over 10 authors in this field, among whom Percival SL and her team had published articles cited 1901 times with an H-index of 22, ranking them first in this research field. Bjarnsholt T was ranked second in the field, with a team that had published over 20 articles cited 1787 times. Also of note is Roy S, who has published 11 articles with a sharp rise in publications from 2018 to 2021 and the publication of highly cited articles since 2013. All of these authors had H-index values of greater than 8.

Highly cited articles in this research space included the most highly cited article by Edwards et al published in *Current Opinion In Infectious Diseases* with 560 citations, followed by a study by Bjarnsholt et al (538 citations) and a review article by Han et al (503 citations; Table 4).

3.6 | Web of science categories

In a category analysis, 96 categories that appeared over 50 times were identified (Table 5). Among these categories, Dermatology, Surgery, Microbiology, Pharmacology Pharmacy, Materials Science Biomaterials, Medicine Research Experimental, Biochemistry Molecular Biology, Nanoscience Nanotechnology, Chemistry Multidisciplinary, and Materials Science Multidisciplinary ranked in the top 10.

TABLE 4 The top 10 authors with the most highly cited articles

Rank	Authors	Title	Journal	Year	Citations
1	Edwards R, Harding KG	Bacteria and wound healing	Current Opinion in Infectious Diseases	2004	560
2	Bjarnsholt T, Kirketerp-Moller K, Jensen PO, Madsen KG, Phipps R, Krogfelt K, Hoiby N, Givskov M	Why chronic wounds will not heal: a novel hypothesis	Wound Repair and Regeneration	2008	538
3	Han G, Ceilley R	Chronic Wound Healing: A Review of Current Management and Treatments	Advances in Therapy	2017	503
4	Yin WY, Yu J, Lv FT, Yan L, Zheng LR, Gu ZJ, Zhao YL	Functionalized Nano-MoS2 with Peroxidase Catalytic and Near-Infrared Photothermal Activities for Safe and Synergetic Wound Antibacterial Applications	ACS Nano	2016	495
5	Thurlow LR, Hanke ML, Fritz T, Angle A, Aldrich A, Williams SH, Engebretsen IL, Bayles KW, Horswill AR, Kielian T	Staphylococcus aureus Biofilms Prevent Macrophage Phagocytosis and Attenuate Inflammation In Vivo	Journal of Immunology	2011	375
6	Dowd SE, Wolcott RD, Sun Y, McKeehan T, Smith E, Rhoads D	Polymicrobial Nature of Chronic Diabetic Foot Ulcer Biofilm Infections Determined Using Bacterial Tag Encoded FLX Amplicon Pyrosequencing (bTEFAP)	PLOS One	2008	347
7	Kirketerp-Moller K, Jensen PO, Fazli M, Madsen KG, Pedersen J, Moser C, Tolker-Nielsen T, Hoiby N, Givskov M, Bjarnsholt T	Distribution, organisation, and ecology of bacteria in chronic wounds	Journal of Clinical Microbiology	2008	335
8	Dowd SE, Sun Y, Secor PR, Rhoads DD, Wolcott BM, James GA, Wolcott RD	Survey of bacterial diversity in chronic wounds using Pyrosequencing, DGGE, and full ribosome shotgun sequencing	BMC Microbiology	2008	315
9	Abrigo M, McArthur SL, Kingshott P	Electrospun Nanofibers as Dressings for Chronic Wound Care: Advances, Challenges, and Future Prospects	Macromolecular Bioscience	2014	307
10	Percival SL, Hill KE, Williams DW, Hooper SJ, Thomas DW, Costerton JW	A review of the scientific evidence for biofilms in wounds	Wound Repair and Regeneration	2012	278

3.7 | Keyword analysis

Next, the VOSviewer application was used to extract keywords from the titles of abstracts of these 1340 studies, revealing 45 keywords that were present a minimum of 25 times (Table 6). These keywords were subsequently grouped into three clusters based upon the number of articles in which they co-occurred (Figure 5A). The first cluster (red) consisted of 16 keywords, the highest frequency of which were chronic wounds, efficacy, management, therapy, and debridement. The second cluster (green) consisted of 14 keywords, the highest frequency of which were antibacterial, nanoparticles, bacterial biofilms, silver nanoparticles, and cytotoxicity. The third cluster (blue) consisted of 14 keywords, the highest frequency of which were resistance, mechanisms, pseudomonas aeruginosa, staphylococcus aureus, and expression.

A co-occurrence overlap map corresponding to the top 45 keywords is shown in Figure 5B. The most current keywords in this network included 'nanoparticles', 'antibiofilm', 'silver nanoparticles', 'hydrogel', 'chitosan', 'diagnosis', and '*Staphylococcus aureus*'.

TABLE 5 Categories represented over 50 times

Rank	Category	Documents
1	Dermatology	257
2	Surgery	229
3	Microbiology	150
4	Pharmacology Pharmacy	146
5	Materials Science Biomaterials	107
6	Medicine Research Experimental	100
7	Biochemistry Molecular Biology	88
8	Nanoscience Nanotechnology	82
9	Chemistry Multidisciplinary	76
10	Materials Science Multidisciplinary	76
11	Engineering Biomedical	75
12	Dentistry Oral Surgery Medicine	74
13	Biotechnology Applied Microbiology	63
14	Cell Biology	59
15	Multidisciplinary Sciences	59
16	Infectious Diseases	58
17	Polymer Science	51

TABLE 6 Keyword clustering analysis

Cluster	Keyword	Rank	Occurrence frequency	Average publication year
1	Bacterial biofilms	4	93	2014.9247
1	Efficacy	5	86	2017.6235
1	Management	7	85	2017.5904
1	Therapy	8	72	2016.9155
1	Chronic wound	15	52	2018.3654
1	Debridement	16	51	2016.7451
1	Inflammation	18	47	2017.6304
1	Dressings	23	42	2017.2857
1	Diabetic foot ulcers	26	39	2016.5897
1	Ulcers	27	38	2016.5263
1	Diagnosis	35	30	2018.3333
1	Microbiology	36	30	2014.5
1	Colonisation	37	28	2014.3214
1	Care	40	27	2018.3462
1	Venous leg ulcers	42	27	2012.8889
1	Matrix	43	26	2018.0769
2	Biofilm formation	1	106	2017.0283
2	Antibacterial	2	99	2019.0909
2	Nanoparticles	6	86	2019.6824
2	Silver nanoparticles	11	63	2019.0794
2	Antimicrobial	14	54	2017.9259
2	Silver	21	44	2016.7045
2	Chitosan	24	41	2018.5854
2	Antimicrobial peptides	29	35	2018.1143
2	Cytotoxicity	30	34	2017.9706
2	Drug-delivery	31	32	2018.0312
2	Hydrogel	32	32	2019.0625
2	Antibiofilm	34	30	2019.2667
2	Surface	39	28	2017.7143
2	Photodynamic therapy	41	27	2017.7037
2	Prevention	45	25	2016.44
3	Resistance	3	94	2016.8723
3	Mechanisms	9	69	2017.4853
3	*Escherichia coli*	10	63	2016.0635
3	*Pseudomonas aeruginosa*	12	61	2017.1639
3	Expression	13	60	2016.4746
3	*Staphylococcus aureus*	17	48	2018.1875
3	Antibiotics	19	45	2017.6136
3	Antibiotic-resistance	20	44	2016.6591
3	Cells	22	42	2017.0714
3	Identification	25	41	2017.122
3	Virulence	28	38	2016.1579
3	Resistant *Staphylococcus aureus*	33	31	2016.6333
3	Mrsa	38	28	2018.0741
3	Susceptibility	44	26	2015.3462

3.8 | Co-cited reference analysis

The top 10 most co-cited references in this analysis included the most highly ranked publication, which was published by James GA et al. (2008), with 292 citations and classification within cluster 1 (Table 7). The most second highly ranked publication was published in Science (IF 2021, 47.728, H-index, 11 186 and JCR Q1).

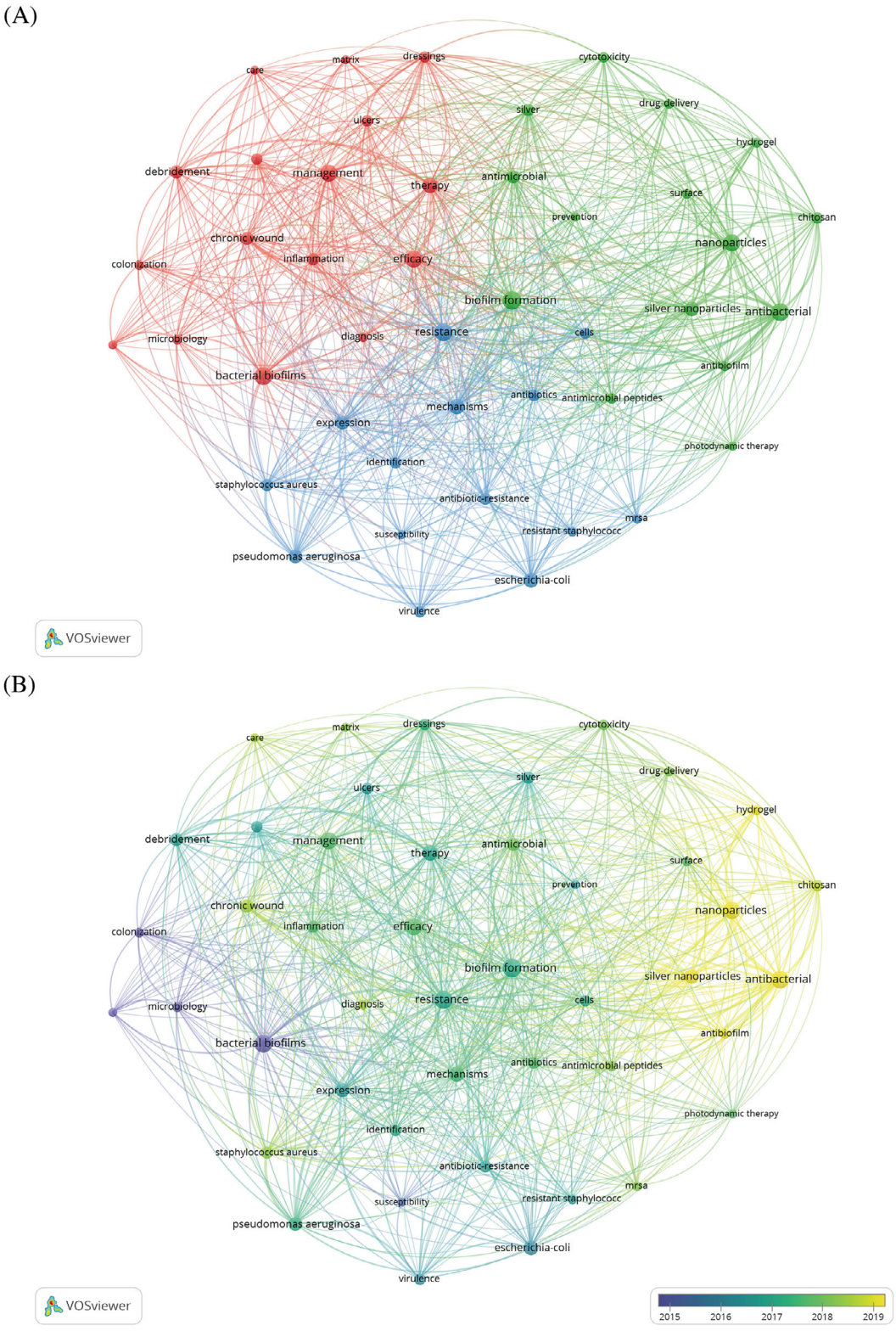

FIGURE 5 A co-occurrence network visualisation map for the top 45 keywords. (A) A visualisation map replicating the publications associated with the top 45 author keywords grouped into 3 clusters consisting of nodes with the same colour. Nodes represent keywords, node size is proportional to publication number, lines correspond to collaborations, and line thickness and the size between nodes are proportional to the relative strength of that relationship. (B) Node colour corresponds to the average publication year associated with the indicated keywords, with blue and yellow respectively corresponding to earlier and more recent publications

TABLE 7 The top 10 co-cited references associated with research focused on biofilms and wound healing

Rank	Co-citation	Centrality	Author	Year	Journals	Vol	Page	DOI	Cluster
1	284	0.44	James GA	2008	Wound Repair Regen	16	37	10.1111/j.1524-475X.2007.00321.x	10
2	167	0.25	Costerton JW	1999	Science	284	1318	10.1126/science.284.5418.1318	1
3	132	0.16	Bjarnsholt T	2008	Wound Repair Regen	16	2	10.1111/j.1524-475X.2007.00283.x	6
4	94	0.03	Wolcott RD	2010	J Wound Care	19	320	10.12968/jowc.2010.19.8.77709	4
5	88	0.65	Dowd SE	2008	BMC Microbiol	8	0	10.1186/1471-2180-8-43	4
6	87	0.11	Bowler PG	2001	Clin Microbiol Rev	14	244	10.1128/CMR.14.2.244-269.2001	1
7	83	0.27	Donlan RM	2002	Clin Microbiol Rev	15	167	10.1128/CMR.15.2.167-193.2002	12
8	81	0.02	Sen CK	2009	Wound Repair Regen	17	763	10.1111/j.1524-475X.2009.00543.x	5
9	78	0.18	Gjodsbol Kristine	2006	Int Wound J	3	225	10.1111/j.1742-481X.2006.00159.x	5
10	78	0.16	Kirketerp-Moller K	2008	J Clin Microbiol	46	2717	10.1128/JCM.00501-08	5

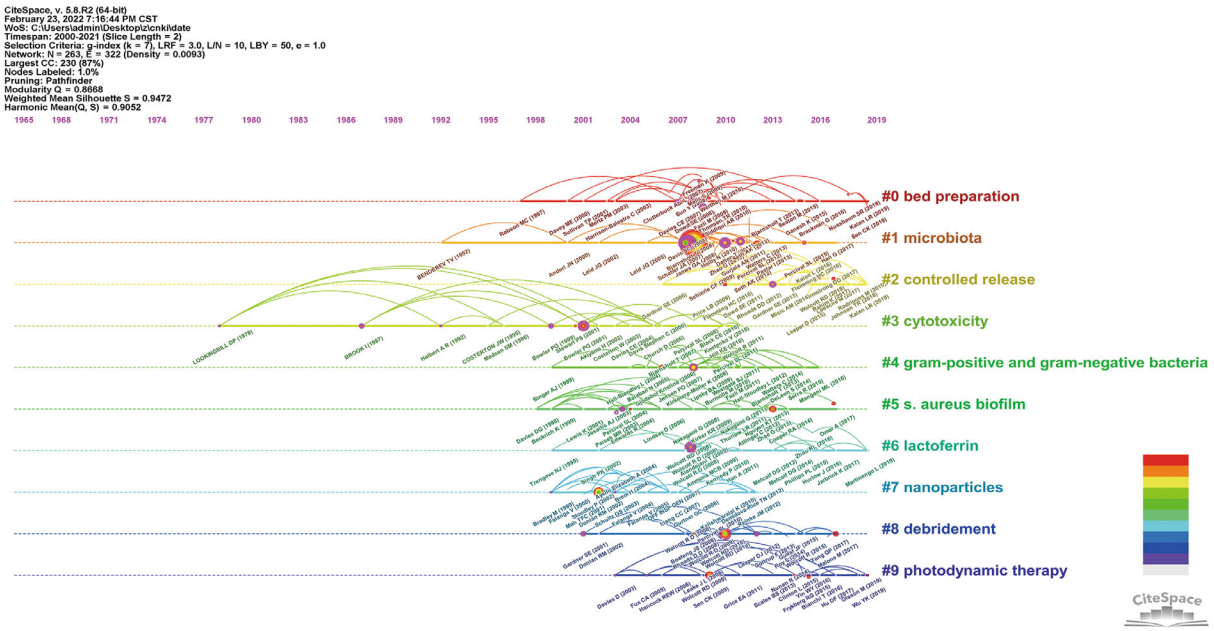

FIGURE 6 Timeline overview of co-cited studies associated with research focused on biofilms and wound healing

Lastly, we conducted a temporal cocitation analysis (Figure 6). This approach revealed that the majority of studies in this research space were published after 1999, with a sharp uptick in publication rates beginning in 2008. Cytotoxicity (cluster #3) and microbiota (cluster #2) emerged as early hotspots in this research space. Bed preparation (cluster #0) contained the greatest number of publications, consistent with the central role of bed preparation as a focus when studying biofilms in the context of wound healing research. Controlled release (cluster #2), lactoferrin (cluster #6) and photodynamic therapy (cluster #9) are the latest hot cocitation in this field in recent years.

4 | DISCUSSION

4.1 | Trends in research pertaining to biofilms and wound healing

Bibliometric and visualised analyses can offer a high-level overview of the current status of a given research field while helping to predict future trends in this research space. In this study, we therefore explored publications pertaining to biofilms and wound healing with a focus on the countries/regions, institutions, journals, authors, and hotspots driving key advances associated

with this topic. Key advances have been made in biofilm research, and it is an actively and rapidly developing area of scientific interest.[2,15] Here, we found that the number of publications focused on biofilms and wound healing is growing annually, with over 89 countries having contributed to this field. In light of these results, we posit that many detailed studies focused on biofilms and wound healing will be published in the coming years.

4.2 | Overview of the global quality and status of publications in this field

By assessing the total number of citations produced by a given country, one can gauge the academic impact of that nation in a given field. Currently, the USA has made had the greatest impact on research pertaining to biofilms and wound healing (422 publications, 14 988 citations), followed by China (170, 3882), England (133, 3984), India (96, 1193), and Germany (86, 2085). While the USA is thus the overall leader in this field to date, the volume and quality of studies conducted in China are continuing to grow, positioning it to supplant the USA in the future. Indeed, in 2021 the number of publications from China (60) is greater than that from the USA (43).

Overall, the number of papers published in this field each year has risen annually since 2010. Overall the USA exhibited 14 988 citations and an H-index of 65, both of which were the highest for any included region or country, and its citation/article ratio (35.51) was greater than that for any other country. In contrast, the H-index for India was relatively low (20), as was the citation/article ratio (12.43). A total of 170 articles have been published in China, with an H-index of 30 and a citation/article ratio of 22.84, both of which are less than the values for the USA. While England has published just 133 articles in this field, it exhibits a relatively higher H-index (35) and citation/article ratio (29.95; Figure 2C and Table 1).

The Journal of Wound Care, *International Wound Journal*, *Wound Repair And Regeneration*, *Wounds a Compendium of Clinical Research And Practice*, and *PLoS One* have published the greatest number of studies focused on biofilms and wound healing. While the number of publications was relatively similar in the top three journals, *The Journal of Wound Care* had more than twice as many publications as *Wounds a Compendium of Clinical Research And Practice* and *PLoS One*.

With respect to IF, 9 of the 10 highest-impact publications were published within the last three years, with the highest IF being observed for *Nature Reviews Material* (IF = 66.308, JCR = Q1). This journal may thus be an important source of key breakthroughs in this field in the coming years.

The top 10 institutes publishing research on biofilms and wound healing largely aligned with the top 10 countries in this research area, attesting to the importance of focused research institutes as mediators of the academic output for a given nation. Researchers that had published higher numbers of studies were more highly represented, suggesting their high reputation in the field and the likelihood that they will generate in-depth discoveries regarding the interplay between biofilms and wound healing. We then performed co-authorship analyses to examine relationships between countries, institutions, and authors in which greater link strength is estimated to correspond to greater collaboration among these entities. Cluster analyses revealed the Chinese Academy of Sciences, Harvard Medical School, Montana State University, Technical University of Denmark, and the University of Florida to be among the most highly represented institutions. As collaboration among these universities was relatively limited, efforts to establish more robust relationships may help to further advance this field in the future.

4.3 | Web of science categories

The numbers of articles published in different categories offer insight into the focus and hotspots in a given research field. The top 17 categories that appeared more than 50 times in the present analysis suggested that research in the biofilm and wound healing space is increasing focus on materials and drug development. Materials sciences and biomaterials are an area of growing interest in this field. In 2004, the first article on this topic entitled 'In vitro attachment of *Staphylococcus epidermidis* to surgical sutures with and without Ag-containing bioactive glass coating' was published in the *Journal of Biomaterials Applications*. This article quantified and visualised the attachment of bacteria to sutures and compared the antibacterial properties of different Ag-containing bioactive glass coatings. The bactericidal properties of these materials may offer value for use in the design of composite sutures to aid in the healing of wounds and incisions.[16] A growing number of studies have been performed in this broad field over the past 3 years, including several studies falling into subcategories within this field including Biochemistry/Molecular Biology, Nanoscience/Nanotechnology, and Multidisciplinary Materials Science.

Dentistry Oral Surgery Medicine is also an area of active research in this field. For example, one recent study published in the *Journal of Endodontics* employed photoactivated chitosan-based nanoparticles in order to inactive endotoxins and eliminate bacterial biofilms

while promoting bone regeneration and improving resistance to resorption/degradation, underscoring the promise of such nanoparticles as therapeutic tools for reducing root resorption and improving healing.[17] In light of the focus of articles published in this category in recent years, materials-related treatments are expected to remain an area of active future interest.

4.4 | Research focus pertaining to biofilms and wound healing

Through co-occurrence analyses, we sought to identify important research interests and topics in this field in order to aid researchers as they navigate through different studies. A co-occurrence network was generated based on the keywords in the titles and abstracts of included studies, with three key clusters within the resultant network corresponding to clinically relevant research, treatment-related research, and mechanism-related research. The most central and highly weighted keywords in this network ('biofilm formation', 'resistant', 'therapy', 'efficacy', 'nanoparticles', 'antibiofilm', 'silver nanoparticles', 'hydrogel', 'chitosan', 'diagnosis' and '*Staphylococcus aureus*') are likely to represent research hotspots in this active field, with a further need for biofilm research pertaining to these topics and the associated research directions.

Visualisation map overlays were identical to the co-occurrence maps other than the coloration scheme, which was adjusted such that nodes were coloured based upon the average year of publication corresponding to a given keyword. This analysis revealed certain keywords (nanoparticles, antibiofilm, silver nanoparticles, hydrogel, chitosan, and staphylococcus aureus) to be coloured in a manner consistent with their more research focus, suggesting them to be important active research areas in this field that warrant further study, with primary research efforts exploring treatments for biofilms in wound healing remaining a primary focus of this research area.

4.5 | Strengths and limitations

This bibliometric analysis is the first to our knowledge to have explored research trends focused on biofilms in the context of wound healing. While this study offers a high-level and comprehensive overview of this research space and offers visual analyses related to current publications on this topic, there are nonetheless certain limitations to this analysis. For one, studies published in languages other than English were omitted from this analysis using the WoS SCIE database. In addition, recently published studies may have been largely overlooked with respect to their significance owing to the low citation frequency inevitably observed during the immediate period following publication. Changing bibliometric trends over time may lead to different conclusions in future analyses. As such, further updated bibliometric analyses incorporating non-English studies are warranted in the future.

Overall, these results highlight global trends pertaining to research regarding biofilms in the context of wound healing. The USA was identified as a leading contributor in this research space, while the greatest percentage of articles in this field were published in *The Journal of Wound Care* published the most articles in the field. Clinical research focused on the treatment and removal of biofilms in the context of wound healing is likely to be an area of future research interest, and current research hotspots in this field include terms such as 'nanoparticles', 'antibacterial', 'hydrogel', 'chitosan', and 'cytokines'.

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CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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