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RESEARCH TREND ON DIABETIC FOOT ULCER WOUND HEALING USING BIOFILM

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Abstract:

This bibliometric analysis explores the research trends on diabetic foot ulcer (DFU) wound healing using biofilm, a topic of increasing importance due to the growing prevalence of diabetes and the associated complications in wound management. DFUs represent a significant healthcare burden, and biofilm formation is recognized as a major barrier to effective healing. Despite the clinical relevance, the integration of biofilm-related strategies in DFU treatment remains an emerging field. To address this gap, we conducted a systematic analysis to identify publication patterns, influential contributions, and collaborative networks. The data search strategy employed three core keywords: “diabetic foot ulcer,” “wound healing,” and “biofilm.” Using the Scopus database and the search string TITLE (["diabetic foot ulcer" OR dfu OR dfus OR "foot ulcer" OR "diabetic foot wound" OR "chronic foot ulcer in diabetes"] AND ["wound healing" OR "skin healing" OR "wound dressing" OR "tissue repair" OR "tissue regeneration"] OR biofilm), a total of 366 relevant documents were retrieved. Data cleaning and standardization were performed using OpenRefine, while Scopus Analyzer and VOSviewer software facilitated bibliometric mapping and visualization. The results show a marked increase in publications over the last decade, with China, the United States, and India being the most prolific contributors. The most cited articles focus on advanced wound dressings, antimicrobial strategies, and the role of stem cells and hydrogels in biofilm disruption and tissue regeneration. Co-authorship analysis reveals strong collaborative networks among Western countries, while Asian nations show increasing research output with moderate

international linkages. Popular keywords include “diabetic foot ulcers,” “wound healing,” “ulcer,” and “biofilm,” highlighting the field’s thematic focus. In conclusion, this study provides a comprehensive overview of the current landscape, key contributors, and emerging directions in DFU wound healing research involving biofilms, offering valuable insights for researchers and clinicians alike.

Keywords:

Diabetic Foot Ulcer, Wound Healing, Biofilm, Bibliometric Analysis

Introduction

Diabetic foot ulcers (DFUs) are a significant complication of diabetes mellitus, often leading to severe outcomes such as lower-limb amputations. A critical factor in the chronicity and difficulty in healing these ulcers is the formation of biofilms. Biofilms are complex structures where bacteria are encased in a self-produced extracellular matrix, making them highly resistant to antibiotics and the host's immune response (Alkhatieb, 2019; Gompelman et al., 2016; Pouget et al., 2020). The presence of biofilms in DFUs promotes persistent inflammation and infection, contributing to delayed wound healing and increased risk of severe complications (Afonso et al., 2021; Pugazhendhi & Dorairaj, 2018). The difficulty in distinguishing between infection and colonization in DFUs further complicates treatment, as biofilms can harbour both pathogenic and non-pathogenic bacteria that act synergistically to maintain chronic infections (Pouget et al., 2020, 2021).

The detection and management of biofilms in DFUs are challenging due to the lack of effective diagnostic methods in clinical settings. Traditional culture techniques are often inadequate, and more advanced methods such as rapid molecular diagnostics and direct microscopy are being explored to improve biofilm detection (Astrada et al., 2024; Gompelman et al., 2016). Techniques like wound blotting with alcian blue staining offer non-invasive and sensitive alternatives for clinical biofilm identification (Astrada et al., 2024). Effective management of biofilms involves regular debridement to remove the biofilm physically and the use of topical antimicrobials and antiseptics. Agents such as sodium hypochlorite and polyhexamethylenebiguanide (PHMB) have shown promising antibiofilm activity, particularly against *Pseudomonas aeruginosa*, a common pathogen in DFUs (Barrigah-Benissan et al., 2022; Srivastava & Sivashanmugam, 2020).

Innovative therapeutic strategies are being developed to target biofilms more effectively. These include the use of antimicrobial peptides that disrupt biofilm formation and enhance bacterial dispersion, and bacteriophage therapy, which targets specific bacteria within the biofilm (Martinet et al., 2025; Zhang et al., 2024). Additionally, topical oxygen therapy has been shown to alter the wound microbiome, promoting the growth of aerobic bacteria and potentially improving healing outcomes (Hunter et al., 2020). Advanced models such as 3D bioengineered skin and hydrogel-based systems are being utilized to better simulate the DFU microenvironment and evaluate the efficacy of these novel treatments (Martinet et al., 2025). These approaches aim to complement or replace traditional antibiotic therapies, offering new hope for improving the management and healing of diabetic foot ulcers.

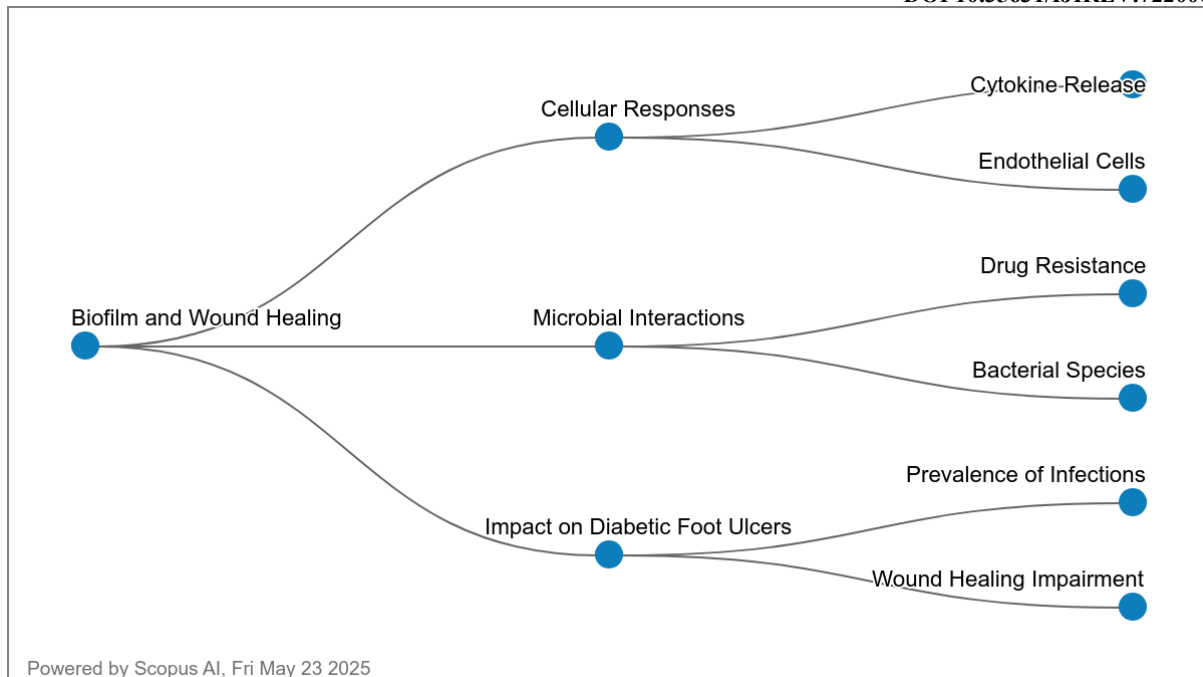


Figure 1: DFUs Concept Map

Research Question

- i. RQ1: How has the research on diabetic foot ulcer wound healing involving biofilms evolved over time based on publication year?
- ii. RQ2: Which articles in this research area have received the highest number of citations?
- iii. RQ3: Which countries contribute the most publications to the field of diabetic foot ulcer wound healing using biofilms?
- iv. RQ4: What are the most frequently used keywords in the literature related to this study?
- v. RQ5: How do countries collaborate in co-authorship within this research domain?

Methodology

Bibliometrics involves gathering, organizing, and analysing bibliographic data from scientific publications (Alves et al., 2021; Assyakur & Rosa, 2022; Verbeek et al., 2002). Beyond basic statistics, such as identifying publishing journals, publication years, and leading authors (Wu & Wu, 2017), bibliometrics includes more sophisticated techniques like document co-citation analysis. Conducting a successful literature review requires a careful, iterative process to select suitable keywords, search the literature, and perform an in-depth analysis. This approach helps to compile a comprehensive bibliography and achieve reliable results (Fahimnia et al., 2015). With this in mind, the study focused on high-impact publications, as they provide meaningful insights into the theoretical frameworks that shape the research field. To ensure data accuracy, SCOPUS served as the primary source for data collection (Al-Khoury et al., 2022; di Stefano et al., 2010; Khiste & Paithankar, 2017). Additionally, to maintain quality, the study only considered articles published in peer-reviewed academic journals, deliberately excluding books and lecture notes (Gu et al., 2019). Using Elsevier's Scopus, known for its broad coverage, publications were collected from 1998 through May 2025 for further analysis."

Data Search Strategy

A literature search was conducted using the Scopus database to identify studies related to diabetic foot ulcers, wound healing, and biofilm. The search strategy targeted article titles using the following string: TITLE (["diabetic foot ulcer" OR DFU OR DFUs OR "foot ulcer" OR "diabetic foot wound" OR "chronic foot ulcer in diabetes"] AND ["wound healing" OR "skin healing" OR "wound dressing" OR "wound dressings" OR "tissue repair" OR "tissue regeneration"] OR biofilm). This comprehensive approach incorporated common synonyms and related terms to ensure broad coverage of relevant literature. A total of 366 documents were retrieved. Due to the manageable number of results, no exclusion criteria were applied, allowing for the inclusion of all identified studies in the subsequent analysis.

Table 1: The Search String

Scopus	TITLE (["diabetic Foot Ulcer" OR dfu OR dfus OR "foot ulcer" OR "Diabetic foot wound" OR "Chronic foot ulcer in diabetes"] AND ["wound healing" OR "skin healing" OR "wound dressing" OR "wound dressings" OR "Tissue repair" OR "Tissue regeneration"] OR biofilm)
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Data Analysis

VOSviewer is a user-friendly bibliometric software developed by Nees Jan van Eck and Ludo Waltman at Leiden University, Netherlands (van Eck & Waltman, 2010, 2017). Widely utilized for visualizing and analysing scientific literature, the tool specializes in creating intuitive network visualizations, clustering related items, and generating density maps. Its versatility allows for the examination of co-authorship, co-citation, and keyword co-occurrence networks, providing researchers with a comprehensive understanding of research landscapes. The interactive interface, coupled with continuous updates, ensures efficient and dynamic exploration of large datasets. VOSviewer's ability to compute metrics, customize visualizations, and its compatibility with various bibliometric data sources make it a valuable resource for scholars seeking insights into complex research domains.

One of the standout features of VOSviewer is its capacity to transform intricate bibliometric datasets into visually interpretable maps and charts. With a focus on network visualization, the software excels in clustering related items, analysing keyword co-occurrence patterns, and generating density maps. Researchers benefit from its user-friendly interface, enabling both novice and experienced users to explore research landscapes efficiently. VOSviewer's continuous development ensures it remains at the forefront of bibliometric analysis, offering valuable insights through metrics computation and customizable visualizations. Its adaptability to different types of bibliometric data, such as co-authorship and citation networks, positions VOSviewer as a versatile and indispensable tool for scholars seeking deeper understanding and meaningful insights within their research domains.

Datasets comprising information on the publication year, title, author name, journal, citation, and keywords in PlainText format were procured from the Scopus database, spanning the period from 1998 to May 2025. These datasets were then analysed using VOSviewer software version 1.6.19. Through the application of VOS clustering and mapping techniques, this software facilitated the examination and generation of maps. Offering an alternative to the Multidimensional Scaling (MDS) approach, VOSViewer focuses on situating items within low-dimensional spaces, ensuring that the proximity between any two items accurately reflects their relatedness and similarity (van Eck & Waltman, 2010). In this respect, VOSViewer shares

a similarity with the MDS approach (Appio et al., 2014). Diverging from MDS, which primarily engages in the computation of similarity metrics like cosine and Jaccard indices, VOS utilizes a more fitting method for normalizing co-occurrence frequencies such as, the association strength (AS_{ij}) and it is calculated as (Van Eck & Waltman, 2007):

$$AS_{ij} = \frac{C_{ij}}{w_i w_j}$$

which is “proportional to the ratio between on the one hand the observed number of cooccurrences of i and j and on the other hand the expected number of co-occurrences of i and j under the assumption that co-occurrences of i and j are statistically independent” (Van Eck & Waltman, 2007).

Results and Discussion

DFU Research Trend

The trend in publications related to "*Diabetic Foot Ulcer Wound Healing Using Biofilm*" demonstrates a clear and steady growth in research interest over the past two decades, particularly gaining momentum in the last ten years. From 1998 to around 2010, publication numbers were consistently low, typically between 1 and 4 articles per year, indicating that the topic was relatively underexplored. This could be attributed to limited awareness of the biofilm's role in diabetic foot ulcer (DFU) chronicity and the emerging nature of wound microbiology research during that period. The gradual increase from 2011 to 2015 marks a shift, likely influenced by growing clinical recognition of biofilms as a key factor in non-healing wounds.

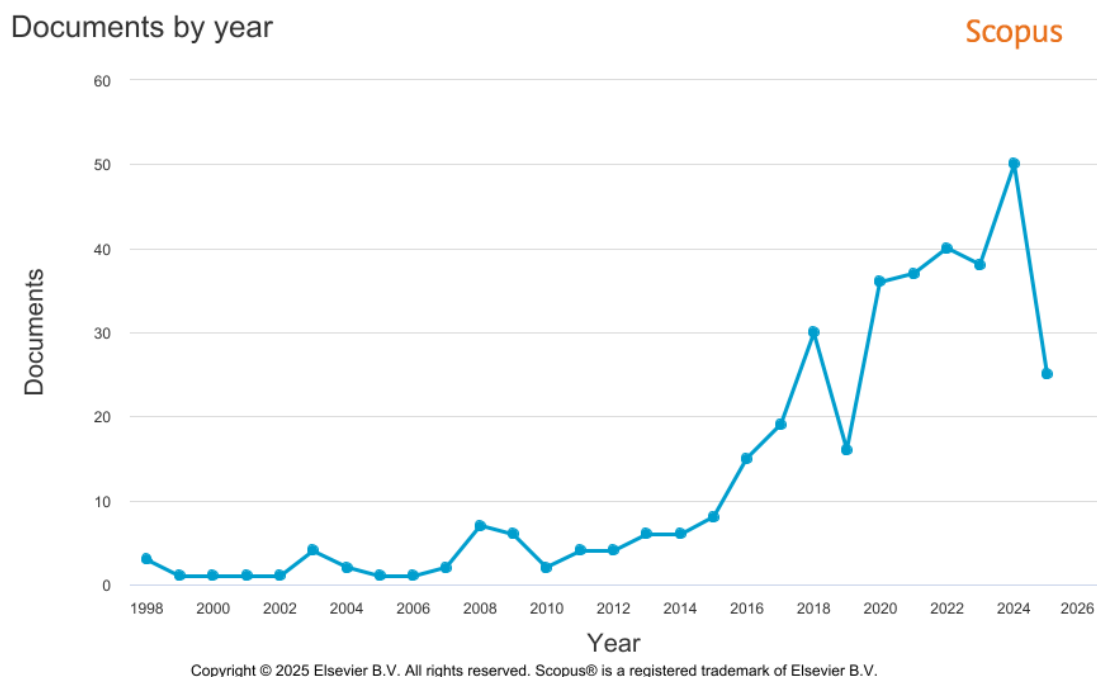


Figure 2: Trend of Research in DFUs By Years

A notable acceleration in research is observed from 2016 onward, with publication counts rising significantly. Between 2016 and 2021, the number of publications remained consistently above 15 annually, peaking at 40 in 2022. This period reflects heightened scientific and clinical interest in integrating microbiological insights with wound care practices, possibly driven by technological advances in biofilm detection and treatment. The surge in publications may also correlate with an increase in interdisciplinary collaboration between microbiologists, wound care specialists, and bioengineers focusing on chronic wound management innovations.

The years 2023 to 2025 continue this upward trajectory, with 2024 recording the highest number of publications (50), accounting for 13.66% of the total. Although 2025 is not yet complete, it has already yielded 25 publications, suggesting sustained research momentum. This recent spike indicates a maturing field, where biofilm-targeted therapies and advanced wound healing technologies are receiving more attention. Overall, the bibliometric data reflect a growing recognition of biofilms in DFU pathology, and an evolving research landscape prioritizing effective interventions for chronic wound healing.

Table 1: Trend of Research in DFUs by Years

Year	Number of Publication	Percentage (%)
2025	25	6.83
2024	50	13.66
2023	38	10.38
2022	40	10.93
2021	37	10.11
2020	36	9.84
2019	16	4.37
2018	30	8.20
2017	19	5.19
2016	15	4.10
2015	8	2.19
2014	6	1.64
2013	6	1.64
2012	4	1.09
2011	4	1.09
2010	2	0.55
2009	6	1.64
2008	7	1.91
2007	2	0.55
2006	1	0.27
2005	1	0.27
2004	2	0.55
2003	4	1.09
2002	1	0.27
2001	1	0.27
2000	1	0.27
1999	1	0.27
1998	3	0.82

Most Cited Articles

The bibliometric analysis of the top 10 most cited authors in the field of diabetic foot ulcer (DFU) wound healing highlight a diverse and evolving research landscape, with a strong emphasis on innovative wound dressing technologies, biofilm understanding, and molecular biology. The most cited article by Moura et al. (2013), with 634 citations, provides a comprehensive review of advanced wound dressings for DFU, indicating its foundational impact in guiding research and clinical practice. Similarly, Liang et al. (2022) garnered 603 citations within a short span, showcasing the field's growing interest in smart, responsive hydrogel dressings, which reflects a paradigm shift toward personalized and adaptive wound care solutions.

Table 2: The Most Top 10 Cited Authors

Authors	Title	Year	Source title	Cited by
(Moura et al., 2013)	Recent advances on the development of wound dressings for diabetic foot ulcer treatment - A review	2013	Acta Biomaterialia	634
(Liang et al., 2022)	pH/Glucose Dual Responsive Metformin Release Hydrogel Dressings with Adhesion and Self-Healing via Dual-Dynamic Bonding for Athletic Diabetic Foot Wound Healing	2022	ACS Nano	603
(Zhao et al., 2019)	Skin-Inspired Antibacterial Conductive Hydrogels for Epidermal Sensors and Diabetic Foot Wound Dressings	2019	Advanced Functional Materials	454
(Dowd et al., 2008)	Polymicrobial nature of chronic diabetic foot ulcer biofilm infections determined using bacterial tag encoded FLX amplicon pyrosequencing (bTEFAP)	2008	PLoS ONE	437
(Li et al., 2018)	Exosomes from adipose-derived stem cells overexpressing Nrf2 accelerate cutaneous wound healing by promoting vascularization in a diabetic foot ulcer rat model	2018	Experimental and Molecular Medicine	392
(Liu et al., 2009)	Increased matrix metalloproteinase-9 predicts poor wound healing in diabetic foot ulcers	2009	Diabetes Care	320
(Muller et al., 2008)	Matrix metalloproteinases and diabetic foot ulcers: The ratio of MMP-1 to TIMP-1 is a predictor of wound healing	2008	Diabetic Medicine	266
(Eginton et al., 2003)	A Prospective Randomized Evaluation of Negative-pressure Wound Dressings for Diabetic Foot Wounds	2003	Annals of Vascular Surgery	250
(Li et al., 2020)	The MSC-Derived Exosomal lncRNA H19 Promotes Wound Healing in Diabetic Foot Ulcers by Upregulating PTEN via MicroRNA-152-3p	2020	Molecular Therapy Nucleic Acids	246

(Davis et al., 2018)	Dysfunctional Wound Healing in Diabetic Foot Ulcers: New Crossroads	2018	Current Diabetes Reports	218
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Several highly cited works also underscore the integration of materials science and bioengineering into DFU management. Zhao et al. (2019) explored conductive hydrogels for both wound healing and sensor applications, accumulating 454 citations, which illustrates the interdisciplinary appeal of such innovations. Dowd et al. (2008) contributed significantly to the understanding of the polymicrobial biofilm nature in chronic DFU infections using advanced sequencing techniques, cited 437 times. This study marked a turning point by highlighting the complex microbiome environment within DFUs, emphasizing the role of biofilms in chronic wound persistence and the necessity for targeted antimicrobial strategies.

Beyond materials and microbiology, several studies explored biological mechanisms driving wound healing. For example, Li et al. (2018) and Li et al. (2020) focused on stem cell-derived exosomes and their regenerative potential, reflecting a growing interest in regenerative medicine. Studies by Liu et al. (2009) and Muller et al. (2008) investigated the predictive value of matrix metalloproteinases in wound healing, while Eginton et al. (2003) validated the clinical efficacy of negative-pressure wound therapy. These findings, together with Davis et al. (2018)'s work on dysfunctional healing pathways, demonstrate that top-cited contributions are not only technologically innovative but also clinically relevant, influencing both academic research and therapeutic interventions in diabetic wound care.

Top Country Based on the Number of Publications

The analysis of influential countries based on citations in diabetic foot ulcer (DFU) wound healing research shows that China is the clear leader, with 114 publications, more than doubling the output of the United States (53 publications), which ranks second. This dominance suggests that China has heavily invested in biomedical and translational research, particularly in advanced wound care, biomaterials, and biofilm management. The large number of Chinese publications reflects both the country's growing scientific infrastructure and a heightened focus on chronic disease management as diabetes prevalence rises domestically.

Following China and the United States, India (28), the United Kingdom (24), and Australia (23) also contribute significantly, forming a secondary tier of influential nations in this field. These countries are known for strong academic and clinical research programs, especially in public health and chronic wound care. The presence of India in this group highlights its growing role in biomedical research, likely driven by a high national burden of diabetes and related complications. The UK and Australia's contributions align with their established expertise in wound management, supported by both academic institutions and national healthcare priorities.

The third tier includes countries with moderate but notable output, such as Iran, Indonesia, Portugal, Germany, and Taiwan, with 9-15 publications each. These nations show regional research strength and growing interest in DFU-related studies. Meanwhile, Malaysia, Netherlands, Saudi Arabia, and South Korea each produced 7 publications, suggesting emerging research activity. These patterns indicate that while high-income countries dominate in volume, middle-income countries are increasingly active, likely due to the global burden of

diabetes and the need for localized solutions to chronic wound care. Overall, the data reflects a geographically diverse and expanding research landscape.

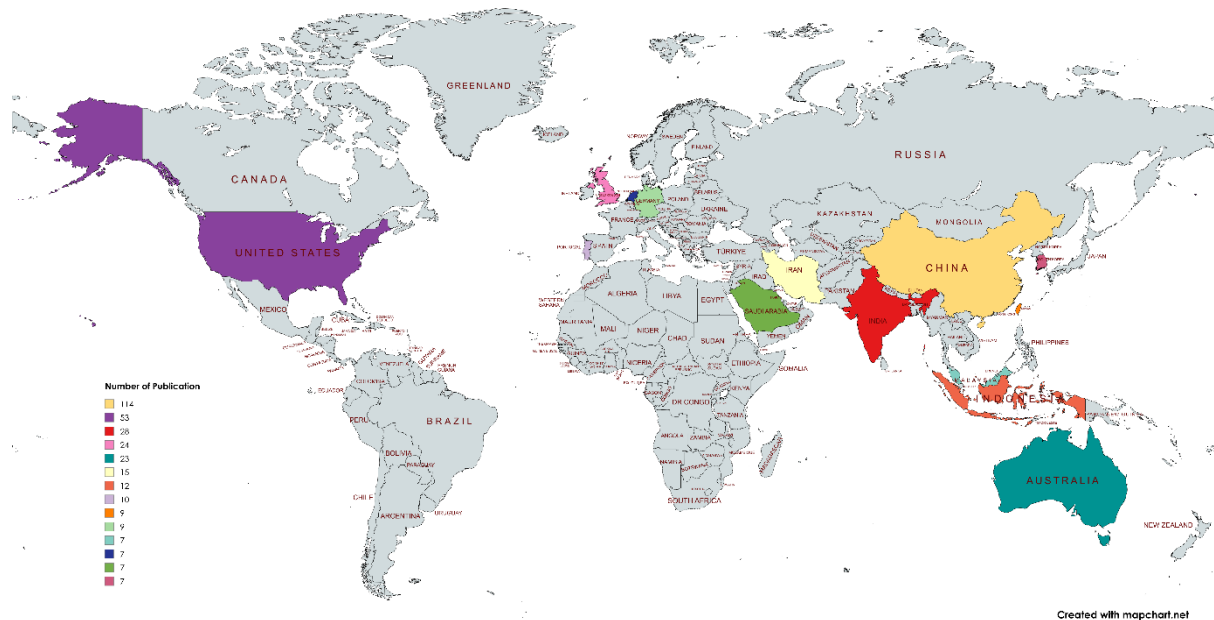


Figure 3: Most Influential Countries by Citations

Popular Keywords Related to the Study

The keyword co-occurrence analysis from VOSviewer highlights “diabetic foot ulcers” as the most dominant term in the research field, appearing 212 times with the highest total link strength of 279, confirming its central role and strong interconnection with other keywords. This is followed by “wound healing” with 101 occurrences and 166 link strength, emphasizing that the core research objective revolves around enhancing healing outcomes in diabetic foot ulcers. The term “diabetes”, with 27 occurrences and a total link strength of 61, serves as a foundational context within which this research area operates, suggesting that much of the literature connects the pathophysiology of diabetes with the development and management of chronic wounds.

Keywords related to treatment approaches and complications—such as “wound dressing” (17 occurrences), “ulcer” (14), “biofilm” (14), and “chronic wound” (12)—demonstrate moderate co-occurrence and link strength, indicating their critical role in the therapeutic landscape. The prominence of “biofilm” highlights the ongoing challenge of infection control in DFUs, as biofilms significantly impair healing. Similarly, terms like “angiogenesis” and “inflammation” (10 occurrences each, 20 link strength) reflect research interest in the biological processes governing wound repair. The inclusion of “amputation” (8 occurrences) underscores the severe consequences of poorly managed DFUs, reinforcing the urgency for effective interventions.

Emerging and specialized topics such as “fibroblasts,” “hydrogel,” “negative pressure wound therapy,” “collagen,” and “staphylococcus aureus” illustrate the field’s multidimensional nature, combining cellular biology, biomaterials, and microbiology. For instance, “hydrogel” and “collagen” point toward advanced wound care technologies, while “staphylococcus aureus” and “antibacterial” terms signal ongoing efforts to address microbial resistance.

Overall, the keyword network demonstrates a mature but still evolving field, with strong thematic clusters centred on wound pathology, treatment innovation, and infection management, all vital to advancing outcomes for diabetic foot ulcer patients.

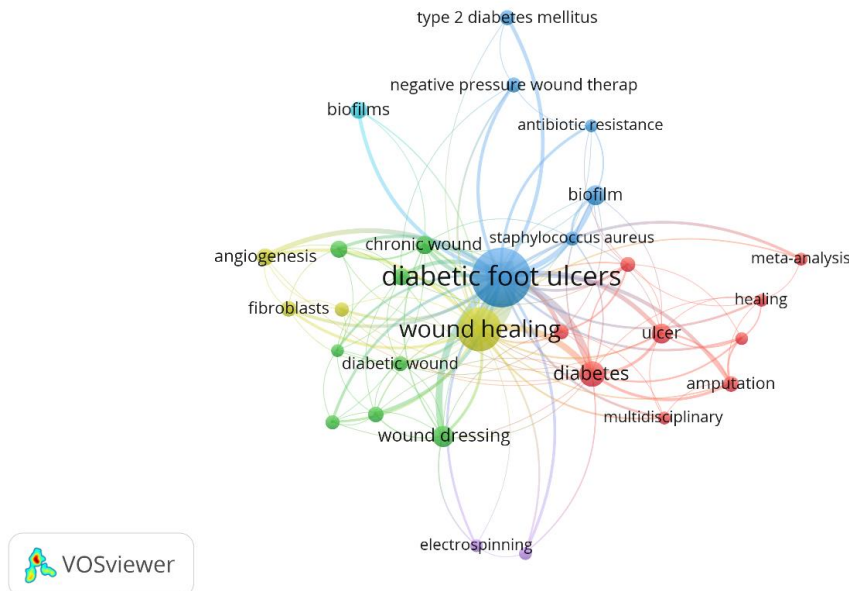


Figure 4: Network Visualization Map of Keywords' Co-Occurrence

Table 3: Distribution of Most Keywords' Co-Occurrence

Keyword	Occurrences	Total link strength
Diabetic Foot Ulcers	212	279
Wound Healing	101	166
Diabetes	27	61
Wound Dressing	17	32
Ulcer	14	28
Biofilm	14	24
Chronic Wound	12	24
Amputation	8	22
Angiogenesis	10	20
Inflammation	10	20
Wound	7	19
Wound Care	7	19
Fibroblasts	8	15
Hydrogel	8	15
Peripheral Artery Disease	5	15
Antibacterial	6	14
Diabetes Mellitus	10	13
Negative Pressure Wound Therapy	7	12
Staphylococcus Aureus	6	12
Collagen	5	12

Co-authorship by Countries' Collaboration

The co-authorship analysis based on country collaboration reveals that the United States leads in both citation count (2875) and total link strength (30), underscoring its central role in international research networks on diabetic foot ulcers and wound healing. Despite producing fewer documents (53) compared to China's 114, the U.S. exhibits stronger collaborative ties and higher impact, suggesting its research is more integrated within global scholarly discourse. Similarly, Australia and the United Kingdom, with 23 and 25 documents respectively, also show robust collaboration with total link strengths of 23 each, reflecting their active participation in international research partnerships.

Interestingly, China, although the most productive in terms of document count (114) and citations (3596), displays a relatively lower total link strength (11). This indicates a more insular research pattern, with fewer international collaborations compared to its Western counterparts. However, the high citation volume suggests that Chinese research is influential, even if less collaborative. The Netherlands and Germany stand out among European countries, not only contributing quality research (249 and 354 citations, respectively) but also engaging in meaningful international cooperation with link strengths of 15 and 12.

Countries in Asia and the Middle East, such as Japan, South Korea, Thailand, Malaysia, Taiwan, Saudi Arabia, and India, contribute moderately to the literature. Their total link strengths ranging from 4 to 8 show a growing but still developing collaborative footprint. While India has a relatively high document count (28), its link strength of 4 indicates limited international co-authorship. Conversely, Iran and Portugal, with fewer publications, show high citation counts (961 and 911, respectively), but minimal collaborative engagement. These findings highlight a global imbalance in research collaboration, suggesting that enhancing international cooperation, especially among highly productive yet less connected countries, could further strengthen the field's advancement.

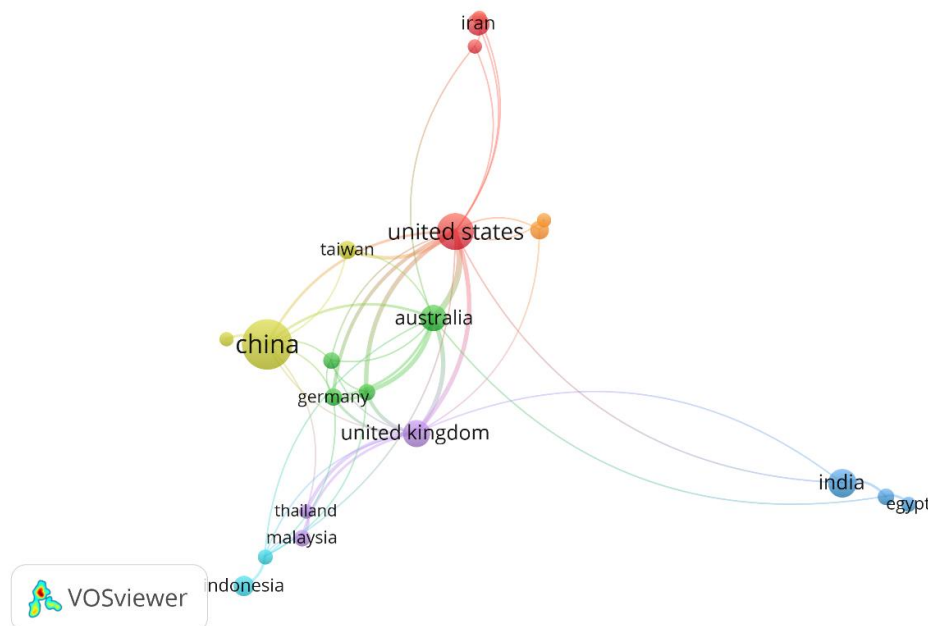


Figure 5: Network Visualization Map of Co-Authorship by Countries' Collaboration

Table 4: Co-Authorship by Countries' Collaboration

Country	Documents	Citations	Total link strength
United States	53	2875	30
Australia	23	1158	23
United Kingdom	25	932	23
Netherlands	7	249	15
Germany	8	354	12
China	114	3596	11
Japan	6	110	8
South Korea	7	174	6
Thailand	5	69	6
Malaysia	7	229	5
Taiwan	9	134	5
Saudi Arabia	7	106	5
India	28	555	4
Iran	15	961	3
Portugal	10	911	3
Canada	5	261	3

Conclusion

This bibliometric analysis aimed to explore research trends in DFU wound healing using biofilm, addressing key questions about publication evolution, influential contributions, country productivity, keyword patterns, and collaborative networks. The study analysed 366 documents from the Scopus database, employing tools like VOSviewer to map the research landscape. The findings revealed a significant increase in publications over the past decade, with China, the United States, and India emerging as the most prolific contributors. Highly cited articles focused on advanced wound dressings, antimicrobial strategies, and regenerative therapies, underscoring the interdisciplinary nature of DFU research. Keyword analysis highlighted "diabetic foot ulcers," "wound healing," and "biofilm" as central themes, reflecting the field's emphasis on infection control and tissue repair. Co-authorship patterns indicated strong collaboration among Western nations, while Asian countries, despite high output, exhibited fewer international linkages.

This study contributes to the field by systematically mapping research trends, identifying gaps, and highlighting the growing importance of biofilm-targeted therapies in DFU management. The findings offer practical insights for clinicians and researchers, emphasizing the need for innovative treatments and enhanced diagnostic tools. Limitations include the reliance on a single database and the exclusion of non-English publications, which may affect the comprehensiveness of the analysis. Future research could expand data sources, incorporate longitudinal studies, and explore under investigated areas such as personalized medicine and cost-effective interventions.

In summary, this bibliometric analysis provides a foundational understanding of DFU wound healing research, demonstrating its dynamic evolution and global significance. The results underscore the value of continued exploration and collaboration to address the challenges posed by biofilm-associated chronic wounds.

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