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Visualization of the Relationship Between Hyaluronic Acid and Wound Healing: A Bibliometric Analysis

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ABSTRACT

Background: Wound healing is a complex process with significant economic implications. Hyaluronic acid (HA), valued for its adaptability and biocompatibility, shows the potential to improve multiple facets of wound healing. Despite the expanding literature on the use of HA in wound care, a comprehensive analysis of its scholarly evolution is lacking. This study employs a bibliometric approach to objectively evaluate trends in scholarly publications regarding HA's role in promoting wound healing.

Methods: We searched in the Web of Science Core Collection (WoSCC) for articles published from January 1, 2000 to March 31, 2024. We extracted relevant information about using HA to promote wound healing following a thorough screening process. Subsequently, a comprehensive analysis was undertaken on a total of 1886 publications. The analysis utilized GraphPad Prism 9, CiteSpace6.1.6, VOSviewer1.6.19, the Online Analysis Platform of Literature Metrology (http://bibliometric.com/), GeneMANIA (https://genemania.org/), and Metascape (https://metascape.org/gp/index.html#/main/step1).

Results: We retrieved 2424 publications on hyaluronic acid (HA) and wound healing from the Web of Science Core Collection, covering the period from January 2000 to March 2024, and selected 1886 for analysis. The results show a significant increase in publications since 2016, reflecting a growing focus on this field. Currently, China's publication volume has surpassed the United States since 2017, indicating a significant rise in China's influence in this area. Using CiteSpace software for co-citation analysis, we identified eight main research clusters, including promoted wound healing, injured tissue, and advanced multi-targeted composite biomaterial. Key research areas involve the role and mechanisms of hyaluronic acid in tissue repair, particularly its applications in growth factor production and regenerative therapy. Analyzing keyword co-occurrence and burst data with VOSviewer, we identified research hotspots focused on biomaterials, such as nanoparticles and hydrogels, and their antibacterial properties. The keyword "CD44" showed a long burst period, while "antibacterial" had the highest burst intensity in 2022. We identified the top 21 genes extensively studied in hyaluronic acid and wound healing, including CD44, VEGF, and TGF-β. These genes are mainly involved in regulating cell migration, adhesion, proliferation, and cytokine activity. GO enrichment and KEGG pathway analyses indicate that these genes are associated with key signaling pathways, such as MAPK and EGFR, revealing the primary mechanisms hyaluronic acid promotes wound healing.

Conclusion: This pioneering study provides the first comprehensive bibliometric analysis of HA in wound healing. Covering the period from January 1, 2000 to March 31, 2024, it reveals a significant expansion in annual scholarly production. Current research emphasizes the development of HA-based biomaterials for enhancing wound healing.

1 | Introduction

The complex procedure of wound recovery, which often leads to chronic injuries or slow healing, is affected by internal and external elements. This procedure entails the harmonized synchronization of different cell types executing unique roles throughout the stages of hemostasis, inflammation, growth, re-epithelialization, and remodeling [1–3]. The financial strain of non-healing wounds in the United States alone is estimated to be around $50 billion annually. Moreover, the healthcare costs of scars from surgical cuts and injuries amount to almost $12 billion annually, while burn wounds represent $7.5 billion of these expenses each year [4].

Hyaluronic acid (HA), a non-sulfated and negatively charged linear glycosaminoglycan, is commonly present in various biological entities. The consistent chemical structure across all species consists of recurring glucuronic acid and N-acetylglucosamine disaccharide units. These units are alternately connected by β-1,4 and β-1,3 glycosidic bonds [5–7]. In the body, HA is synthesized by hyaluronan synthases (HAS) in the cell membrane and released into the extracellular matrix (ECM) [8]. Upon tissue injury, HA synthesis is upregulated [9], and hyaluronidase expression increases, breaking down high molecular weight HA (HMW-HA) into its low molecular weight HA (LMW-HA) form. Due to varying numbers of disaccharide units, HA has a broad molecular weight range [10]. Natural HA consists of 2000–25 000 disaccharide units [11], and is classified into high (HMW > 1000 kDa), medium (MMW 250–1000 kDa), low (LMW 10–250 kDa), and oligomeric HA (<10 kDa) based on its molecular weight. Different molecular weights of HA exhibit distinct biological functions. HMW-HA, in addition to forming the ECM, has anti-angiogenic, anti-inflammatory, and immunosuppressive properties, promoting wound healing and preventing scar formation [12]. Conversely, LMW-HA shows pro-inflammatory, angiogenic, and immunostimulatory activities.

Increasing research indicates that HA is crucial for wound healing. As a natural macromolecular polymer, HA has been used to create hemostatic materials, with hydrogel forms promoting coagulation by thickening the blood and increasing platelet and clotting factor concentrations [13]. HA also aids wound healing by modulating inflammation. During the early stages of wound healing, LMW-HA acts as an inflammatory stimulant, promoting the production of cytokines like IL-8 and TNF-α [14]. In later stages, HMW-HA reduces TNF-α levels and increases IL-10, encouraging the polarization of M1 to M2 macrophages, thus aiding tissue repair [15, 16]. In the re-epithelialization phase, HA binds to CD44 on cell surfaces, playing a pivotal role in keratinocyte proliferation, migration, and differentiation [17]. HA regulates fibroblast collagen production during the final remodeling stage, forming new ECM and restructuring the wound area [18]. Studies have shown that HA-based creams or gauze pads applied to wounds of various etiologies significantly enhance granulation tissue growth, collagen deposition, and re-epithelialization. The use of HA in wound healing has been made possible due to its biocompatibility, biodegradability (via the enzymatic activity of hyaluronidase), and the simplicity of its chemical alteration to improve blood clotting, regulate inflammation, and encourage re-epithelialization [19, 20]. Therefore, HA plays a crucial role in wound healing. Various HA-based wound dressings, including HylaSponge, Hyalomatrix, and Hylase Wound Gel, are available for clinical use.

However, there is a notable lack of comprehensive and coherent evaluation of the progression and trajectory of HA in its role of facilitating wound healing through bibliometric analysis. Bibliometric analysis is a quantitative statistical method used to analyze published literature on a specific topic [21]. It is widely used across various fields, including information science, economic management, and biomedicine [22, 23]. This study employed bibliometric methodology to objectively measure and analyze published articles on the use of HA for wound healing enhancement. The analysis was conducted on articles retrieved from the WoSCC database, covering the period from January 1, 2000 to March 31, 2024.

2 | Method

2.1 | Data Search and Collection Strategy

Our study used the Web of Science Core Collection (WoSCC), specifically the Science Citation Index Expanded (SCI-E), to search the literature and collect data. The search integrated all published literature from January 1, 2000 to March 31, 2024. As shown in Figure S1, to ensure reliable results, we used the search formula TS = ("Hyaluronic Acid" OR "Acid Hyaluronic" OR "Sodium Hyaluronate" OR "Hyaluronate Sodium" OR "Hyaluronan" OR Healon) AND TS = ("Wound Healing" OR "Wound Repair" OR "Wound Closure"). A total of 2424 documents were retrieved, with 1886 articles in English. Only original research articles published in English were included in the analysis. Other types of publications, such as review articles, clinical trials, meeting abstracts, editorials, letters, and notes, were excluded.

2.2 | Data Analysis

After data collection, we utilized various tools for visual analysis. In 2009, Eck and Waltman from Leiden University developed VOSviewer, a software program for constructing scientific networks and visualizing knowledge maps. A bibliometric analysis tool, VOSviewer (version 1.6.19), which extracts critical information from numerous publications, is widely used to establish collaborative, co-citation, and co-occurrence networks [24, 25]. In our study, it was used for keyword co-occurrence analysis. CiteSpace (version 6.1.6), a Java application developed by Professor Chen C, is designed for bibliometric analysis and visualization [26, 27]. It aids in mining and visualizing knowledge within bibliographic databases, with objectives such as investigating authorship, international collaboration, institutional cooperation, knowledge domains, subject emergence, and future research trends. The R package "bibliometrix" (version 3.2.1) was used to create a global distribution network of publications related to HA and wound repair. GraphPad Prism 9 (GraphPad Software, La Jolla, USA) was used to analyze and plot bar charts of hotspot genes. The protein-protein interaction (PPI) network was constructed using the online platform GeneMANIA (https://genemania.org/), and functional enrichment analysis of the top studied genes was performed using Metascape (https://metascape.org/gp/index.html#/main/step1). The versions of

software used in this study were the latest available at the time, and updates in newer versions do not affect the validity or outcomes of our bibliometric analysis.

3 | Result

3.1 | Annual Publication and Country Distribution

We initially retrieved 2424 publications on hyaluronic acid (HA) and wound healing from January 2000 to March 2024 through the Web of Science Core Collection (WOSCC). Based on the criteria of articles and the English language, we included 1886 publications for this study. Using an online bibliometric platform, we analyzed the annual publication trends post-2000 (Figure 1B). The results indicate a significant increase in the number of publications in this field since 2016, highlighting the increasing attention to the relationship between hyaluronic acid and wound healing. The potential applications of hyaluronic acid in wound treatment are up-and-coming, and recent studies have progressively elucidated its roles and mechanisms in wound healing. Consequently, various countries are actively engaging in research within this domain.

To determine the contributions of different countries to this field, we analyzed the publication volume by country/region. Using the "bibliometrix" R package, we visualized the data

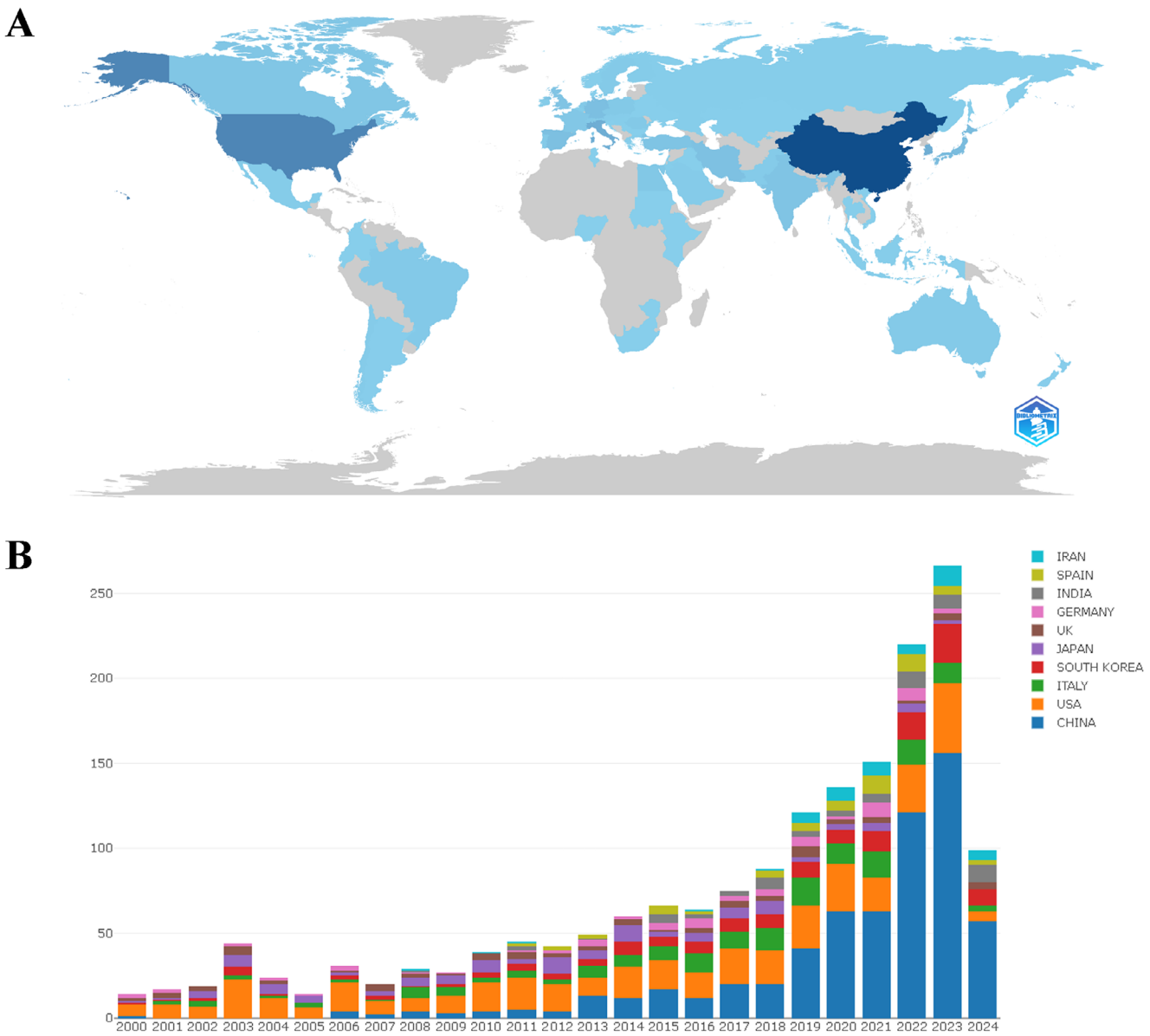

FIGURE 1 | Annual number of publications of articles on HA and wound healing. (A) Global distribution of publications on hyaluronic acid (HA) and wound healing, shown by country. The map displays the total number of publications from the Web of Science Core Collection (WoSCC) between 2000 and 2024. Darker shades show countries with more publications, highlighting the strong contributions from China and the United States. The analysis shows the increasing research interest in HA's role in wound healing in different regions. (B) Annual publication trends and publication volume by country for articles on hyaluronic acid (HA) and wound healing. The bar graph shows the number of publications per year from 2000 to 2024, with a clear rise in research activity after 2016.

TABLE 1 | Total publication volumes by country (2000–2024).

Rank	Country	Total publications
1	CHINA	1769
2	USA	1024
3	ITALY	440
4	SOUTH KOREA	437
5	JAPAN	243
6	GERMANY	201
7	SPAIN	188
8	IRAN	156
9	TURKEY	142
10	UK	131

in a map (Figure 1A), with darker colors indicating higher publication volumes. The contributions by country are summarized in Table 1. China has emerged as the leading contributor, with 1769 publications, surpassing the United States, which contributed 1024 publications. The results reveal that China currently leads in publication volume, signifying its meaningful impact on this research area. Additionally, Figure 1B shows that from 2000 to 2017, the United States consistently held the top position globally in publication volume. However, after 2017, China gradually surpassed the United States, indicating a significant rise in China's influence on hyaluronic acid and wound healing.

In summary, the important role of hyaluronic acid in wound healing is being recognized more, as shown by its increased use in wound treatment. More research on hyaluronic acid, especially in China and the United States, highlights its therapeutic potential and the growing interest in studying how it works.

3.2 | Co-Citation Analysis of References

Co-citation occurs when two papers are cited by multiple other papers, establishing a co-citation relationship between them. Co-citation analysis evaluates these relationships by examining frequently co-cited references. Using CiteSpace software, we divided the co-citation network into distinct clusters, each defined by a representative title. Figure 2A displays the top eight clusters: #0 promoted wound healing, #1 injured tissue, #2 advanced multi-targeted composite biomaterial, #3 adipose-derived stem cell, #4 hepatocyte growth factor, #5 hyaluronan binding domain, #6 regenerative therapy, #7 mouse epidermis, and #8 epidermal keratinocyte. Cluster #0 ("Promoted wound healing") focuses on studies investigating how hyaluronic acid (HA) enhances wound healing through mechanisms such as inflammation modulation, angiogenesis, and epithelial regeneration. For example, Zhao et al. [28] developed HA-based hydrogels with antibacterial and antioxidant properties that effectively promote wound closure. Cluster #1 ("Injured tissue") highlights the role of HA in addressing tissue injury, emphasizing its interactions with key cellular components such as fibroblasts and macrophages, which are critical for extracellular matrix remodeling and inflammation resolution. Cluster #2 ("Advanced multi-targeted composite biomaterial") explores advanced HA-based biomaterials, such as curcumin-loaded hydrogels and nanoparticle-enhanced wound dressings, designed to deliver growth factors or antibacterial agents to accelerate wound healing. Cluster #3 ("Adipose-derived stem cell") examines HA's role in stem-cell-based therapies, such as the work of Lee et al. [51], where HA combined with adipose-derived stem cells enhanced cell proliferation, migration, and collagen synthesis in wound models. Cluster #4 ("Hepatocyte growth factor") focuses on HA's regulation of growth factors like hepatocyte growth factor (HGF), which synergistically promotes angiogenesis and tissue regeneration. Cluster #6 ("Regenerative therapy") highlights HA's applications in regenerative medicine, including cartilage and skin repair, as well as its ability to stimulate the production of VEGF to support vascularization. Finally, Clusters #7 ("Mouse epidermis") and #8 ("Epidermal keratinocyte") explore HA's role in epidermal biology, particularly in keratinocyte proliferation and migration, as seen in studies showing HA-CD44 interactions facilitating re-epithelialization. Together, these clusters provide a comprehensive understanding of HA's multifaceted role in wound healing, supported by its diverse applications in biomaterials, stem cell therapies, and regenerative medicine. Clusters #3, #4, #7, and #8 highlight essential tissues and factors in tissue damage repair, showing potential targets for HA. Cluster #2 indicates HA's development and application value as a biomaterial. Cluster #6 is closely related to cluster #4, demonstrating HA's role in promoting growth factor production and its application in regenerative therapy.

Additionally, we used CiteSpace to identify the 10 most influential references based on their citation bursts. Figure 2B depicts the timeline from 2000 to 2024, with line lengths indicating the duration. Red lines mark the intervals of citation bursts. The burst strength of the top 25 HA-related publications for wound healing ranged from 6.31 to 18.37, with endurance spanning 1–4 years, and their main information was listed in Table 2. Among the top 25 references, the highest citation burst was by Zhao in 2017 [28]. This study produced self-healing, injectable, conductive hydrogels using quaternized chitosan-g-polyaniline (QCSP) and poly (ethylene glycol)-co-poly (glycerol sebacate) (PEGS-FA) with a benzaldehyde group functionalization, striving to develop a dressing for skin wound healing that is antibacterial, antioxidant, and electroactive. The study provided substantial evidence that these hydrogels have significant potential for treating full-thickness skin wounds.

The second-highest citation burst is attributed to a 2021 review by Liang et al. This review explores using functional hydrogels as wound dressings to enhance wound healing [29]. It analyzes the advanced features of hydrogel dressings, including antibacterial properties, adhesion, and hemostasis, anti-inflammatory and antioxidant effects, substance delivery, self-repair, stimuli responsiveness, conductivity, and wound monitoring, as well as the potential future directions for the development of these materials.

The co-citation analysis shows that more focus is being placed on hyaluronic acid's role in promoting wound healing. This is especially through its effect on tissue regeneration and growth factor production. It shows that hyaluronic acid-based biomaterials are becoming an important area of research.

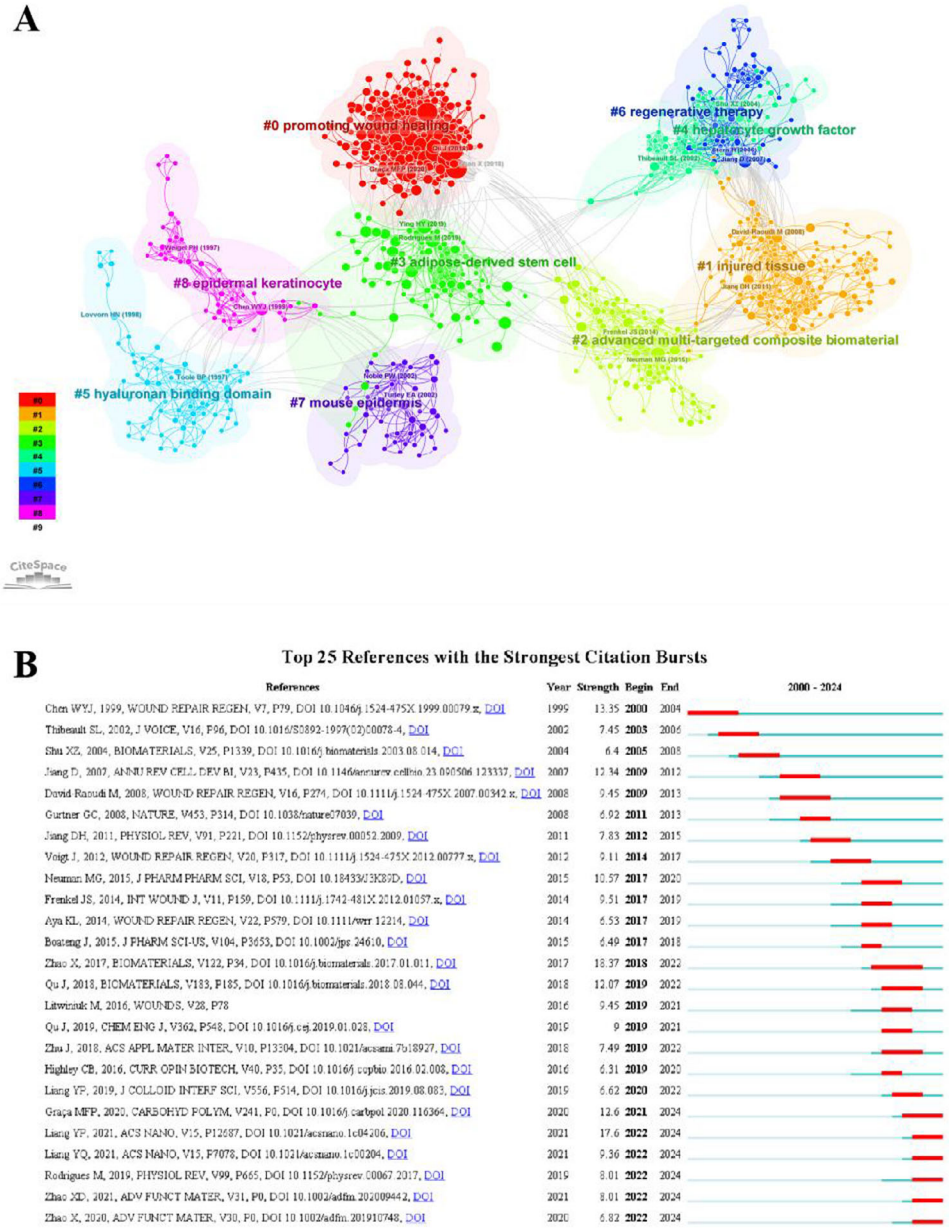

FIGURE 2 | Co-citation and burst reference analysis of references. (A) Visualization of the co-citation network of literature created by CiteSpace. (B) Citation burst analysis of the top 25 references in the field of hyaluronic acid and wound healing. This figure shows the citation burst strength (red lines) and duration (line length) of the most cited articles from 2000 to 2024. A stronger burst means a paper was cited more during that time.

3.3 | Visualization Analysis of Keyword Co-Occurrence and Bursts

Analyzing hot words and frontier words in published research helps summarize research focuses and identify hot topics. We identified the main topics by examining the keywords in each published paper and creating network maps using VOSviewer, a tool for bibliometric analysis. It groups related terms by analyzing how often they appear together. Keywords that often appear together are shown as nodes in a network, with connections weighted by the strength of their co-occurrence. VOSviewer uses an algorithm to form clusters, grouping terms with stronger connections into the same cluster. For example, keywords linked to biological research (like "growth factor," "inflammation," "proliferation") formed one cluster, while terms related to biomaterials (like "nanoparticles," "hydrogels," "wound dressing") formed another. We also looked at when keywords appeared over time to find trends, with newer terms pointing to emerging research areas. This method helps show distinct but connected themes in the research field. Figure 3A showed that 50 keywords were identified, appearing more than 44 times in titles or abstracts. These keywords were primarily categorized into five distinct clusters, each assigned a unique color. There are three main clusters among them. The green cluster, consisting of 19 keywords, predominantly represents biological research. Key terms in this cluster include "growth factor," "expression," "inflammation," and "proliferation." The red cluster, with 15 keywords, mainly represents biomaterials composed of hyaluronic acid, featuring keywords such as "hyaluronic acid," "chitosan," "nanoparticles," and "wound dressing." The blue cluster, with

TABLE 2 | Information of top 25 references with citation bursts.

Title	Author	Year	Journal	Strength	IF
Functions of hyaluronan in wound repair	Chen WYJ	1999	Wound Repair and Regeneration	13.35	3.8
Histologic and rheologic characterization of vocal fold scarring	Susan L. Thibeault	2002	Journal of Voice	7.45	2.5
In situ crosslinkable hyaluronan hydrogels for tissue engineering	Xiaozheng Shu	2004	Biomaterials	6.4	12.8
Hyaluronan in tissue injury and repair	Dianhua Jiang	2007	Annual Review of Cell and Developmental Biology	12.34	11.4
Differential effects of hyaluronan and its fragments on fibroblasts: Relation to wound healing	Maha David-Raoudi	2008	Wound Repair and Regeneration	9.45	3.8
Wound repair and regeneration	Geoffrey C. Gurtner	2008	Nature	6.92	50.5
Hyaluronan as an immune regulator in human diseases	Dianhua Jiang	2011	Physiological Reviews	7.83	29.9
Hyaluronic acid derivatives and their healing effect on burns, epithelial surgical wounds, and chronic wounds: A systematic review and meta-analysis of randomized controlled trials	Jeffrey Voigt	2012	Wound Repair and Regeneration	9.11	3.8
Hyaluronic acid and wound healing	Manuela G. Neuman	2015	Journal of Pharmacy & Pharmaceutical Sciences	10.57	2.9
The role of hyaluronan in wound healing	Joseph S. Frenkel	2014	International Wound Journal	9.51	2.6
Hyaluronan in wound healing: Rediscovering a major player	Kessiena L. Aya	2014	Wound Repair and Regeneration	6.53	3.8
Advanced therapeutic dressings for effective wound healing—A review	Joshua Boateng	2015	The Journal of Pharmaceutical Sciences	6.49	3.7
Antibacterial anti-oxidant electroactive injectable hydrogel as self-healing wound dressing with hemostasis and adhesiveness for cutaneous wound healing	Xin Zhao	2017	Biomaterials	18.37	12.8
Antibacterial adhesive injectable hydrogels with rapid self-healing, extensibility, and compressibility as wound dressing for joints skin wound healing	Jin Qu	2018	Biomaterials	12.07	12.8
Hyaluronic acid in inflammation and tissue regeneration	Malgorzata Litwiniuk	2016	Wounds	9.45	1.4
Degradable conductive injectable hydrogels as novel antibacterial, anti-oxidant wound dressings for wound healing	Jin Qu	2019	Chemical Engineering Journal	9	13.3
Hyaluronic acid and polyethylene glycol hybrid hydrogel encapsulating nanogel with hemostasis and sustainable antibacterial property for wound healing	Jie Zhu	2018	ACS Applied Materials & Interfaces	7.49	8.3
Recent advances in hyaluronic acid hydrogels for biomedical applications	Christopher B. Highley	2016	Current Opinion in Biotechnology	6.31	7.1
Mussel-inspired, antibacterial, conductive, antioxidant, injectable composite hydrogel wound dressing to promote the regeneration of infected skin	Yongping Liang	2019	Journal of Colloid and Interface Science	6.62	9.4

(Continues)

TABLE 2 | (Continued)

Title	Author	Year	Journal	Strength	IF
Hyaluronic acid-based wound dressings: A review	Mariana F. P. Graça	2020	Carbohydrate Polymers	12.6	10.7
Functional hydrogels as wound dressing to enhance wound healing	Yongping Liang	2021	ACS Nano	17.6	15.8
Dual-dynamic-bond cross-linked antibacterial adhesive hydrogel sealants with on-demand removability for post-wound-closure and infected wound healing	Yuqing Liang	2021	ACS Nano	9.36	15.8
Wound healing: A cellular perspective	Melanie Rodrigues	2019	Physiological Reviews	8.01	29.9
Green tea derivative-driven smart hydrogels with desired functions for chronic diabetic wound treatment	Xiaodan Zhao	2021	Advanced Functional Materials	8.01	18.5
Physical double-network hydrogel adhesives with rapid shape adaptability, fast self-healing, antioxidant, and NIR/pH stimulus-responsiveness for multidrug-resistant bacterial infection and removable wound dressing	Xin Zhao	2020	Advanced Functional Materials	6.82	18.5

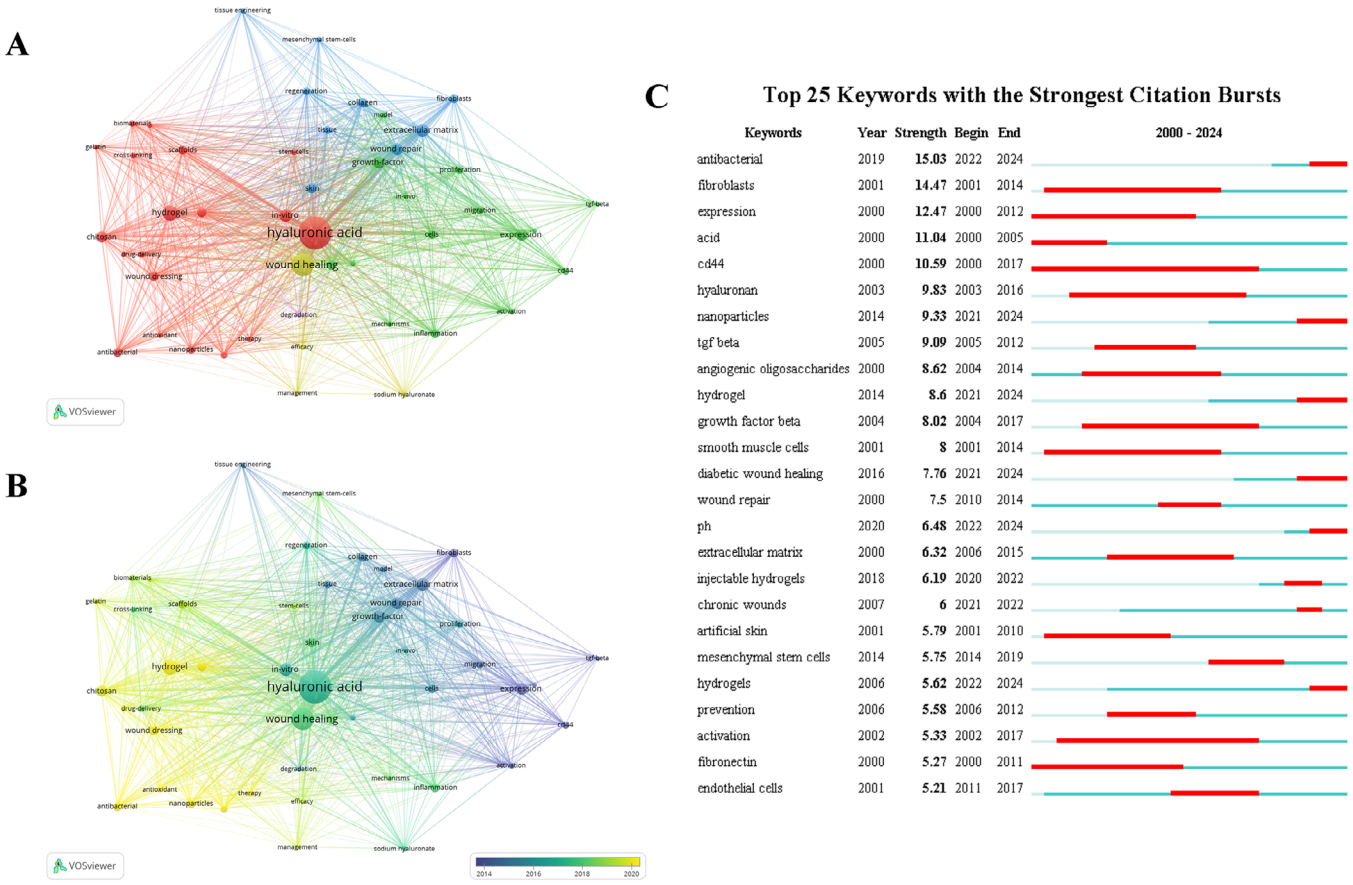

FIGURE 3 | Visualization analysis of co-occurrence keywords. (A) Network visualization of keywords using VOSviewer. (B) Temporal distribution of keywords according to VOSviewer. (C) Keyword burst analysis of the top 25 keywords related to HA and wound healing. This figure shows the keywords with the highest burst strength, highlighting the most rapidly emerging topics in the field. The burst strength is shown by the length of the red bars, while the duration of the burst is represented by the horizontal length of the red lines.

nine keywords, typically indicates research on using hyaluronic acid in wound healing. Keywords in this cluster include "wound healing," "extracellular matrix," "fibroblasts," and "regeneration." Figure 3B shows that yellow keywords appeared later than the blue ones. The results indicate that "chitosan," "nanoparticles," and "stem cells" are recent primary topics in the field of hyaluronic acid for promoting wound healing.

Detecting keyword bursts reveals research hotspots and trends over time. Figure 3C lists the top 25 keywords with citation bursts, sorted by burst strength. "CD44" had the longest burst duration, from 2000 to 2017, indicating its significance as the primary receptor of hyaluronic acid. "Antibacterial" had the highest burst strength starting in 2022. Duan et al. successfully developed an antibacterial material, Cur-HA-SPu, by chemically conjugating curcumin to hyaluronic acid-modified pullulan polysaccharide [30], which material is designed to enhance wound healing and prevent infections. Additionally, research hotspots on the application of hyaluronic acid in wound healing evolved to focus on "nanoparticles" and "hydrogel" in 2024.

Visualizing keyword co-occurrence and citation bursts is crucial for understanding current research hotspots. The results indicate that recent research on hyaluronic acid for wound healing primarily focuses on novel materials like nanoparticles and the development of antibacterial properties.

3.4 | Analysis of Hot Spot Genes

To further explore current research hotspots in hyaluronic acid (HA) and wound healing, we used an online data analysis platform to identify the most extensively studied genes. The top 21 genes are TGF-β, VEGF, CD44, IL-6, TNF, FN1, HMMR, HAS2, EGF, U023126, CXCL8, DIF, ELN, HAS1, IL-1β, MAPK1, IL-10, AKT1, FGF2, IL-1A, and HAS3 (Figure 4A). We have listed the role of these genes in wound healing and the associated pathways in Table 3. Among these, CD44 and HMMR are important receptors for HA, while HAS1, HAS2, and HAS3 are the three hyaluronic acid synthases. Other genes such as EGF, VEGF, and FGF2 are crucial factors in wound healing, with HA promoting the secretion of these growth factors [31]. CD44, the main receptor of HA, supports cell adhesion, movement, and growth by activating signaling pathways like MAPK and PI3K-Akt, which are vital for wound healing. TGF-β works together with HA to help fibroblasts turn into myofibroblasts, boosting extracellular matrix production and tissue repair. HA also increases VEGF expression, which promotes endothelial cell growth and angiogenesis, helping form new blood vessels and supply nutrients to the wound. These processes highlight HA's key role in regulating gene activity to improve tissue repair.

Next, to explore the relationships between these genes, we used an online network tool to create a protein interaction network (Figure 4B). In this network, proteins positioned towards the center have closer relationships with other proteins. Different colored lines indicate various types of interactions between the proteins. Purple indicates co-expression, red signifies physical interactions, yellow represents shared protein domains, blue denotes co-localization, green indicates genetic interactions, and orange represents predicted interactions. Thicker lines indicate stronger

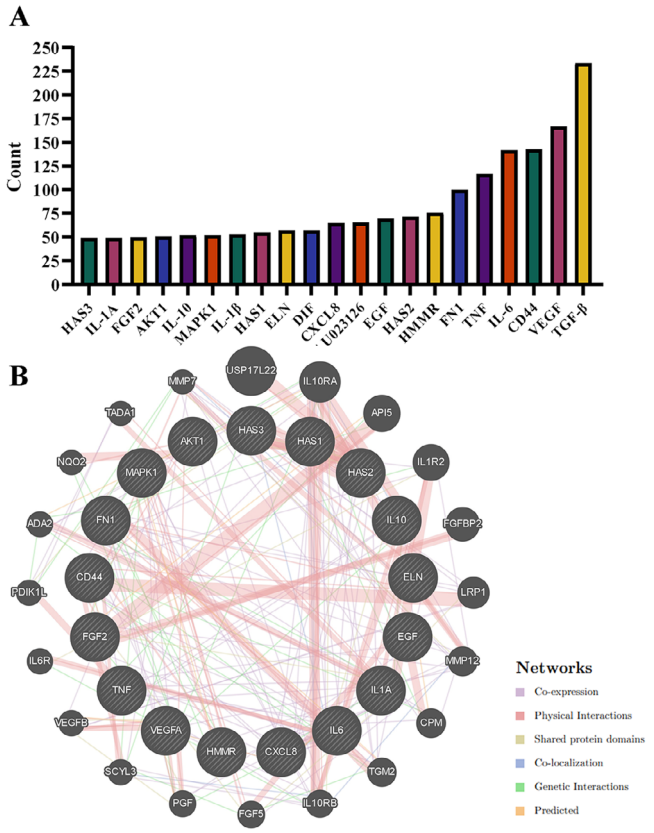

FIGURE 4 | Analysis of hot genes. (A) Counts of the top 21 most researched genes related to HA and wound healing. The gene count indicates how often each gene has been studied in the context of wound healing. (B) Protein interaction network of the top 21 most researched genes.

relationships. Notably, CD44 and the low-density lipoprotein receptor-related protein 1(LRP-1) exhibit strong interactions. The fourth ligand-binding cluster of LRP-1 is essential for its interaction with CD44, and CD44 internalization mediated by LRP-1 is critical in regulating cell adhesion [32].

In summary, hyaluronic acid promotes wound healing through complex mechanisms, including its anti-inflammatory effects, regulation of cell proliferation and migration, and stimulation of angiogenesis. These findings, coupled with the identified key genes like CD44 and TGF-β, underline the multifaceted roles of HA in tissue repair and its potential as a therapeutic target.

3.5 | GO Enrichment Analysis and KEGG Pathway Analysis

To further investigate the potential mechanisms by which HA promotes wound healing, we performed GO enrichment analysis on the identified genes using an online platform (Figure 5A). The results indicate that these genes are mainly associated with regulating cell migration, adhesion, proliferation, and cytokine activity.

We conducted KEGG pathway enrichment analysis to explore further the molecular signaling pathways related to these genes

TABLE 3 | Top 21 hot genes.

Gene	Count	Function in wound healing	Relative pathway
HAS3	49	Involved in the synthesis of hyaluronic acid, influencing cell migration and proliferation, crucial for ECM formation and tissue repair during wound healing.	Hyaluronic acid metabolism, ECM formation
IL-1A	49	Promotes inflammation by activating immune cells, regulating the inflammatory phase of wound healing.	Inflammatory response, NF-κB pathway, IL-1 pathway
FGF2	50	Stimulates angiogenesis and cell proliferation, especially in early wound healing, promoting epithelial cell migration and regeneration.	VEGF pathway, MAPK pathway, Angiogenesis
AKT1	51	Involved in cell survival, proliferation, migration, and angiogenesis, aiding cellular responses and tissue repair during wound healing.	PI3K/Akt pathway, Cell cycle regulation
IL-10	52	Inhibits inflammatory responses and regulates immune reactions, promoting tissue repair during the later stages of wound healing.	Anti-inflammatory pathway, Th2 immune response
MAPK1	52	Participates in cell proliferation, migration, and differentiation, regulating inflammation and repair during wound healing.	MAPK pathway, Cell cycle regulation
IL-1β	53	Promotes inflammation, activates immune cells, and increases cytokine release, assisting early wound healing in the inflammatory phase.	Inflammatory response, NF-κB pathway, IL-1 pathway
HAS1	55	Involved in the synthesis of hyaluronic acid, promoting cell migration and tissue repair during wound healing.	Hyaluronic acid synthesis, ECM formation
ELN	57	Involved in the synthesis of elastin and the restoration of tissue elasticity, playing a crucial role in skin and blood vessel reconstruction during wound healing.	Elastin synthesis, ECM repair pathways
DIF	57	Participates in immune responses and inflammation regulation, possibly playing a role in immune cell modulation during wound healing.	Immune modulation, Inflammatory response
CXCL8	65	Attracts neutrophils to the wound site, promotes inflammation, and regulates the inflammatory phase of wound healing.	Inflammatory response, Chemokine pathway
AU023126	66	Likely involved in cell migration, proliferation, and immune response, regulating cellular activities during wound healing.	Cell migration, Immune response pathways
EGF	70	Promotes cell proliferation, migration, and epithelial regeneration, facilitating the epithelialization process during wound healing.	EGF pathway, MAPK pathway, Cell proliferation
HAS2	72	Involved in the synthesis of hyaluronic acid, contributing to cell migration and tissue repair during wound healing.	Hyaluronic acid metabolism, ECM repair
HMMR	76	Regulates cell migration, proliferation, and ECM formation, playing an important role in the early stages of wound healing.	Cell migration, ECM reconstruction
FN1	100	Involved in ECM synthesis and reconstruction, crucial for tissue repair during wound healing.	ECM synthesis, ECM repair pathways
TNF	117	Activates immune responses, promotes cytokine secretion, and regulates the inflammatory phase of wound healing.	NF-κB pathway, Inflammatory response
IL-6	142	Regulates inflammatory and immune responses, involved in the modulation of wound healing.	Inflammatory response, JAK/STAT pathway
CD44	143	Involved in cell migration, adhesion, and interactions with ECM, promoting cell migration during wound healing.	Cell migration, ECM formation pathways
VEGF	167	Stimulates angiogenesis, regulating new blood vessel formation, a key factor in wound healing.	VEGF pathway, Angiogenesis
TGF-β	234	Regulates fibrosis, promoting fibroblast proliferation and collagen synthesis, playing a role in the repair phase of wound healing.	TGF-β pathway, Fibrosis pathway

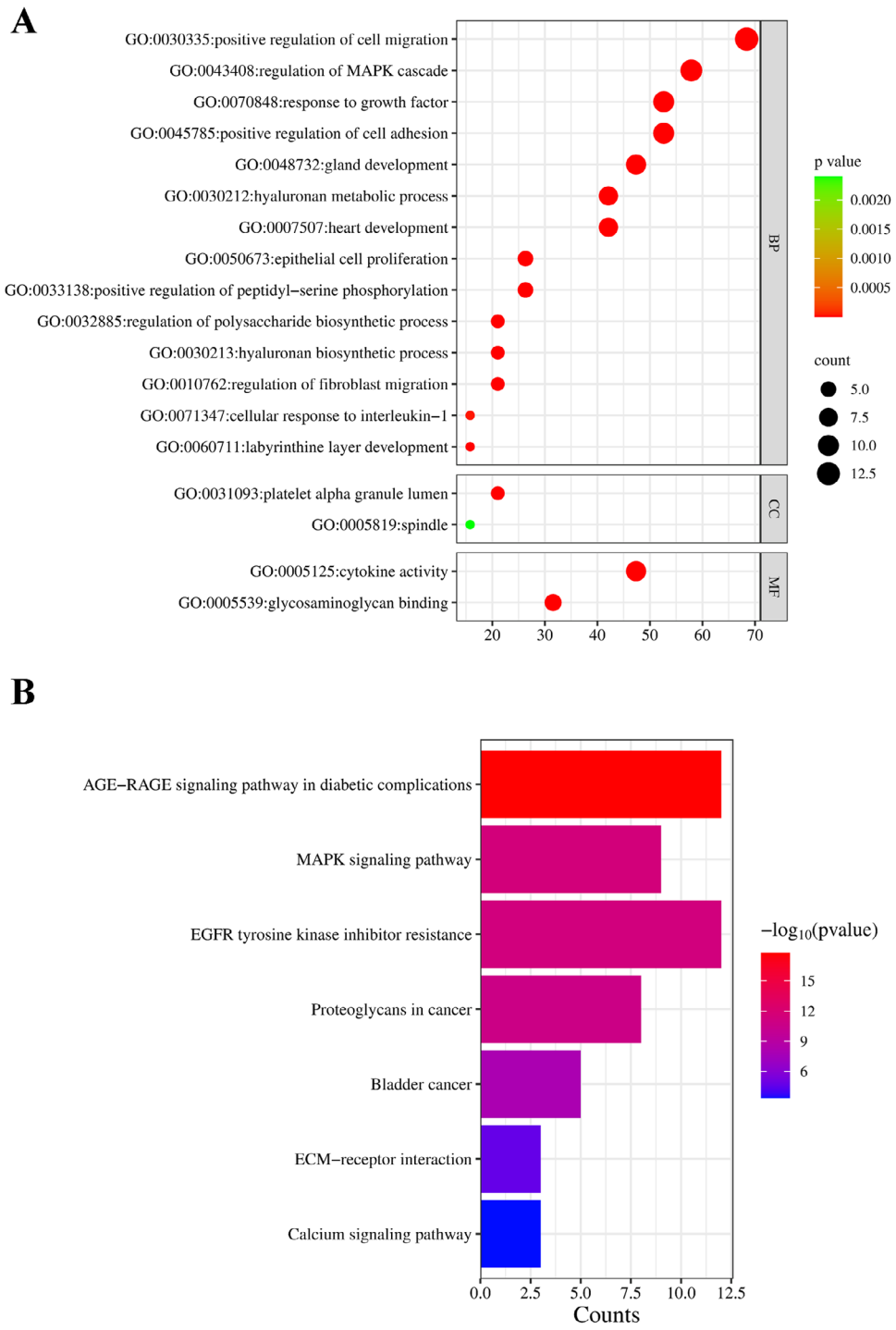

FIGURE 5 | GO enrichment and KEGG pathway analysis of key genes. (A) GO enrichment analysis of the top 21 most studied genes related to HA and wound healing. This analysis categorizes the biological processes, molecular functions, and cellular components most associated with the identified genes. (B) KEGG pathway analysis of the top 21 most researched genes.

(Figure 5B). The results show that these genes are enriched in seven pathways, including the MAPK, EGFR, and AGE-RAGE pathways. The KEGG pathway analysis revealed several pathways linked to the role of hyaluronic acid (HA) in wound healing. The AGE-RAGE signaling pathway in diabetic complications showed the highest significance ($-\log_{10}$ p value = 17.775), highlighting its importance in controlling inflammation and macrophage polarization, especially in diabetic patients. The MAPK signaling pathway ($-\log_{10}$ p value = 11.47) was also significantly enriched, emphasizing its role in supporting cell growth, differentiation, and movement. Additionally, the EGFR tyrosine kinase inhibitor resistance pathway ($-\log_{10}$ p value = 11.294) points to HA's involvement in epidermal growth factor receptor signaling, which is essential for tissue repair and re-epithelialization. ERK, JNK, p38/MAPK, and ERK5 are four subfamilies into which the evolutionarily conserved serine-threonine

kinases known as MAPK can be categorized [33]. JNK and p38 are similar in function and are related to inflammation, apoptosis, and growth [34]. EGFR, upon binding with its ligand, forms a dimer that undergoes autophosphorylation, enhancing tyrosine kinase activity [35]. Proteins in downstream signaling pathways bind to phosphorylated tyrosine sites on EGFR, triggering various intracellular responses, further inducing cell dedifferentiation, rapid proliferation, apoptosis inhibition, and angiogenesis [36]. The AGE-RAGE signaling pathway is triggered by the interaction between advanced glycation end-products (AGEs), which are formed under hyperglycemic conditions, and their receptor (RAGE) [37]. This pathway plays a critical role in diabetic complications, particularly in the context of diabetic wounds. In diabetic patients, the activation of the AGE-RAGE pathway accelerates wound healing impairments by promoting inflammatory responses, impairing macrophage function, and delaying tissue repair [38]. Studies have shown that topical application of anti-RAGE antibodies to diabetic wounds in mouse models significantly improves wound healing [39]. This improvement happens by reducing inflammatory markers and improving macrophage function. It also helps change the macrophages to a form that supports tissue repair. Targeting the AGE-RAGE pathway is important to help wound healing in diabetic patients.

In summary, hyaluronic acid helps wound healing by controlling key biological processes like reducing inflammation, cell growth, and movement. GO enrichment and KEGG pathway analyses show that HA affects wound healing through pathways like MAPK, EGFR, and AGE-RAGE. This highlights its important role in tissue repair and controlling inflammation during healing.

4 | Discussion

4.1 | General Information

This study uses bibliometric analysis to systematically evaluate the progress and trends in HA research for wound healing. This approach helps identify key advancements and emerging research areas.

Results indicate that since 2016, there has been a significant annual increase in research publications on HA and wound healing. This rise reflects growing interest and recognition of HA's importance in wound healing. The trend suggests that HA's potential benefits and applications in wound treatment are becoming more widely known and accepted. Analysis of national contributions shows that the United States had a strong foundation and long-term interest in this field, maintaining the highest publication volume until 2017. After 2017, China surpassed the United States in publication volume, indicating significant investment and prioritization in this research area. The global distribution of research efforts highlights the international recognition of HA's importance in wound healing, with substantial contributions from established and emerging research centers worldwide.

Citation Burst analysis is valuable for identifying emerging dynamic concepts and potential research inquiries within a specific field. This approach is particularly practical in examining the emergence of trends and abrupt shifts in disciplinary development, thereby providing insights into active or pioneering research nodes [40, 41]. Reference citation burst analysis characterizes the emerging topics of a subject. Six out of the top 25 references exhibiting the most pronounced citation bursts continue to be in the active burst phase. These articles exemplify the most recent emerging subjects about HA in the context of wound healing, thereby indicating potential avenues for future research. Qu et al. have developed a self-healing injectable micelle/hydrogel composite that can treat joint skin damage with multiple functions [42]. This article was published in 2018 with a citation burst strength of 12.07. His team carried out another research that shed new light on designing electroactive injectable hydrogels with promising applications in wound dressing in 2019.

The literature increasingly emphasizes HA's significant role in novel composite materials and its therapeutic effects on wound healing. Therefore, developing new HA-based materials presents a promising direction for future wound treatment interventions.

4.2 | Hotspots and Frontiers

Keyword co-occurrence analysis reveals some relationship between hyaluronic acid and wound healing/growth factor/chitosan/nanoparticles/stem cells. (1) HA can accelerate wound healing by promoting the secretion of growth factors. Zhou et al. discovered that a gel formed by combining hyaluronic acid with curcumin nanoparticles enhances wound healing by stimulating the expression of growth factors like VEGF, increasing collagen formation, and reducing inflammation [43]. (2) Chitosan is notable as the only cationic natural polysaccharide with excellent biocompatibility, antibacterial properties, and hemostatic capabilities. Que et al. developed a hydrogel using gallic acid-grafted quaternized chitosan (GA-QCS) and oxidized hyaluronic acid (OHA), which demonstrated multifunctional properties, including injectability, hemostasis, degradation, and drug release to enhance wound healing [20]. (3) The advancement of nanomaterials, particularly gold nanoparticles (GNPs), presents a promising approach for wound management [44]. Organic nanoparticles offer a variety of functional groups for improved drug and growth factor binding, while metal nanoparticles provide antibacterial properties through their ion content [45, 46]. Many types of metal-ion-loaded nanoparticles have been designed for wound dressings to enhance healing and combat bacteria [47–50]. (4) In recent years, stem cells have also been utilized in wound treatment. In 2023, Lee et al. discovered that exosomes derived from adipose tissue mesenchymal stem cells (ASC-EXOs) significantly enhance the proliferation, migration, and collagen synthesis of human skin fibroblasts. Additionally, in wound models of pigs and mice, the combined application of ASC-EXOs and HA further accelerated wound healing and tissue regeneration [51].

Another area of solid relevance and concern for HA is "Antibacterial." Since HA does not have antibacterial properties, combining antibacterial agents with HA can significantly enhance its effectiveness in wound treatment. One method involves combining HA with antibacterial agents such as silver ions. In 2017, Abdel-Mohsen et al. added various concentrations of silver nitrate to an HA solution at room temperature [52], and then increased the pH to 8 by adding sodium hydroxide. They used wet-dry

spinning technology to create in situ formed HA/Ag-NPs for making fibers/non-woven fabrics. The resulting wound dressings demonstrated significant antibacterial activity and healing effects, making them useful as cell carriers in biological research and tissue engineering. Another approach is combining HA with chitosan. In 2017, Ilaria Silvestro et al. incorporated different percentages of HA into a chitosan matrix, resulting in materials that promote healing and prevent infection [53].

Analysis via online platforms identified vital genes such as CD44, TGF-β, VEGF, CD44, and IL-6. Firstly, CD44 and HMMR are critical HA receptors. The interaction of HA with CD44 can activate multiple signaling pathways, enhancing wound healing by promoting cell proliferation, migration, and adhesion, thus aggregating cells at the wound site [54–56]. Additionally, HA-CD44 can regulate cell differentiation, including keratinocyte keratinization and fibroblast differentiation into myofibroblasts [57–59]. TGF-β is a multifunctional cytokine that regulates embryonic development and tissue regeneration, stimulates ECM production and remodeling, and enhances wound healing and tissue repair [60, 61]. Jason Webber and colleagues discovered that inhibiting hyaluronic acid synthesis reveals its necessity for TGF-β-dependent myofibroblast differentiation [62]. VEGF is essential for angiogenesis, promoting endothelial cell proliferation and migration to form new blood vessels [63, 64]. As recently noted by Zhou et al. using a healer made up of HA/Cur in wound care boosts the number of VEGF-positive cells in the recovering wound bed [43]. Identifying these essential genes and their interaction networks can guide the development of new HA-based therapeutic strategies. For instance, targeting HA receptors or synthases can enhance HA's efficacy in wound healing [65–69].

Subsequent GO enrichment analysis of these genes revealed their involvement in cell proliferation, migration, adhesion, and cytokine activity, underscoring their significant roles in inflammation and tissue regeneration. KEGG pathway analysis further highlighted the enrichment of pathways related to cell proliferation, migration, and tissue regeneration, such as the MAPK and EGFR pathways. In 2023, Chen et al. discovered that combining human umbilical cord mesenchymal stem cells (hucMSCs) and HA gel holds significant potential in treating diabetic foot ulcers. This effect is achieved through a paracrine mechanism mediated by the MAPK pathway, which promotes the phosphorylation of signaling pathways such as p38, ERK1/2, JNK, and Akt [70]. Adam C. and colleagues found that HA is crucial in differentiating fibroblasts into myofibroblasts through its interaction with the EGFR [71]. This HA-EGFR synergy activates the MAPK/ERK and CaMKII signaling pathways, promoting effective wound healing. Ahana and colleagues developed an immunomodulatory hydrogel that significantly improved wound healing in models of chronic hyperglycemia-induced healing impairment. This effect was achieved by simultaneously inhibiting the AGE/RAGE signaling pathway and reducing the excessive expression of MMP-9 [72]. The echinacoside-zinc coordination polymers (ECH-Zn) were synthesized and wrapped with hyaluronic acid/poly, which complex shows a better antiglycation effect in the skin by promoting RAGE transcriptional activation [73]. These findings suggest the potential mechanisms through which HA promotes wound healing and indicate future targets for developing new HA-based biomaterials.

4.3 | Hyaluronic Acid-Based Biomaterials in Wound Healing

Recent advancements in HA-based functional materials have significantly expanded their therapeutic potential in wound management. For instance, electrospun HA nanofibers have emerged as a promising platform for diabetic wound healing. Astaneh and Fereydouni demonstrated that HA-containing nanofibers enhance drug delivery and mechanical stability, while maintaining biocompatibility in chronic wound models [74]. These nanofibers not only mimic the extracellular matrix but also sustain the release of growth factors, addressing the prolonged inflammatory phase in diabetic ulcers.

Additionally, HA-chitosan hybrid hydrogels have gained attention for their dual functionality in infection control and tissue regeneration. Bai et al. developed an injectable HA-chitosan hydrogel embedded with gallic acid, which exhibited potent antibacterial activity against *Staphylococcus aureus* while accelerating epithelialization through VEGF upregulation [19, 20]. This synergy between HA's immunomodulatory properties and chitosan's inherent antimicrobial effects highlights its versatility in complex wound environments.

Moreover, the integration of HA with metal nanoparticles has opened new avenues for combating multidrug-resistant infections. Mendes et al. reported that HA-gold nanoparticle composites, combined with microcurrent therapy, synergistically reduced oxidative stress and enhanced collagen deposition in full-thickness burns [48]. The HA component facilitated targeted delivery of gold nanoparticles to wound sites, minimizing systemic toxicity—a critical consideration for clinical translation.

4.4 | Research Trends

Since 2016, the number of publications on hyaluronic acid (HA) for wound healing has grown a lot (Figure 2A). This increase matches progress in biomaterials and regenerative medicine, showing more global focus on HA solutions for chronic wounds and reducing scars.

After 2017, China became the leader in publication volume, which shows more investment in HA research, especially in creating HA-based biomaterials. Top institutions like the CHINESE ACADEMY OF SCIENCES in China have worked on HA hydrogels for wound healing, making a big part of the global research.

Recent keyword trends show a change from basic research on HA's effects on cell growth and inflammation to more practical topics like nanoparticles, antibacterial properties, and stem cell treatments. These new focuses show HA's potential for advanced wound care solutions.

One important study by Zhao et al. [28] developed an injectable hydrogel with antibacterial and antioxidant properties, which was a big step for HA-based wound dressings. This study is still highly cited because it combined HA with materials that have multiple uses. Zhao's team has continued working on HA-based materials, focusing on hydrogels with better antibacterial and

healing properties. Their work has helped move HA research closer to clinical use. Current products like Hyalomatrix show that HA works well to speed up tissue growth and healing. But future improvements could add antibacterial agents or growth factors to make treatments even better.

While HA has demonstrated substantial efficacy in wound healing, particularly in diabetic ulcers, future research should focus on optimizing nanofiber-based formulations. Astaneh and Fereydouni highlight the continued exploration of HA-containing nanofiber technologies, aiming to enhance the biocompatibility, mechanical properties, and drug-delivery capabilities of these materials [74]. Future studies might combine HA with new technologies like nanomedicine and gene therapy. For example, HA-based nanoparticles with gene-editing tools could provide customized wound care solutions for individual patients.

Future research should focus on bridging the gap between HA-based material innovation and clinical practicality. For instance, combining HA with emerging technologies like gene-editing tools (e.g., CRISPR-Cas9 delivery via HA nanoparticles) could enable personalized wound therapies. Additionally, 4D-printed HA scaffolds that adapt to wound pH or temperature changes may revolutionize dynamic wound management. However, challenges such as scalability, long-term biocompatibility, and regulatory hurdles must be systematically addressed.

4.5 | Limitations

Using synonyms like "Acid Hyaluronic" and "Hyaluronate Sodium" in the search strategy may bring up some papers that are not very closely related to the main focus of this review. While this broad search helps cover all important studies, it may also include articles that are only loosely connected to the topic. This choice was made to avoid missing any research that might be important.

The study included only publications in English, which may result in language bias and the exclusion of relevant studies published in other languages. While this ensures accessibility to a wider audience, it may limit the global scope of the analysis.

One limitation of the clustering analysis is that the level of detail in the keyword clusters depends on VOSviewer's algorithm. It may group different research topics, like "growth factor" and "inflammation," into broader categories within the biological research cluster. This gives a general view of the field but may miss the finer details of specific research topics. Future studies could use other tools or manual methods to create more detailed categories.

This study is subject to several additional limitations. First, the data utilized for analysis were solely obtained from the WoSCC database. Several studies have been excluded from consideration due to their publication in non-SCI journals or other databases [75]. Second, the potential for bias exists due to data extraction using software tools. Last, our study did not incorporate publications published after March 31, 2024, due to their incomplete availability during our database search.

5 | Conclusion

This study represents the initial comprehensive analysis of HA utilization in wound healing promotion through a bibliometric approach. This study effectively synthesizes and methodically examines global research patterns related to HA's role in promoting wound healing from January 1, 2000 to March 31, 2024. The annual production of relevant scholarly articles has shown significant growth, with current research focusing on advancing HA-based biomaterials for enhancing wound healing.

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Ethics Statement

This study does not involve human participants or animals and therefore did not require ethical approval.

Conflicts of Interest

The authors declare that they have no known competing financial interests in this article.

Data Availability Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.