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Therapeutic Potential of Hyaluronic Acid in Diabetic Foot Ulcer Healing: A Systematic Review and Bibliometric Analysis

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ABSTRACT

Diabetic foot ulcers are one of the most difficult chronic complications to treat in patients with diabetes mellitus, with a high risk of amputation and long-term morbidity. Wound healing in diabetic patients is often hampered by poor vascular conditions, chronic inflammation, and impaired tissue regeneration. In recent years, hyaluronic acid (HA) has been increasingly studied for its potential to accelerate wound healing, especially through its role in tissue hydration, cell proliferation, regulation of inflammation, and stimulation of angiogenesis. The purpose of this study was to systematically analyze the publication trends and scientific findings regarding the effect of hyaluronic acid on accelerating diabetic foot healing during the period 2020 to 2024. This study used the Systematic Literature Review (SLR) method with a combination of analysis tools such as Publish or Perish for bibliometric data collection, NVivo for thematic classification, and VOSviewer for visual mapping of relationships between keywords. The keywords used in the literature search included “hyaluronic acid” OR “HA” AND (“diabetic foot ulcer” OR “diabetic foot” OR “DFU”) AND (healing OR regeneration OR “wound healing”) with the exception of cosmetic, dermatological, aesthetic, and ophthalmological topics. The results showed that HA has been shown to significantly accelerate the healing process of diabetic foot wounds, especially when combined with biomaterials or stem cells, and when used in the form of smart hydrogels that are adaptive to the wound environment. The majority of publications came from China and Indonesia, with research focusing on the regenerative and anti-inflammatory aspects of HA. This study confirms the strategic position of HA as a modern therapeutic agent in the management of diabetic foot wounds and opens up exploration space for more innovative and precise advanced formulations.

KEYWORDS: Hyaluronic Acid, Diabetic Foot Ulcer, Wound Healing, Tissue Regeneration.

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INTRODUCTION

Diabetic foot is one of the most serious and common complications of diabetes mellitus which has become a global concern in the field of public health. Diabetes mellitus, which is characterized by chronic hyperglycemia, not only affects glucose metabolism, but also affects vascular function, the immune system, and tissue regenerative processes (1). In the context of wounds, diabetic patients often experience decreased healing function due to impaired microcirculation, chronic inflammation, and imbalance in the activity of wound healing cells such as macrophages, fibroblasts, and keratinocytes (2). One of the most dangerous conditions that arise from uncontrolled diabetes is diabetic foot ulcers (DFU), which have a high risk of causing lower limb amputation (3). The medical and scientific world is now focused on finding therapeutic interventions that can accelerate the healing process of diabetic wounds, improve the wound microenvironment, and reduce the rate of amputations and associated morbidity.

In an effort to overcome the major challenges in healing diabetic wounds according to (4,5) Biomaterial-based therapies have undergone significant development. One of the most promising materials is hyaluronic acid (HA), a natural polysaccharide that is a major component of the extracellular matrix.(6). HA has viscoelastic, biocompatible, and bioactive properties that support various phases of wound healing, from hemostasis, inflammation, proliferation, to tissue remodeling (7). The advantages of HA lie in its ability to maintain wound moisture, regulate cell migration, modulate immune responses, and accelerate angiogenesis and tissue regeneration (8). The combination of physical and biological characteristics makes HA a potential therapeutic agent that has been applied in various dosage forms such as gels, dressings, scaffolds, and nanoparticle-based delivery systems.

Although many interventions have been used to treat diabetic foot ulcers, the reality on the ground shows that slow wound healing rates and high amputation rates are still major problems, especially in countries with increasing diabetes prevalence rates (9). The World Health Organization (WHO) estimates that 15–25% of people with diabetes will develop a foot ulcer during their lifetime, and approximately 85% of non-traumatic amputations start with a non-healing foot wound (10). In Indonesia, based on the 2018 Riskesdas (Basic Health Research), the number of diabetes sufferers continues to increase from year to year, with a national prevalence reaching more than 10%, and diabetic foot ulcers are recorded as the leading cause of hospitalization in diabetes patients in various hospitals (11). This reflects that even though conventional interventions such as debridement, antibiotics, and negative pressure therapy have been performed, optimal wound healing is still difficult to achieve.

According to (12) The use of hyaluronic acid has shown positive results in the healing of chronic wounds, including burns, surgical wounds, and diabetic foot ulcers. Research by (13) stated that the use of HA combined with iodine significantly increased tissue granulation and decreased wound scores based on clinical evaluation. Another study by (14) who developed a pH-responsive HA-based hydrogel system showed that HA can accelerate wound healing by regulating inflammation and supporting new tissue formation in a diabetic rat wound model. The study by (15) who used a combination of HA with platelet-rich fibrin (PRF) also found that HA contributed to increased angiogenesis and accelerated wound epithelialization time in patients with DFU. These studies indicate that HA not only has physical benefits as a wound moisturizer, but also works actively in the wound microenvironment to accelerate tissue regeneration.

Technological innovation has driven the development of HA formulations in the form of nanoparticles, self-healing hydrogels, and bioactive patches combined with stem cells, growth factors, and anti-inflammatory drugs. Research by (16) introduced HA-based hydrogel modified with miRNA nanoparticles to suppress chronic inflammation and enhance angiogenesis simultaneously. (17) developed HA-hydrogel combined with deferoxamine to stimulate new blood vessel formation in necrotic tissue of diabetic foot wound patients. Although these findings demonstrate the extraordinary potential of HA in wound healing, the distribution of these research results is still scattered and has not been systematically reviewed in terms of global publication trends, countries of origin of researchers, and dominant research themes that have emerged in the past five years. This raises fundamental questions about the dynamics of global scientific knowledge in exploring the use of HA for diabetic foot wound healing.

Based on previous studies above, it seems that most researchers only focus on the clinical effectiveness and biomedical tests of hyaluronic acid in accelerating wound healing, both through in vitro and in vivo tests. However, there is less focus on globa l bibliometric mapping of research trends, country collaborations, institutions, and the evolution of keywords related to the topic. In fact, this kind of literature mapping is very important to determine the direction of scientific development, identify research gaps, and develop more targeted future research strategies. Therefore, to fill this gap, this study will focus more on bibliometric analysis of publication trends regarding the effect of hyaluronic acid in healing diabetic feet, especially in the period 2020 to 2024.

The purpose of this study was to determine the frequency of publication and the number of citations related to research on the effect of hyaluronic acid in healing diabetic feet in the period 2020 to 2024. In addition, this study also aims to analyze the frequency of publications based on the country of origin of the researcher, as well as identify patterns of international collaboration, co-authorship networks, and trends in key keywords that appear in related research through a bibliometric approach based on VOSviewer software. By using comprehensive bibliometric data, this study is expected to provide important contributions to the scientific community and health practitioners in understanding the direction of global research developments and strengthening HA-based interventions as a scientific solution in accelerating diabetic foot healing.

LITERATURE REVIEW

2.1 Diabetic Foot and the Complexity of the Healing Process

According to (18), “Diabetic foot ulcer is a complex, chronic complication of diabetes mellitus that involves peripheral neuropathy, peripheral arterial disease, and infection.” This statement confirms that diabetic foot ulcer (DFU) is not just an ordinary wound, but a chronic condition that arises due to multifactorial damage in the body of a diabetic. Neuropathic disorders make sufferers not feel small wounds that then develop, while peripheral arterial disease inhibits the blood supply that is important for the regeneration process (19). According to (20) infections that easily attack the wound area also worsen the condition and prolong the healing duration. This complexity makes DFU a major clinical challenge, because it not only risks causing wounds that do not heal, but can also lead to amputation if not treated optimally and quickly. The wound healing process in diabetic patients also involves a weakened immune response and unbalanced enzymatic activity, making healing efforts slower compared to healthy individuals.

(21) stated that “The wound healing process in diabetic foot ulcer is prolonged due to impaired angiogenesis, decreased fibroblast proliferation, and persistent inflammation.” This underlines that delayed diabetic wound healing is not only due to external factors, but also caused by disruption of internal biological mechanisms that affect each stage of healing. According to (Inci Kazkayası, 2023) The wound healing process consists of the inflammatory, proliferative, and remodeling phases that occur sequentially and in balance. In DFU patients, inflammation tends to be prolonged, thus inhibiting the transition to the proliferative phase and disrupting the formation of new tissue. According to (HJ Wu et al., 2023) Fibroblasts that should be active in synthesizing collagen become less productive, and angiogenesis needed to bring oxygen and nutrients to the wound tissue is sharply reduced. Therefore, an effective healing strategy must be able to overcome these biological barriers holistically, not just treating the wound surface.

2.2 The Role of Hyaluronic Acid in Wound Healing

(24) states that “Hyaluronic acid plays an important role in tissue hydration, cell proliferation, and inflammation regulation, all of which are essential for wound healing.” This quote shows that hyaluronic acid (HA) is not only a physical support material, but also has an important biological function in accelerating wound healing. As a polysaccharide that is naturally found in the extracellular matrix, HA is able to create a moist environment, which is very much needed in the process of cell migration and differentiation. This moist environment not only accelerates epithelialization, but also prevents further tissue necrosis. HA also plays a role in regulating the local immune response and supporting the recruitment of immune cells needed in the early phase of healing. According to (25) Due to its viscoelastic and bioactive properties, HA can be widely used in various dosage forms such as gels, sheets, and wound dressings for chronic wounds such as DFU.

(Kartika, Alwi, Suyatna, et al., 2021) explains that “Hyaluronic acid-based dressings have been shown to significantly reduce healing time and improve wound closure in chronic ulcers, including diabetic foot ulcers." This provides a concrete illustration that the clinical application of HA has a real impact in accelerating the healing of chronic wounds. According to (8) The use of HA in diabetic wound dressings not only increases the healing rate, but also improves the quality of the tissue formed after wound closure. In addition, HA is able to reduce the colonization of pathogenic microorganisms on the wound surface by creating a natural barrier that also supports tissue regenerative activity. The combination of anti-inflammatory and promotive properties against cell growth makes HA very potential as part of standard therapy for chronic wounds. Several HA-based products that have been marketed have shown positive clinical results, both in the form of monotherapy and in combination with other bioactive components such as PRF or growth factors.

RESEARCH METHODS

The research method used in this study is the Systematic Literature Review (SLR), which aims to summarize and analyze various scientific studies that have been published in a structured, transparent, and replicative manner related to the role of hyaluronic acid (HA) in accelerating the healing of diabetic foot ulcers (27). This SLR procedure follows the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) principle, starting with the identification stage, screening, eligibility checking, to the final study inclusion stage (JW Creswell & Creswell, 2018). The keywords used in the scientific article search included the Boolean combination: ("hyaluronic acid" OR "HA") AND ("diabetic foot ulcer" OR "diabetic foot" OR "DFU") AND (healing OR regeneration OR "wound healing" OR "ulcer healing") NOT cosmetic NOT aesthetic NOT ophthalmology NOT dermatology. These keywords were designed to obtain articles that were specifically relevant to the clinical context of diabetic foot wound healing, while excluding publications from non-medical fields such as aesthetics or ophthalmology to focus the results (29). Article searches were conducted through international scientific databases such as Scopus, PubMed, ScienceDirect, and Google Scholar, with a publication range between 2020 and 2024 to ensure the recency of data and the relevance of findings in the latest developments in medical technology (30).

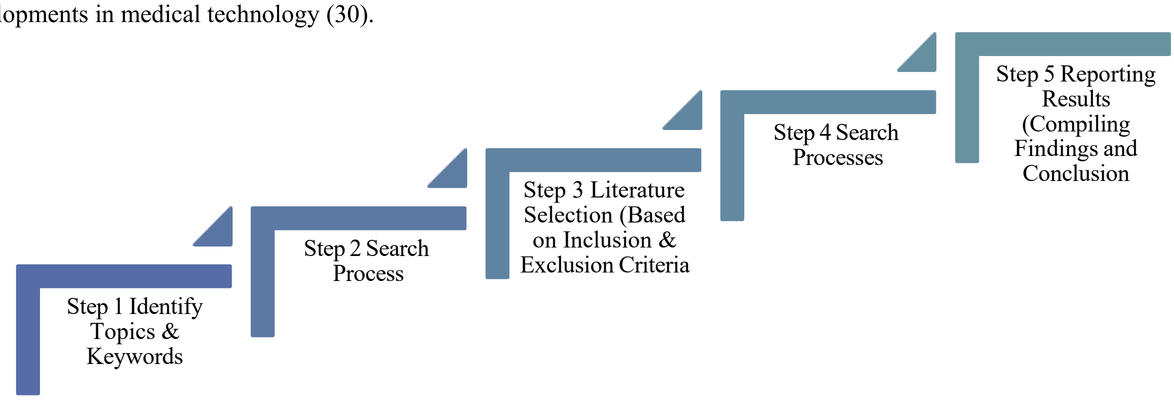
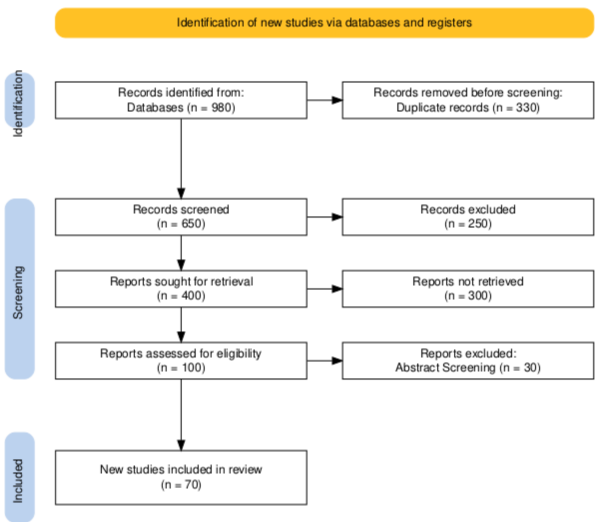


Figure 1. Research Flow Diagram



Source : PRISMA Database (2025)
Figure 2. PRISMA Table

Figure 2 shows a PRISMA flowchart depicting the study selection process in this study. Of the total 980 articles identified through the database, 330 articles were removed due to duplication. Next, 650 articles were screened, and 250 of them were excluded due to irrelevance. Of the 400 reports that were further searched, only 100 were successfully retrieved for eligibility evaluation because 300 reports were unavailable. After abstract screening, 30 reports were excluded, resulting in a total of 70 studies finally included in this systematic review. This diagram illustrates the rigorous and systematic selection process in ensuring that only the most relevant and high-quality articles were analyzed in this study (31).

The inclusion criteria in this study included: (1) articles written in English, (2) scientific publications in the form of journal articles, (3) focusing on the use of hyaluronic acid in the context of diabetic wound healing or diabetic foot ulcers, (4) publication period between 2020–2024, and (5) available in full access for content analysis. The exclusion criteria included: (1) articles discussing the use of hyaluronic acid in non-wound or cosmetic contexts, such as dermatology and ophthalmology, (2) articles in the form of editorials, letters to the editor, or conference abstracts without peer-review, and (3) duplicate publications from the same source (32). To analyze and visualize data from selected articles, tools such as Publish or Perish are used to determine the frequency of publication and citations, NVivo to conduct thematic analysis and narrative synthesis of article content, and VOSviewer to map the visualization of keyword linkage networks and collaborations between countries or authors (Sugiyono, 2019b, 2021; PD Sugiyono, 2019). The analysis technique used is a combination of bibliometric analysis and qualitative content analysis, which allows researchers to not only quantitatively measure publication trends, but also to deeply understand the developing scientific narrative regarding the influence of HA in the healing process of diabetic feet (Sugiyono, 2019a; FX Sugiyono, 2017). This approach is expected to provide significant contributions in scientific mapping and identification of research gaps that are still open in the field of biomaterial-based chronic wound therapy.

RESULTS AND DISCUSSION

A. Research Results

The results of this systematic review show that hyaluronic acid (HA) has consistently been shown to play an important role in accelerating the wound healing process in patients with diabetic foot ulcers. In a study conducted by (38), it was stated that "Hyaluronic acid combined with platelet-rich fibrin showed superior outcomes in granulation tissue formation and wound area reduction in DFU patients." The combination of HA with PRF enhances the granulation process and accelerates wound closure, indicating that HA is not only protective, but also active in the regenerative process. In addition, a study by (39) also supports the effectiveness of HA, explaining that "Self-healing hyaluronic acid hydrogels responsive to pH and glucose have demonstrated enhanced wound healing performance in diabetic models." This finding proves that HA modification in the form of smart hydrogels is able to adjust the response to complex wound conditions, such as acidic pH and high glucose levels in DFUs. In another study by (40), explained that "Topical application of hyaluronic acid-iodine compound resulted in improved epithelialization and reduced healing time." Integration of HA with antiseptics such as iodine enhances the protective power and accelerates epithelialization. These three studies cumulatively underline that the presence of HA in wound therapy not only optimizes the wound microenvironment, but also accelerates all phases of healing synergistically with other therapeutic agents. The effectiveness of HA is also supported by the development of increasingly sophisticated biomaterial technology. (41) noted that "Hyaluronic acid-based dressings have been shown to significantly reduce healing time and improve wound closure in chronic ulcers, including diabetic foot ulcers." HA-based wound dressings have been clinically proven to shorten wound healing time and enhance the quality of the formed tissue. This study shows that topical formulations of HA in the form of gels or dressing sheets can be applied widely with significant results. In line with that (42,43) explains that "Hyaluronic acid plays an important role in tissue hydration, cell proliferation, and inflammation regulation, all of which are essential for wound healing." This quote shows the biological contribution of HA, not only as a coating material, but also as a bioactive agent that promotes tissue regeneration through optimal regulation of inflammation and hydration. The study by (44) also added a new dimension by stating that "HA-deferoxamine hydrogels improved angiogenesis and accelerated tissue repair in diabetic ischemic wounds." The addition of deferoxamine to HA hydrogels successfully stimulated new blood vessel growth and accelerated tissue repair. These three studies support the conclusion that combining HA with other bioactive ingredients can improve the therapeutic quality and expand the scope of its clinical use.

Research by (45) stated that "Human foreskin-derived dermal stem/progenitor cell-conditioned medium combined with hyaluronic acid promotes extracellular matrix regeneration in diabetic wounds." This study revealed that the integration of HA with stem cell culture medium accelerates the formation of a healthy extracellular matrix, strengthening the structure of wound tissue. (46) in another study stated that "miRNA-loaded hyaluronic acid hydrogels promoted anti-inflammation and angiogenesis in chronic wounds." The innovation in the use of miRNA nanoparticles with HA brought remarkable results in suppressing inflammation and increasing angiogenesis simultaneously. Research by (47) added that "Topical application of HA significantly upregulated VEGF and TGF-β expression in wound sites." Increased expression of growth factors such as VEGF and TGF-β is an important indicator that HA promotes proliferation and remodeling processes. These three studies emphasize that HA not only works as a stabilizer of wound conditions, but also as a directing agent for molecular biological processes in important phases of chronic wound healing.

In research based on antibacterial and immunomodulation approaches, the results obtained further strengthen the position of HA as the main ingredient in diabetic wound therapy. According to (48), "Catechol-functionalized hyaluronic acid patches combined with adipose-derived stem cells accelerated wound healing and reduced macrophage infiltration." This study combined chemically modified HA with fat stem cells, resulting in significant anti-inflammatory effects and accelerated wound granulation. (49) also found that "Collagen/hyaluronan hydrogels releasing sulfated hyaluronan improved healing by reducing pro-inflammatory macrophages in diabetic mice." The reduction in inflammatory macrophages suggests that HA may also modulate the local immune system, helping wounds transition from the inflammatory phase to the proliferative phase. The study by (50) strengthens these findings by stating that "Self-healing HA hydrogel loaded with BM-MSCs regulated inflammatory microenvironment and enhanced tissue regeneration in diabetic rat models." These three studies concluded that HA has strong immunomodulatory potential in controlling the diabetic wound environment, making it a very promising therapeutic strategy for chronic wound conditions that are unresponsive to conventional treatments.

Studies based on clinical methods and bioactive delivery systems also prove the significant contribution of HA. (51) in its clinical trials stated that "Combination of hyaluronic acid with advanced platelet-rich fibrin improved inflammation markers and granulation index in diabetic foot ulcer patients." The decrease in IL-6 levels and the increase in granulation index indicate a substantial positive biological response in this combination application. (52) adding that "Low molecular weight heparin and hyaluronic acid therapies demonstrated significant wound size reduction in DFU patients within four weeks." The combination of anticoagulants and HA opens up new potential in the management of diabetic wounds with vascular compromise. (53) observed that "Hyaluronic acid functionalized scaffolds enhanced cell migration and neovascularization, facilitating complete wound closure." The complete wound closure is evidence that HA not only accelerates the process but also improves the quality of the healing results. These three studies show that in a real clinical context, the use of HA has proven to be effective and can be applied in various formulations for optimal healing results in diabetic foot wounds.

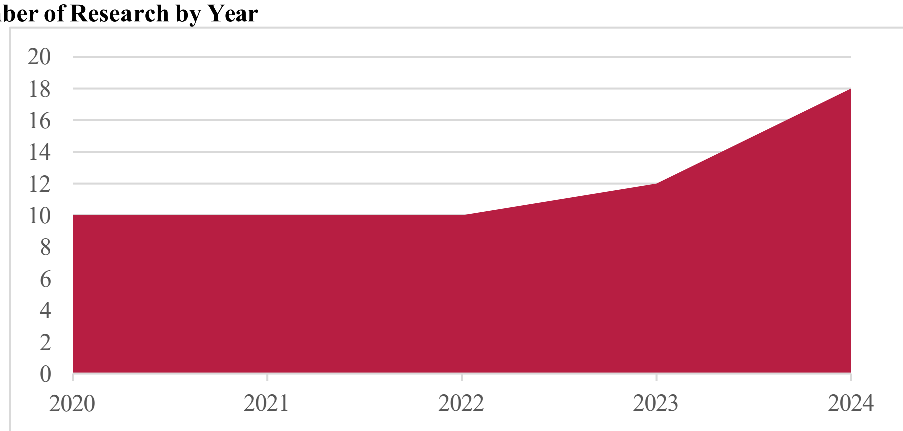
Table 1.Grouping of Previous Research Results

Category	Researcher Name	Findings
Combination Therapy	Guan et al. (2024)	The combination of HA and PRF strengthens tissue granulation and accelerates DFU wound closure.
	Van et al. (2020)	HA and advanced PRF decreased IL-6 and increased granulation index.
	Lin et al. (2023)	HA and low molecular weight heparin effectively reduced wound size within 4 weeks.
Smart Hydrogel	Lan et al. (2024)	pH and glucose responsive HA hydrogel improves diabetic wound healing performance.
	The Last Supper (2022)	HA self-healing hydrogel with BM-MSCs regulates inflammatory microenvironment and tissue regeneration.
	Jia et al. (2022)	HA-deferoxamine hydrogel stimulates angiogenesis and accelerates tissue repair.
Antiseptic and Anti-inflammatory	Zhai et al. (2024)	HA with iodine enhances epithelialization and accelerates healing.
	Zhao et al. (2020)	Collagen/HA hydrogel reduces inflammatory macrophages and accelerates healing.
	(2021)	HA patch with catechol and fat stem cells accelerates healing and reduces macrophage infiltration.
Cell Activation and Tissue Regeneration	Wang et al. (2022)	HA dressing shortens healing time and improves tissue quality.
	N. Li et al. (2022)	HA is important in hydration, cell proliferation, and regulation of inflammation.
	Tang et al. (2023)	Stem cell + HA medium accelerates the regeneration of wound extracellular matrix.
Growth Factors & Molecular	Hauck et al. (2021)	HA increases the expression of VEGF and TGF-β which support wound proliferation and remodeling.
	Y. Chen et al. (2024)	HA scaffold accelerates cell migration and neovascularization, supporting perfect wound closure.
	Pecová et al. (2023)	HA hydrogel with miRNA suppresses inflammation and enhances angiogenesis simultaneously.

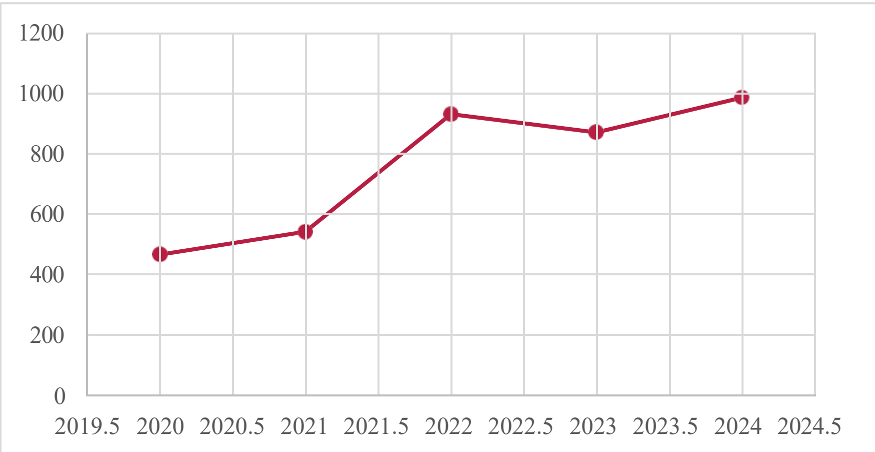
Table 1 shows the diversity of scientific approaches in investigating the effect of hyaluronic acid (HA) on diabetic foot healing through various thematic categories. In the Combination Therapy category, it is seen that researchers focus on the use of HA in synergy with other therapeutic agents such as platelet-rich fibrin (PRF) and heparin, which have been shown to enhance the tissue granulation process and accelerate wound closure. This approach suggests that HA can be utilized not only as a single material, but also as a complementary element in more complex and effective combination therapies. Meanwhile, the Smart Hydrogel category reflects advances in biomaterial technology, where HA is modified into a hydrogel form that is responsive to the diabetic wound environment such as pH and glucose levels. This innovation provides a more adaptive and dynamic solution to chronic wounds with complex metabolic characteristics.

In the Antiseptic and Anti-Inflammatory category, it was found that HA plays an important role in strengthening the antiseptic effect and regulating the local immune response in the wound area. This is evident from the effectiveness of the combination of HA with iodine, collagen, and other chemical compounds in reducing inflammatory cell infiltration and accelerating epithelialization. In the context of Cell Activation and Tissue Regeneration, researchers emphasized HA's ability to improve tissue hydration, cell proliferation, and extracellular matrix formation, all of which are crucial for wound regeneration. Finally, the Growth Factor and Molecular category highlights HA's role in inducing the expression of biomolecules such as VEGF and TGF-β and stimulating angiogenesis, indicating that HA is also able to direct the molecular biological response in diabetic wound healing. All of these groupings reflect that HA has multifunctional potential in chronic wound therapy, depending on the formulation, combination, and application technology used.

Relevance of Number of Research by Year



(A) Distribution of Number of Research Based on Publication Year Period (2020-2024)



(B) Distribution of Number of Citations Based on Publication Year Period (2020-2024)

Figure 3.

The distribution of the number of publications presented in Figure 3A shows an increasing trend of scientific interest in the topic of hyaluronic acid (HA) in the context of diabetic foot ulcer (DFU) healing during the period 2020 to 2024. In early 2020 to 2022, the number of publications was relatively stable, at 10 articles per year, reflecting the initial exploration phase of HA's therapeutic potential in chronic wounds. Research by Chen and Abatangelo (1999) had previously explained that HA plays an important role in tissue hydration and regulation of inflammation, but during this period the attention of researchers began to shift to the specific application of HA for DFU. The increase in the number of publications in 2023 (12 articles) and a sharp spike in 2024 (18 articles) indicate a shift in research focus towards clinical and applied. This is in line with the findings (54) who developed a smart HA-based hydrogel that is responsive to pH and glucose, as well as (55) who reported that the combination of HA with platelet-rich fibrin (PRF) was able to significantly increase tissue granulation. Both studies became important turning points that led to the emergence of a new wave of studies based on the combination of HA with biomaterials or stem cells, which may explain the increasing volume of publications in recent years.

Figure 3B shows that the number of citations to articles on this topic does not always move in line with the number of publications. The year 2022 shows a high spike in citations even though the number of publications is still on par with previous years, indicating that the articles published in that year are of high quality and relevance in the scientific community. This is in line with findings from (56) who reported that HA hydrogel combined with deferoxamine significantly increased angiogenesis and accelerated diabetic ischemic wound healing. This study is widely referenced because it integrates bioactive and tissue engineering approaches in one therapeutic platform. Research by (57) about modified HA to reduce inflammatory macrophages in diabetic wounds also attracted attention because it opened a new path of immunomodulation therapy. The peak citations in 2024 showed that the latest articles were not only innovative, but also had a high impact because they successfully answered the clinical challenges in slow and complex DFU healing. Thus, both in terms of quantity and quality, research on the effect of HA in diabetic foot healing shows rapid development and is increasingly relevant to be studied in the context of precision and personalized regenerative therapy.

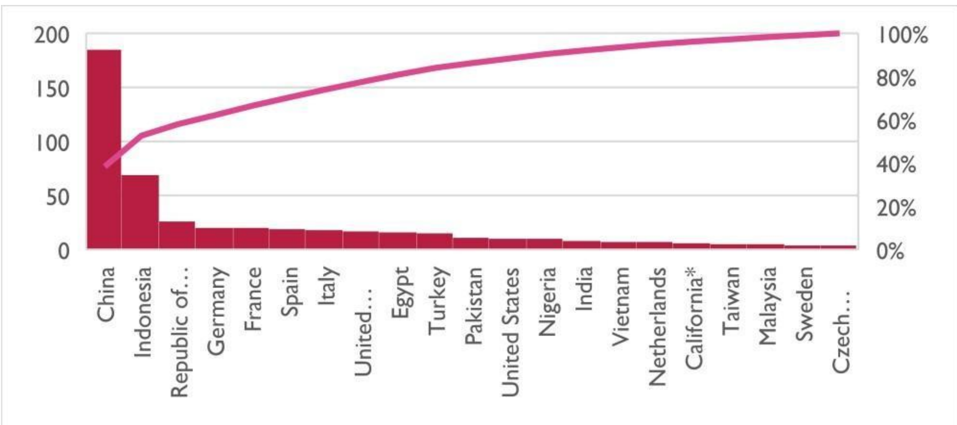
Relevance of Research Numbers by Country

Research on the role of hyaluronic acid in accelerating diabetic foot healing has attracted the attention of the global scientific community in recent years. This phenomenon is not only marked by the increasing number of publications from year to year, but also by the active involvement of various countries in contributing their research results. Mapping country contributions is important to understand the extent of scientific development and clinical innovation in each region, as well as to identify centers of research excellence that are the main drivers in the development of HA-based regenerative therapies. The relevance of data by country also provides an overview of the disparity in international collaboration, the dominant thematic focus in each country, and opportunities for cross-border research synergy to optimize the approach to complex chronic wound healing. Therefore, the following analysis of publication distribution by country is an important foundation in reading the global dynamics of research related to HA and diabetic foot ulcers.

Table 2. Distribution of Number of Research by Country in the Period (2020-2024)

Rank	Country	Number of Articles
1	China	185
2	Indonesia	69
3	Republic of Korea	26
4	Germany	20
5	France (France)	20
6	Spain	19
7	Italy	18
8	United Kingdom (England)	17
9	Egypt	16
10	Turkey	15
11	Pakistan	11
12	USA	10
12	Nigeria	10
14	India	8
15	Vietnamese	7
15	Netherlands (Netherlands)	7
17	Taiwan	5
17	Malaysia	5
19	Sweden (Sweden)	4
19	Czech Republic (Czech Republic)	4
21	California	6

Source : Processed Data (2025)



Source : Processed Data (2025)

Figure 4. Visualization of Distribution of Number of Research by Country in the Period (2020-2024)

The distribution of the number of publications by country as shown in Table 2 and Figure 4 shows that China occupies a dominant position with 185 articles, followed by Indonesia (69), the Republic of Korea (26), and several European countries such as Germany, France, and Spain. China's high contribution reflects the country's commitment to the development of regenerative therapy, especially in the field of chronic wound treatment. This is in line with research by (58) originating from China, where they developed a hyaluronic acid-based hydrogel that is self-healing and responsive to pH and glucose. This research not only demonstrates a high-tech approach, but also reflects China's very significant biomaterial research strength. Meanwhile, Indonesia's contribution, which is in second place with 69 publications, shows an increase in national interest and capability in research related to diabetic foot ulcers (DFU), as seen in several clinical studies such as those conducted by (59) regarding the combination of hyaluronic acid with platelet-rich fibrin to improve wound granulation index.

Other countries such as the Republic of Korea, Germany, and France also show important contributions with a relatively high number of publications in a global context. For example, research by (60) from South Korea showed that stem cell medium combined with hyaluronic acid can promote the formation of a healthier extracellular matrix in diabetic wound healing. This reflects the research trend from developed countries to focus on cell therapy and biomaterial integration in bioactive delivery systems. Researchers from Germany such as (47) also showed that the combination of collagen and hyaluronan can suppress inflammatory macrophages and accelerate wound healing in a diabetic rat model. This shows that although the number of articles from European countries is not as many as China, the quality and focus of the research are very profound, especially in the aspects of immunomodulation and tissue engineering.

Countries such as Malaysia, Taiwan, Sweden, and the Czech Republic have a smaller number of publications, but still show participation in research on this topic. The involvement of these countries is generally focused on local application research and clinical studies based on teaching hospitals. On the other hand, the presence of names such as California needs to be further examined because it is not a country, but rather part of the United States; this could indicate a segmentation of institutions that are reported geographically separately. However, the presence of the United States with 10 publications shows a stable contribution, although in many cases further studies are carried out through multinational collaborations. In a global context, the visualization in Figure 4 also shows a trend of significant inequality in scientific contributions between countries, where almost 80% of publications come from less than the top five countries. Therefore, strengthening cross-country collaboration, especially with developing countries such as Indonesia and Egypt, is important to expand hyaluronic acid-based innovations in diabetic foot ulcer therapy to a wider and more equitable realm.

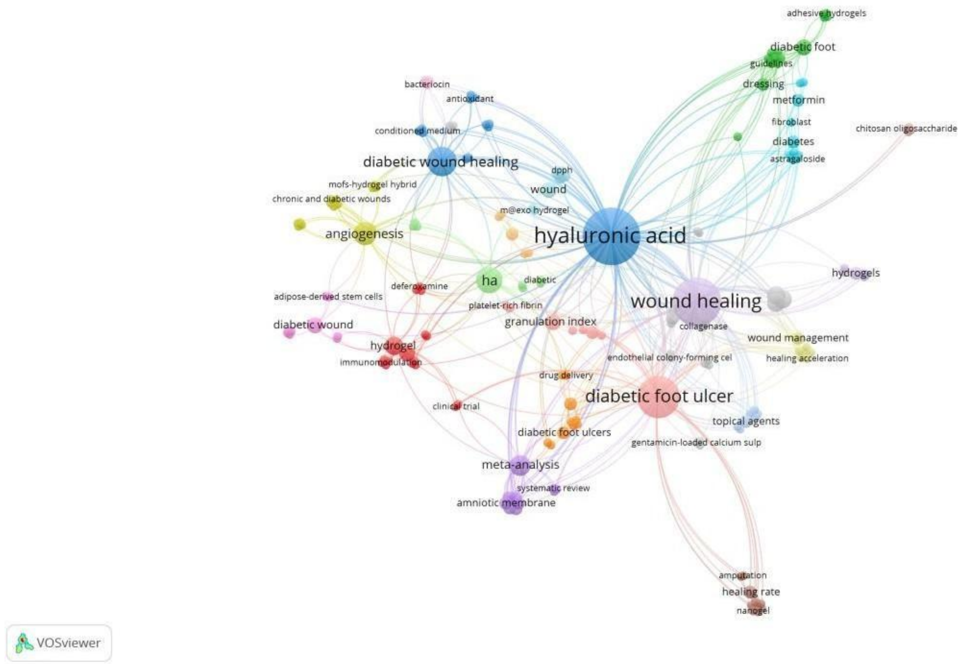
Source : Processed Data (2025)

Figure 5. Visualization of Distribution of Number of Research by Country in the Period (2020-2024) in a Map Chart

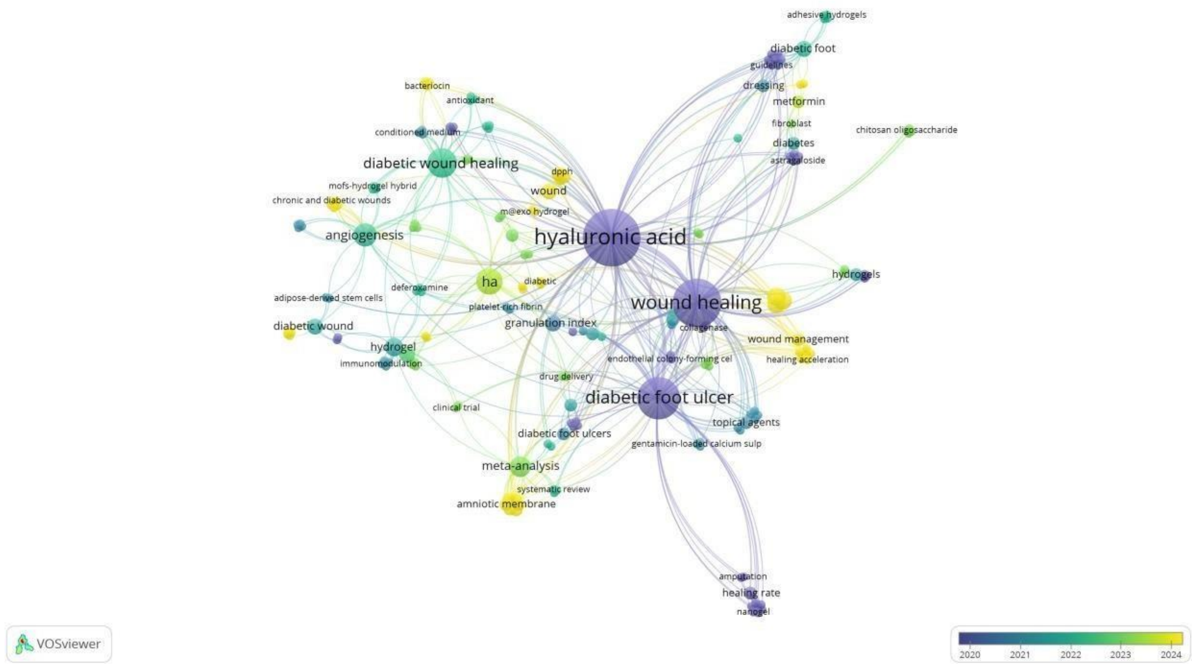
Figure 5 presents a visualization of the distribution of the number of studies by country in the form of a world map, which shows China's dominance as the main center of scientific production related to the use of hyaluronic acid in healing diabetic foot wounds. The dark red color in the Chinese region indicates the highest publication intensity (185 articles), which is supported by the high activity of biomaterials and regenerative therapy research in the country. This is in line with the research (61), which developed a smart HA-based hydrogel that responds to pH and glucose, was shown to be effective in a diabetic wound model. In Southeast Asia, Indonesia also stands out with a high number of contributions (69 articles), one of which is shown by a clinical study (62) regarding the combination of HA with platelet-rich fibrin which successfully accelerated the wound granulation process. Meanwhile, countries such as South Korea, Germany, France, and Italy also appeared with moderate color gradations, reflecting moderate but significant contributions. Research (63) highlights the success of HA in supporting extracellular matrix regeneration through integration with stem cell media. Thus, this map not only shows the geography of scientific contributions, but also illustrates how the global distribution of research is influenced by each country's infrastructure, institutional support, and health policy focus.

VOSviewer Output Analysis

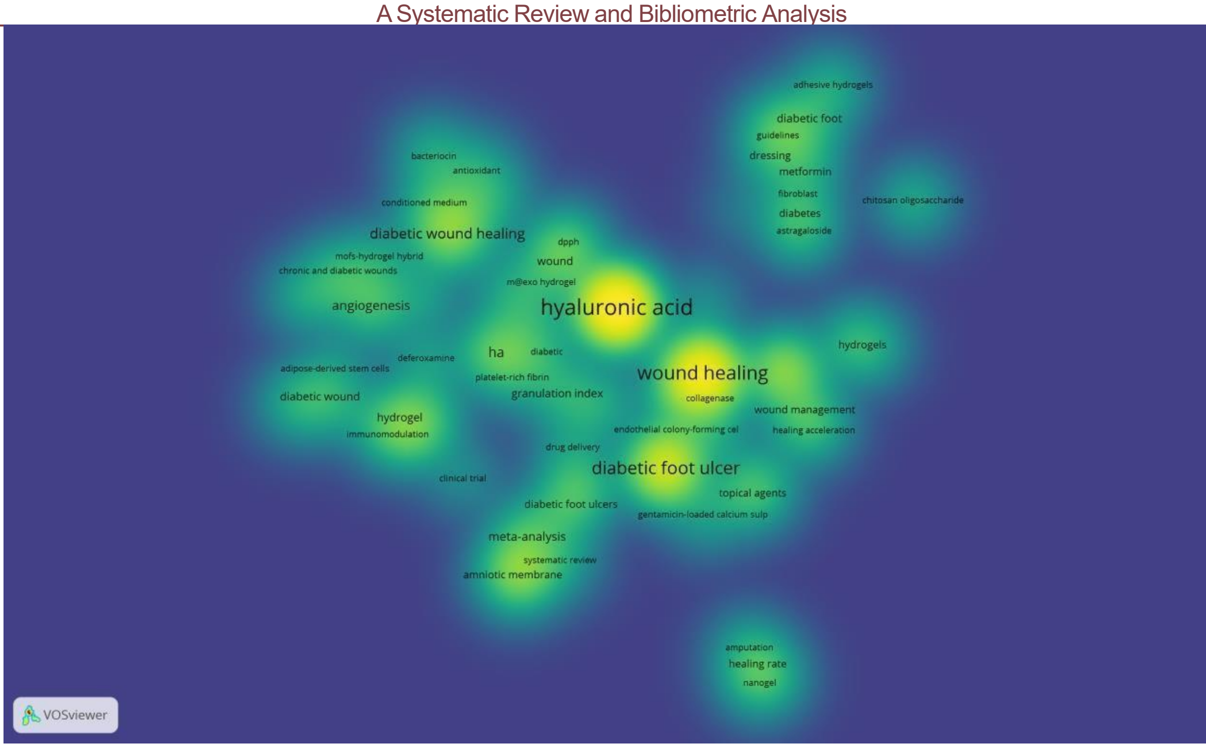
VOSviewer analysis allows researchers to visually and interactively map relationships between keywords, collaborations between authors, and networks of institutions and countries within a research field. In the context of this study, bibliometric analysis was used to evaluate global trends related to the use of hyaluronic acid in diabetic foot ulcer healing during the period 2020 to 2024. With this tool, researchers were able to identify key themes that frequently appeared, the most frequently associated terms, and connectivity between studies that provide an overview of the main focus of the scientific community. This analysis is not only descriptive, but also interpretive, so it can indicate the direction of research development, potential collaborations, and scientific gaps that have not been widely explored.



(A) Network visualization



(B) Overlay visualization



(C) Density visualization

Source : VOSviewer (2025)

Figure 6. VOSviewer Output

The network visualization in Figure 6A shows that the term “hyaluronic acid” is the main hub in the literature ecosystem related to diabetic foot ulcer healing. The “hyaluronic acid” node is strongly connected to other terms such as “wound healing,” “diabetic foot ulcer,” and “hydrogel,” indicating that related research focuses heavily on the biological mechanisms and applications of HA in the wound healing process. The emergence of terms such as “angiogenesis,” “granulation index,” and “drug delivery” also indicates that research has progressed beyond basic clinical trials to the development of more complex therapeutic delivery systems. These findings reinforce the results of (64), who developed pH and glucose-responsive HA hydrogels to enhance angiogenesis in diabetic wounds. The study by (65) is also relevant, as it shows the effectiveness of the combination of HA with PRF in accelerating tissue granulation. The emergence of nodes such as “stem cells” and “immunomodulation” indicates the direction of increasingly complex research trends, integrating regenerative and immunological approaches.

In the overlay visualization (Figure 6B), the color distribution from blue to yellow shows the temporal development of research topics. Terms such as “wound healing,” “diabetic foot ulcer,” and “hyaluronic acid” emerged early on (2020–2021), appearing from blue to green, indicating that these topics have been the mainstay of research in recent years. Meanwhile, terms in more yellow tones such as “healing acceleration,” “metformin,” “adhesive hydrogels,” and “chitosan oligosaccharide” emerged as newer research trends (2023–2024), indicating recent innovations exploring combinatorial approaches in diabetic wound therapy. Research by (66) utilizing the combination of HA and platelet-rich fibrin can be clinically associated with the trends of “granulation index” and “amniotic membrane” that also appear in this visualization. This shows how the research focus is evolving from conventional interventions towards molecular approaches and more adaptive biomaterial combinations for the complex diabetic wound condition.

Figure 6C, which displays density visualization, provides an overview of the intensity of the frequency of term usage in publications. The terms “hyaluronic acid,” “wound healing,” and “diabetic foot ulcer” appear the brightest (bright yellow), indicating that these topics are the most frequently discussed in the literature and are the core of the overall research. Other terms such as “angiogenesis,” “granulation index,” “hydrogel,” and “drug delivery” also appear quite brightly, indicating that studies not only examine the effects of HA in general, but also explore specific mechanisms and application strategies. The study by (67) shows how the use of HA combined with deferoxamine can enhance angiogenesis in ischemic wounds, according to the intensity of the words “angiogenesis” and “hydrogel” appearing in this visualization. The highest density clustered around the main nodes indicates that in the period 2020–2024, the global research concentration will be more directed towards HA-based smart biomaterial strategies aimed at accelerating diabetic wound regeneration with precise molecular and clinical interventions.

B. Discussion

Based on the overall results of the research that have been systematically reviewed, the effect of hyaluronic acid (HA) in accelerating the healing of diabetic feet is not only clinical-practical, but also touches on deep biological-molecular aspects. HA is no longer positioned as a mere wound moisturizer or dressing support material, but has developed into a bioactive agent that is able to regulate various stages of wound healing simultaneously, starting from controlling inflammation, stimulating cell migration, to activating angiogenesis. In cases of diabetic feet where the healing process is hampered by chronic hyperglycemia, immune cell dysfunction, and circulatory disorders, the presence of HA functions as a biological catalyst that is able to restore wound tissue homeostasis. Study by (67) which states that HA supports tissue hydration and cell proliferation is now further strengthened by contemporary studies that integrate HA in more complex active substance delivery systems, such as smart hydrogels, nanoparticles, and bioactive scaffolds.

One dimension that is increasingly prominent in recent HA studies is its ability to collaborate with other therapies, including the use of platelet-rich fibrin, stem cells, and anti-inflammatory compounds. This combination has been shown to improve the quality of tissue regeneration and accelerate epithelialization better than monotherapy. (68), showed that the combination of HA and PRF gave significant results in the formation of granular tissue and diabetic wound closure. This suggests that the effectiveness of HA can be synergistically enhanced through a multimodal approach. In addition, the use of HA in a self-healing hydrogel format as developed by (69) enables wound therapy that is adaptive to changes in the wound environment such as pH or glucose levels. This innovation is very important considering that diabetic foot wounds are dynamic and require treatment that adapts to local conditions in real time. Thus, HA not only accelerates healing, but also presents a new paradigm in the approach to wound therapy that is precise and responsive.

The role of HA in immunomodulation is an aspect that has not been widely highlighted but is starting to show great potential. Diabetic wounds are generally dominated by chronic inflammation that persists due to failure of the inflammatory phase transition to the proliferative phase. In the study (70), the use of a combination of collagen and HA has been shown to reduce inflammatory macrophage activity, indicating that HA plays a role in balancing the local immune response. This aspect is very important because diabetic wound care is not enough to only accelerate regeneration, but also to create a stable and supportive immunological environment for healing. Furthermore, the involvement of HA in stimulating growth factors such as VEGF and TGF-β also indicates that the role of this biomolecule is upstream of many complex healing processes. Therefore, future research directions should deepen the understanding of the mechanisms of HA in immune modulation and genetic expression relevant to tissue regeneration, especially in the context of chronic wounds in diabetic patients.

In a global perspective, literature distribution and bibliometric analysis show that countries such as China, Indonesia, and South Korea play an important role in the development of HA research for diabetic foot wounds. However, from a thematic perspective, there is still a fairly large research gap related to the exploration of more specific HA formulations for patient subpopulations, such as the elderly, patients with severe neuropathy, or ischemic wound sufferers. In addition, most of the research is still experimental or early studies, while longitudinal studies and large-scale clinical trials are still very limited. This is an opportunity that can be answered by researchers through the development of community-based clinical studies that integrate translational approaches from the laboratory to clinical applications. Research by (71), which combines stem cell culture media with HA, provides an initial basis for this approach. Thus, the effect of HA in healing diabetic feet needs to be continuously studied across sectors and disciplines, not only to strengthen empirical evidence, but also to produce more equitable, sustainable, and contextual therapeutic solutions with socio-medical conditions in various countries.

CONCLUSION AND SUGGESTIONS

Based on the overall results and discussions that have been carried out, it can be concluded that hyaluronic acid (HA) has a significant effect in accelerating the healing of diabetic foot wounds through various mechanisms, ranging from tissue hydration, stimulation of cell proliferation, regulation of inflammation, to support for extracellular matrix regeneration and angiogenesis. The effectiveness of HA increases when combined with other bioactive agents such as platelet-rich fibrin, deferoxamine, stem cells, and miRNA nanoparticles, and formulated in the form of smart hydrogels that are responsive to wound environmental conditions such as pH and glucose levels. Findings from various studies indicate that HA is not only passive as a wound coating, but also active as a therapeutic agent that is able to direct the wound healing process systemically and molecularly, making it a prime candidate in the development of more effective and adaptive diabetic wound therapy.

For future development, further research is needed that focuses more on long-term and large-scale clinical trials to ensure the effectiveness and safety of hyaluronic acid in various formulations and patient populations. Research also needs to be directed at exploring the interaction of HA with digital therapies such as sensor-based wound monitoring or integration with 3D printing technology in creating personalized dressings. In addition, it is important to expand studies in developing countries, includ ing Indonesia, to understand the clinical dynamics and challenges of HA implementation in the context of limited healthcare systems, so that the use of HA can be optimized globally to improve the quality of life of patients with diabetic feet.

DECLARATIONS

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Author contribution
1. Jeconia Sinatra: conceptualization and study design, article writing and editing
2. Yan Efrata Sembiring: data acquisition, advice and study validation, final approval

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THERAPEUTIC POTENTIAL OF HYALURONIC ACID IN DIABETIC FOOT ULCER HEALING: A SYSTEMATIC REVIEW AND BIBLIOMETRIC ANALYSIS

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FIGURES

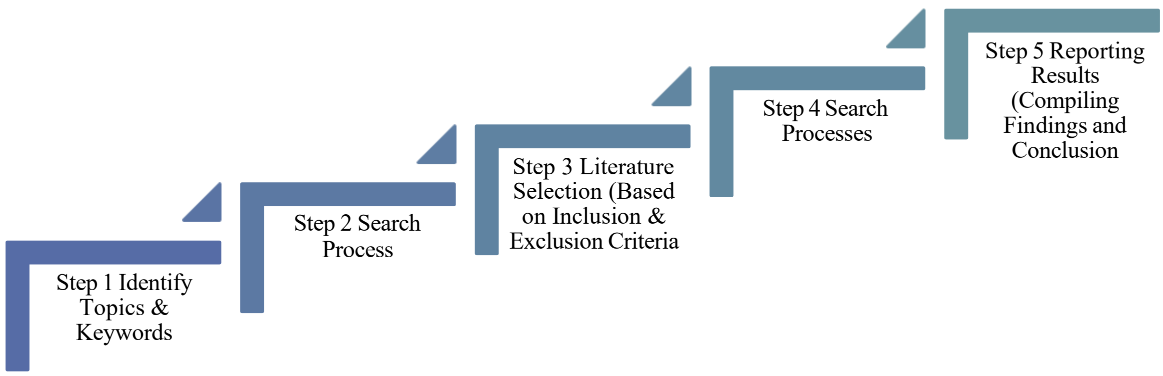
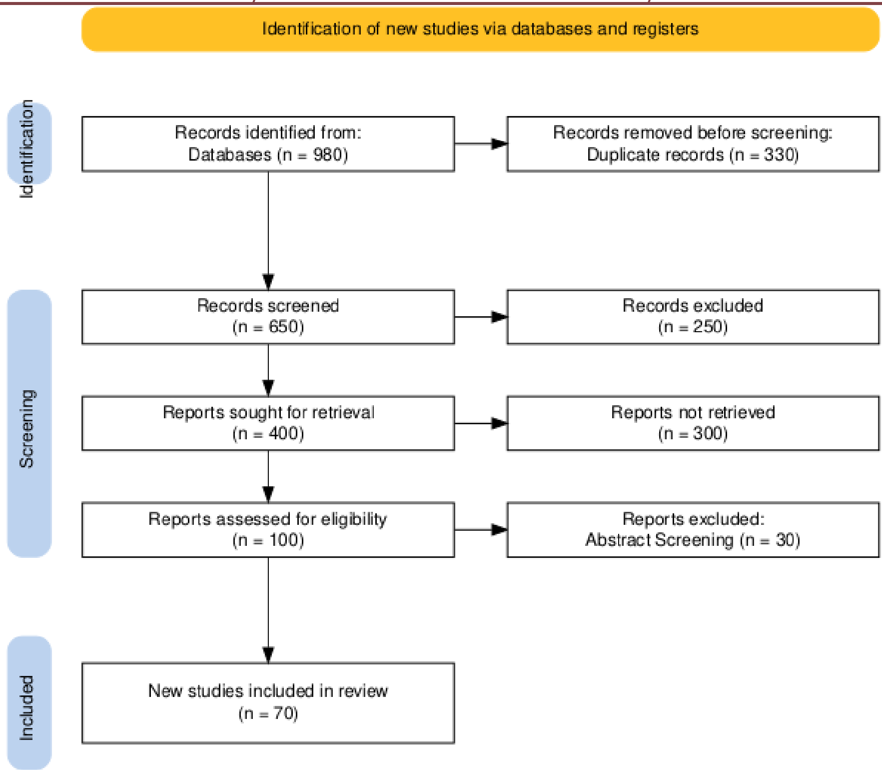
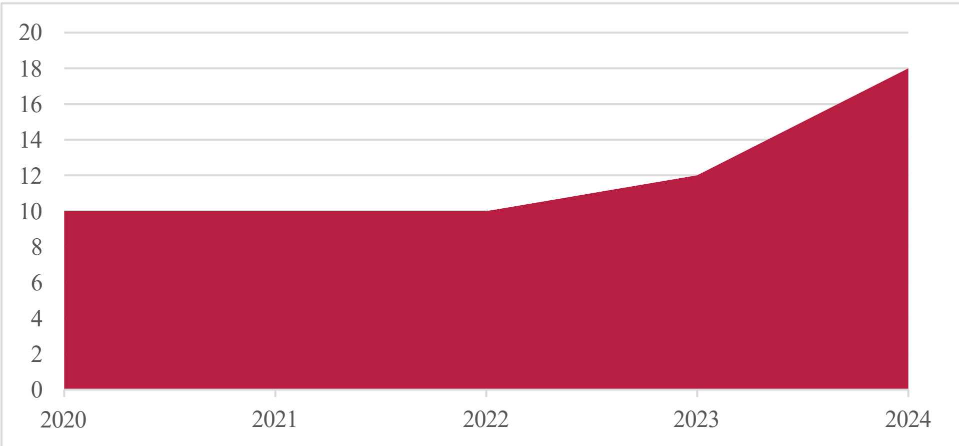


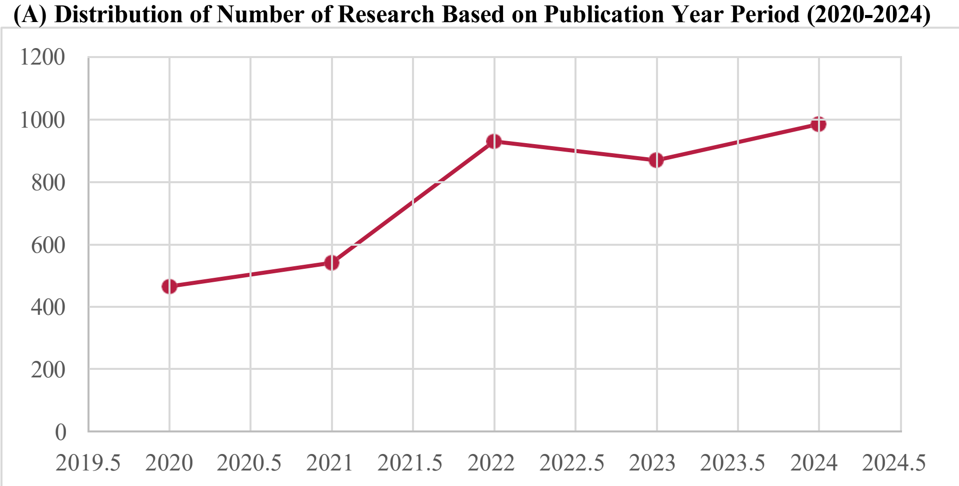
Figure 1. Research Flow Diagram



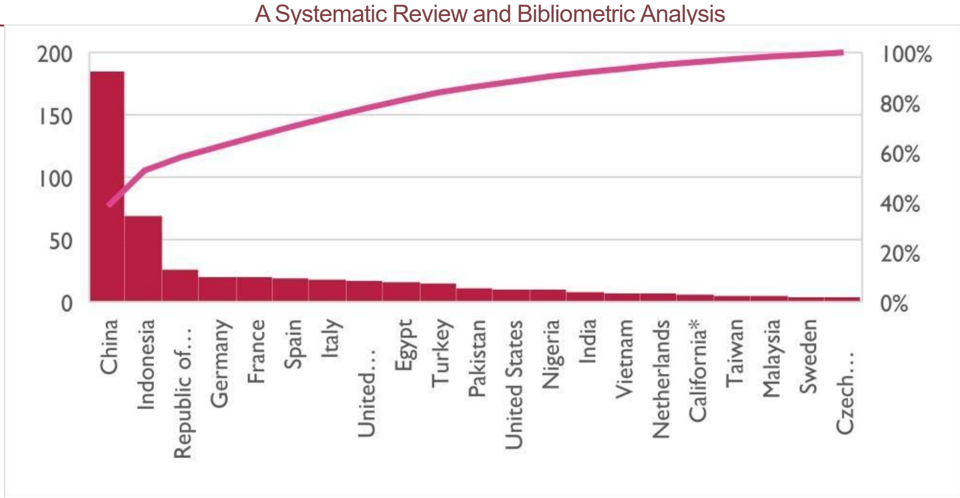
Source : PRISMA Database (2025)
Figure 2. PRISMA Table



(A) Distribution of Number of Research Based on Publication Year Period (2020-2024)



(B) Distribution of Number of Citations Based on Publication Year Period (2020-2024)
Figure 3.

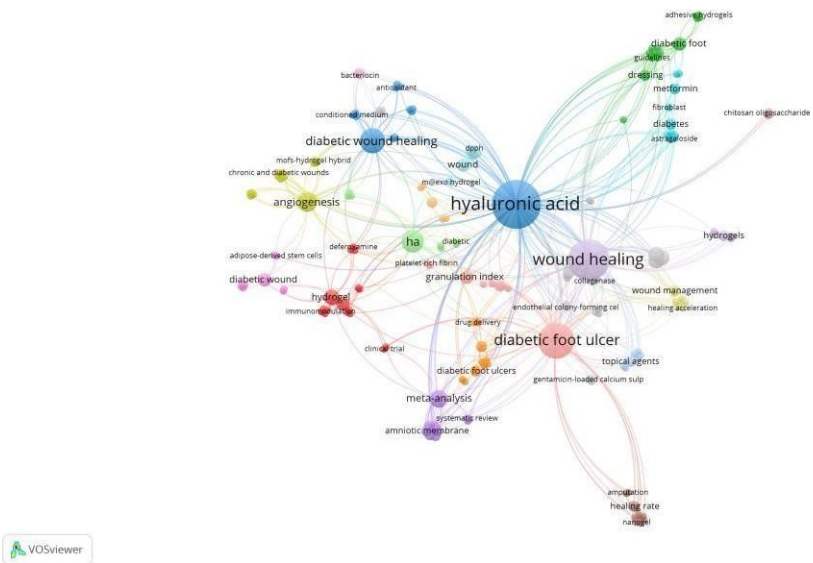


Source : Processed Data (2025)

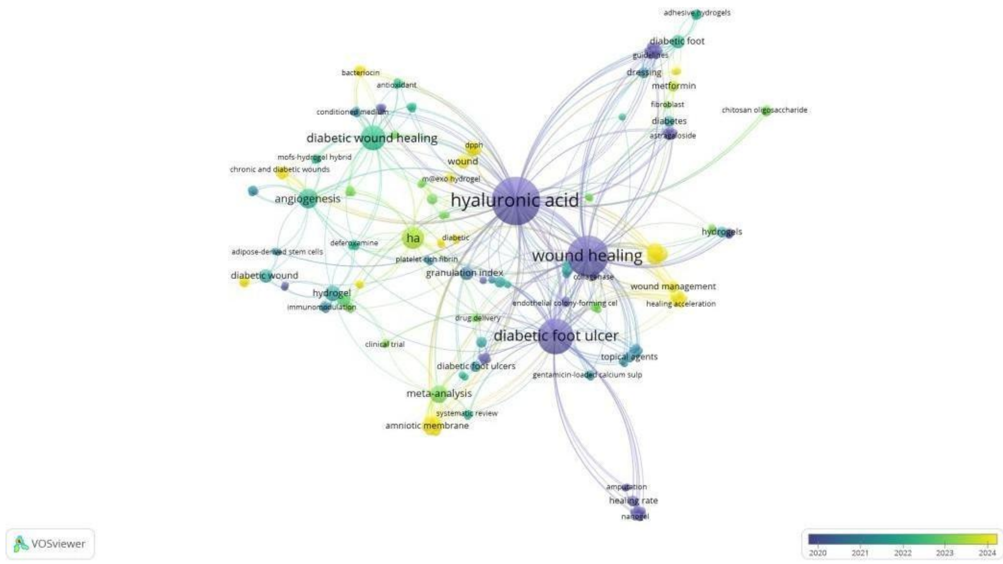
Figure 4. Visualization of Distribution of Number of Research by Country in the Period (2020-2024)

Source : Processed Data (2025)

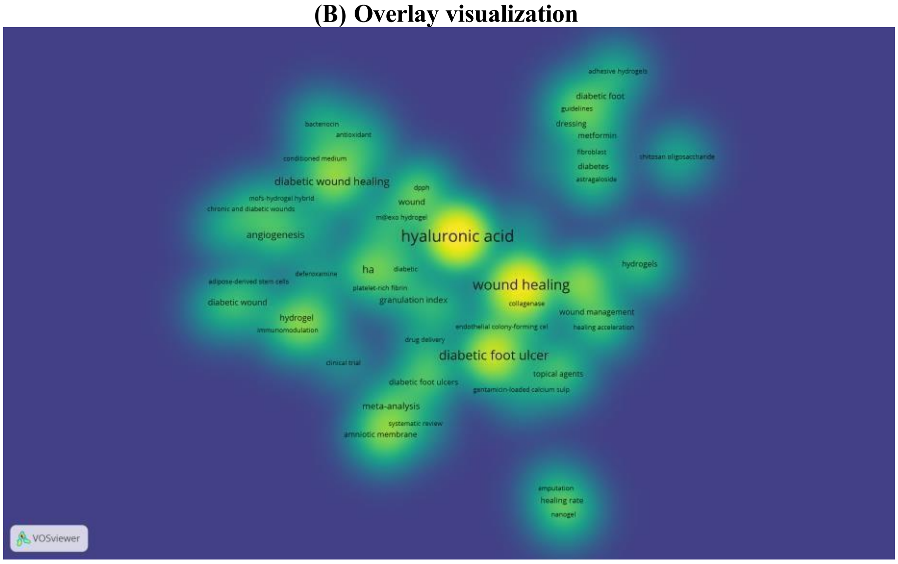
Figure 5. Visualization of Distribution of Number of Research by Country in the Period (2020-2024) in a Map Chart



(A) Network visualization



(B) Overlay visualization



(C) Density visualization

Source : VOSviewer (2025)

Figure 6. VOSviewer Output

TABLES

Table 1.Grouping of Previous Research Results

Category	Researcher Name	Findings
Combination Therapy	Guan et al. (2024)	The combination of HA and PRF strengthens tissue granulation and accelerates DFU wound closure.
	Van et al. (2020)	HA and advanced PRF decreased IL-6 and increased granulation index.
	Lin et al. (2023)	HA and low molecular weight heparin effectively reduced wound size within 4 weeks.
Smart Hydrogel	Lan et al. (2024)	pH and glucose responsive HA hydrogel improves diabetic wound healing performance.
	The Last Supper (2022)	HA self-healing hydrogel with BM-MSCs regulates inflammatory microenvironment and tissue regeneration.
	Jia et al. (2022)	HA-deferoxamine hydrogel stimulates angiogenesis and accelerates tissue repair.
Antiseptic and Anti-inflammatory	Zhai et al. (2024)	HA with iodine enhances epithelialization and accelerates healing.

	Zhao et al. (2020)	Collagen/HA hydrogel reduces inflammatory macrophages and accelerates healing.
	(2021)	HA patch with catechol and fat stem cells accelerates healing and reduces macrophage infiltration.
Cell Activation and Tissue Regeneration	Wang et al. (2022)	HA dressing shortens healing time and improves tissue quality.
	N. Li et al. (2022)	HA is important in hydration, cell proliferation, and regulation of inflammation.
	Tang et al. (2023)	Stem cell + HA medium accelerates the regeneration of wound extracellular matrix.
Growth Factors & Molecular	Hauck et al. (2021)	HA increases the expression of VEGF and TGF-β which support wound proliferation and remodeling.
	Y. Chen et al. (2024)	HA scaffold accelerates cell migration and neovascularization, supporting perfect wound closure.
	Pecová et al. (2023)	HA hydrogel with miRNA suppresses inflammation and enhances angiogenesis simultaneously.

Table 2. Distribution of Number of Research by Country in the Period (2020-2024)

Rank	Country	Number of Articles
1	China	185
2	Indonesia	69
3	Republic of Korea	26
4	Germany	20
5	France (France)	20
6	Spain	19
7	Italy	18
8	United Kingdom (England)	17
9	Egypt	16
10	Turkey	15
11	Pakistan	11
12	USA	10
12	Nigeria	10
14	India	8
15	Vietnamese	7
15	Netherlands (Netherlands)	7
17	Taiwan	5
17	Malaysia	5
19	Sweden (Sweden)	4
19	Czech Republic (Czech Republic)	4
21	California	6

Source : Processed Data (2025)