Heliyon 10 (2024) e32311

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

Analysis of current trends in angiogenesis research for wound healing: A bibliometric study from 2013 to 2023

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ARTICLE INFO

Keywords:
Angiogenesis
Wound healing
Bibliometric
VOSviewer
CiteSpace
Hotspot

ABSTRACT

Background: Traumatic injuries, surgery, and chronic diseases lead to soft tissue wounds. Stimulating normal wound healing (WH) is important for tissue repair and restoration of homeostasis. Lack of angiogenesis impedes wound healing and is noted in chronic wounds. The goal of this investigation was to thoroughly assess the present state and patterns of investigations on angiogenesis in WH by the use of bibliometric analysis.
Methods: Studies examining angiogenesis and WH were sourced from the database of the Web of Science Core Collection. Only studies that fulfilled the inclusion criteria were chosen for the purpose of investigation. To analyze the publications included in this research, bibliometric and visual analysis techniques were applied utilizing tools like VOSviewer and CiteSpace.
Results: For the analysis, 11,558 papers were considered. The number of publications increased annually from 2013 to 2023. China, the USA, and South Korea were the top nations in this subject, accounting for 41.1 %, 19.4 %, and 5.8 % of published articles, respectively. The author and institution with the greatest number of publications were found to be Chang J and Shanghai Jiao Tong University. PLOS One had the greatest publication count among journals, whereas Biomaterials had the greatest number of citations and was often mentioned in co-citations. Angiogenesis-related biomedical engineering and tissue engineering were the topics that received the most research attention. Recent studies have focused on vascular endothelial growth factor and carboxymethyl chitosan as emerging areas of interest.
Conclusion: In this investigation, we compiled the features of publications and determined the most impactful nations, organizations, writers, periodicals, popular subjects, and patterns concerning the process of angiogenesis in the context of WH.

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https://doi.org/10.1016/j.heliyon.2024.e32311
Received 24 February 2024; Received in revised form 30 May 2024; Accepted 31 May 2024
Available online 4 June 2024

1. Introduction

Injuries from trauma rank as the sixth most prevalent reason for mortality and the fifth most common reason for moderate and severe disability globally [1]. Millions of wounds from surgery are generated each year as a result of normal medical procedures, along with trauma [2]. The intricate process of wound healing (WH) and tissue repair, particularly angiogenesis, has been a focal point of medical research. Angiogenesis refers to the mechanism of new blood vessel formation from existing vessels, which has a vital function in supplying nutrients and oxygen to the site of wounds [3]. Despite advancements in understanding these mechanisms, challenges in effective wound management persist, mainly owing to the complexity of the cellular and molecular interplay related to the process of healing [4]. Moreover, complications in wound repair, particularly in chronic wounds, are often intensified by underlying conditions such as diabetes, vascular disease, and aging, which affect millions worldwide [5,6].

Chronic wounds that fail to undergo orderly and timely repair pose a significant clinical challenge. These wounds often result in excessive scarring or persistent ulcerations [7]. The healing of such wounds involves a delicate balance of processes, including inflammation, cellular migration, matrix deposition, and angiogenesis [8]. Disruptions in these processes, particularly in the angiogenic phase, significantly contribute to the pathology of chronic wounds, highlighting the need for therapeutic intervention [9,10].

Considerable resources have been committed to understanding the role of angiogenesis in WH, with research extending from cellular and molecular studies to medical uses [11–13]. Growth factors, including vascular endothelial growth factor (VEGF), fibroblast growth factor 2, and platelet-derived growth factors, were tested for their potential to stimulate angiogenesis and enhance WH [14]. However, the medical use of these factors has been restricted due to challenges related to dosing, delivery, and safety. This led to the development of combination therapies and novel approaches to stimulate the WH process more effectively [15]. The complexity of WH, particularly in the context of chronic wounds, underscores the necessity for a multidisciplinary approach that integrates insights from basic science, clinical research, and therapeutic development [4].

Bibliometrics uses mathematical and statistical methods to provide a thorough, unbiased evaluation of knowledge sources [16,17]. Bibliographic analysis improves comprehension of scientific progress and evolving trends within a field. In this investigation, we assessed the angiogenesis role in WH to uncover insights that could inform future therapies aimed at augmenting angiogenesis.

2. Methods

2.1. Data collection and strategy for data retrieval

Thomson Reuters' Science Citation Index-Expanded (SCI-E) within the Web of Science (WOS) is well suited for bibliometric research. Consequently, we performed a detailed WOS search from 2013 to 2023, focusing on original articles. Due to the data being publicly available and not involving human individuals, ethical consent was considered unnecessary. The searches were conducted on October 31, 2023, to prevent omissions due to database updating. The search approaches were as follows: Teram search (TS) = ("wound healing" or "wound repair" or "tissue closure" or "wound regeneration" or "wound remodeling" or "tissue regeneration" or "tissue remodeling" or "wound healing process" or "wound recovery" or "wound management" or "cutaneous healing" or "soft tissue healing" or "scar formation" or "epithelialization" or "granulation tissue formation" or "chronic wound" or "non-healing wound") AND TS = (angiogenesis or vascularization or "blood vessel growth" or "endothelial cell proliferation" or "capillary formation" or "microvessel formation" or "blood vessel development" or "blood vessel formation" or "vascular formation" or "vascular development"

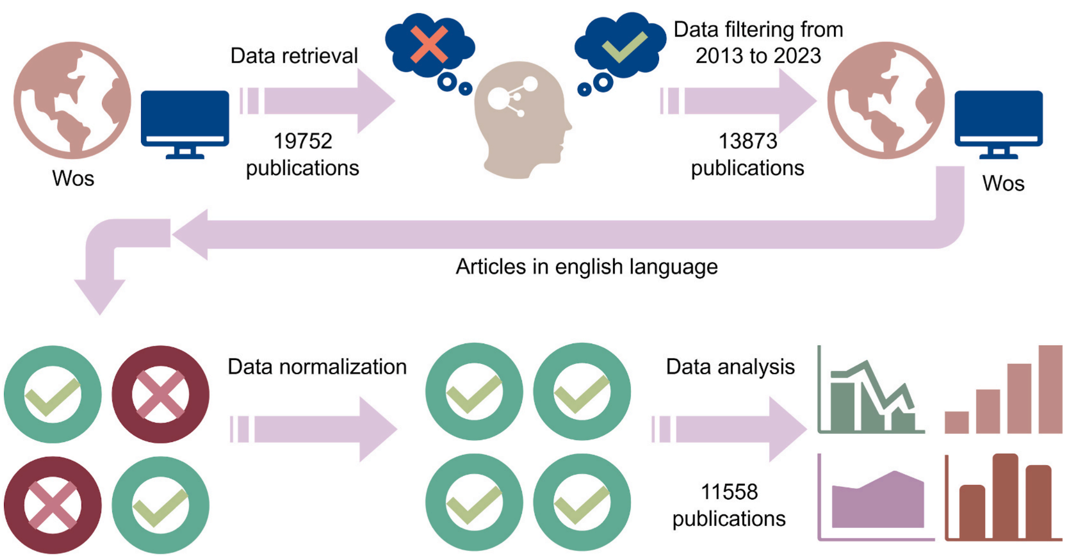

Fig. 1. Bibliometric workflow followed in the analysis.

or “vessel sprouting” or “vascular remodeling” or “vascular maturation” OR VEGF OR “vascular endothelial growth factor”) AND Language = (English). We considered peer-reviewed original articles as potentially eligible, excluding other types of publications. The enrollment and screening procedures are detailed in Fig. 1.

2.2. Study selection

The assessment of relevant papers was conducted in two phases by both authors (C. X. and M. W.) separately. The third author (J. L.) engaged in comprehensive discussions to address disagreements. During the first inspection phase, the publishing language was limited only to English. Furthermore, investigations that were not articles (such as reviews, conference proceedings, and letters) were not included. During the second step, the titles and abstracts of the other investigations were precisely assessed based on the following criteria: I (intervention): The use of biomaterials, P (patient): The investigation included individuals with angiogenesis in WH, animal models of angiogenesis for WH, and cell models, and S (study design): Clinical and basic research.

2.3. Data extraction

The publications were separated into several file formats for the purpose of analysis. The data retrieved from the papers include the title, author, institution, nation, journal (with the journal impact factor (IF) for 2023), publishing year, number of citations, and H-index.

2.4. Data collection and bibliometric analysis

For the purpose of conducting bibliometric analysis and visualization, the publications and cited references were exported in plain text format. Two authors independently gathered data from publications, including title, keywords, publication date, country of origin, authors, institution, journal, citation count, and H-index. VOSviewer (version 1.6.19) and CiteSpace (version 6.2. R4) were used to generate visual graphs. VOSviewer was employed to evaluate the most prolific countries and institutions. The software tool VOSviewer was utilized for an analysis of the nations, institutions, and authors with the highest productivity, in addition to the journals with the most citations and the keywords that often appear together. The software CiteSpace was utilized to create a timeline graph and identify bursts of keyword phrases. Every dot on the graphic graphs corresponds to a certain nation, institution, author, or publication. The dots were organized into several clusters based on their level of cooperation. The dot size was based on the quantity of publications. Link strength (LS) refers to the width of the line that connects the nodes and indicates the cooperation degree between them. The total link strength (TLS) shows the entire amount of cooperation [18]. During the process of keyword analysis, irrelevant terms were eliminated, and keywords with comparable meanings were combined. In CiteSpace graphs, a modularity value (Q-value) more than 0.3 and a mean silhouette value (S-value) greater than 0.7 are considered to show significant and appropriate clustering [19].

3. Results

3.1. Number of publications and evolution over time

The data collection yielded 11,558 articles published between 2013 and 2023 related to angiogenesis in WH. Fig. 2A illustrates the increase in the publication rate. An exponential growth function ($y = 539.85e^{0.1022x}$) was used to evaluate the correlation between cumulative publications and years and aligned well with the overall publication trend ($R^2 = 0.9781$). The correlation suggests substantial growth in research pertaining to angiogenesis in WH.

National publication counts were analyzed to investigate the countries that contributed the most to this field. China ranked first with 4753 publications (41.1 %), followed by the United States (US) (n = 2,241, 19.4 %), South Korea (n = 667, 5.8 %), Germany (n = 611, 5.3 %), and Japan (n = 561, 4.9 %) (Fig. 2B). The remaining countries had fewer than 500 publications. The rate of increase in publications was greatest in China.

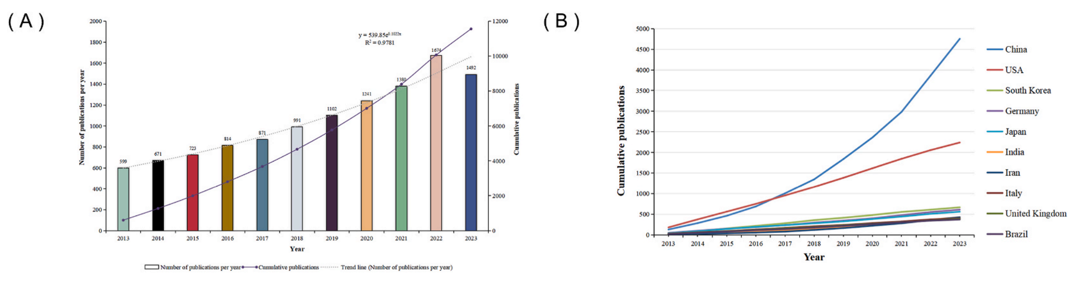

Fig. 2. Cumulative number of publications per year. (A) Global annual number of cumulative publications. (B) Regional cumulative annual number of publications.

3.2. Analysis of the characteristics of the country and institution of publications on angiogenesis in WH

Articles on angiogenesis in WH arose from authors in 111 countries (Fig. 3A). The most prominent collaborations were observed between the US and China (LS = 400), followed by the US and Germany (LS = 96). Subsequent notable collaborations involved the US and South Korea (LS = 85), Australia and China (LS = 71), and the US and United Kingdom (LS = 66). More than 50 articles were published by researchers from 35 countries.

Angiogenesis in WH research was conducted at 8806 institutions. Shanghai Jiao Tong University had the greatest number of publications (423, 3.7 %). Among the top 20 institutions, 18 were Chinese institutions, and two were US institutions. The top ten active institutions in China are illustrated in Table 1. Institutional cooperation analysis showed that Shanghai Jiao Tong University had relationships with many institutions (Fig. 3B). Additionally, we examined the top 10 universities that had the most significant increases in citations. The University of California System achieved the top ranking with a citation strength of 18.4. Furthermore, Korea University has a strong performance in terms of article citations (Supplementary material 1).

3.3. Analysis of the authors of publications

Publications arose from contributions from 60,670 authors. Table 2 displays the top 10 authors who have the highest number of publications. Author J.C. had the most publications, with a total of 50. Y.J.Z. came in second place with 42 publications, followed by Y. Z. Y with 39 publications. J.C. achieved the greatest amount of overall citations and the greatest H-index. Fig. 3C displays a map of a network of collaboration. C.G. exhibited the highest level of desire to interact with other authors, as indicated by a TLS score of 79.

3.4. Analysis of source and cited journals

Ten journals published the majority of papers (1,586, 13.72 %) (Table 3). *PLOS One*, *Acta Biomaterialia*, and the *International Journal of Molecular Sciences* were the top three journals. *Biomaterials* exhibited the greatest amount of citations and the greatest mean number of citations per manuscript. Biomaterials had the greatest H-index of 337, while PLOS One had an H-index of 268. The journal IF is a crucial metric employed to assess its worth. Biomaterials achieved the greatest IF of 14, while *Acta Biomaterialia* had a little lower IF of 9.7. Fig. 3D displays the network map of journal cogitation.

Fig. 4 illustrates the subject distribution of academic journals employing a dual-map overlay. Every point on the graph presents a journal. The horizontal axis represents the spectrum of disciplines covered by the journals in which the cited articles are published, providing a broad categorization of the fields. The vertical axis indicates the citation connections between the citing and cited journals, showing how knowledge flows between disciplines. The cited journal is on the right, while the citing journal is on the left. The connection between the two journals is shown by a colored track. The mapping reveals three distinct colored primary citation

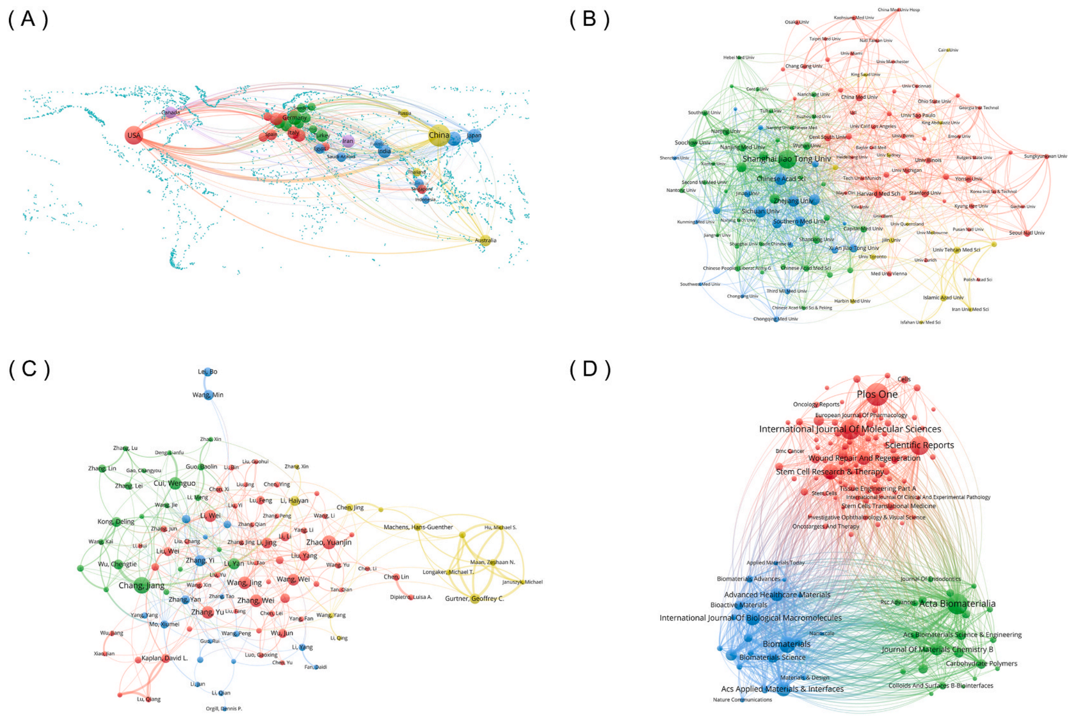

Fig. 3. Co-authorship network map. (A) Countries; (B) institutions; (C) authors; and (D) journals.

Table 1
Top ten institutions that published literature related to angiogenesis in wound healing from 2013 to 2023.

Rank	Institution	Country	No. of studies	Total link strength	Total citations	Average No. citations
1	Shanghai Jiao Tong University	China	423	379	13476	31.9
2	Chinese Academy of Sciences	China	308	252	11488	40.4
3	Sichuan University	China	193	96	4873	25.2
4	Zhejiang University	China	188	119	4611	24.5
5	Sun Yat-sen University	China	175	141	4177	23.9
6	Southern Medical University	China	168	135	3536	21.0
7	Huazhong University of Science and Technology	China	153	108	4122	26.9
8	Fudan University	China	150	198	2520	16.8
9	Wenzhou Medical University	China	145	106	4605	31.8
10	Tongji University	China	135	147	2878	21.3

Table 2
Top ten most productive authors regarding angiogenesis in wound healing from 2013 to 2023.

Rank	Authors	Counts	Total citations	Average citations	H-index
1	Chang, Jiang	50	4011	80.2	93
2	Cui, Wenguo	37	1631	44.1	63
3	Gurtner, Geoffrey C.	32	1521	47.5	73
4	Kong, Deling	31	1484	47.9	76
5	David Kaplan	31	1269	40.9	157
6	Wu, Chengtie	30	2284	76.1	87
7	Lei, Bo	26	2222	85.5	42
8	Lu, Feng	26	583	22.4	28
9	Machens, Hans-Guenther	23	609	26.6	31
10	Yar, Muhammad	23	322	14	18

Table 3
Top ten most productive journals regarding angiogenesis in wound healing from 2013 to 2023.

Rank	Journal title	Record	Total citations	Average citations	H-index	IF (2023)	JCR (2023)
1	*PLOS One*	239	6410	26.82	268	3.7	Q2
2	*Acta Biomaterialia*	204	9635	47.23	155	9.7	Q1
3	*International Journal Of Molecular Sciences*	199	2112	10.61	114	5.6	Q1
4	*Scientific Reports*	184	5677	30.85	149	4.6	Q2
5	*Biomaterials*	150	13865	92.43	337	14	Q1
6	*Stem Cell Research & Therapy*	136	4200	30.88	56	7.5	Q1
7	*ACS Applied Materials & Interfaces*	127	4369	34.40	169	9.5	Q1
8	*International Journal Of Biological Macromolecules*	124	2273	18.33	101	8.2	Q1
9	*Wound Repair And Regeneration*	113	3056	27.04	96	2.9	Q3
10	*Advanced Healthcare Materials*	110	3229	29.35	63	10	Q1

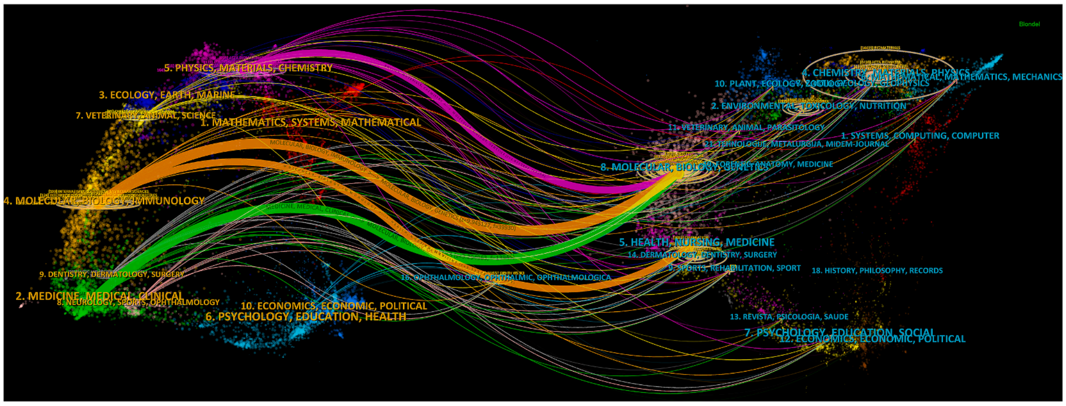

Fig. 4. Dual-map overlay of journals related to angiogenesis in wound healing research. The citing journals are on the left, the cited journals are on the right, and the colored path represents the citation relationship.

mechanisms, indicating that research published in journals in the fields of molecular/biology/genetics and health/nursing/medicine was primarily cited by those published in physics/materials/chemistry/molecular/biology/immunology and medicine/medical/clinical journals. Therefore, angiogenesis research in WH is closely connected to basic and clinical subjects.

3.5. Analysis of highly cited studies

Table 4 provides a comprehensive overview of the 10 studies that have received the highest number of citations. Of these studies, three were from Xi'an Jiaotong University (China), two were from Columbia University (US), and the others were from Harvard University (US), University of Chicago Medicine (US), Chinese Academy of Science (China), University of Huddersfield (England), and Shanghai Jiao Tong University (China). Specifically, a study entitled "3D Bioprinting of Vascularized, Heterogeneous Cell-Laden Tissue Constructs," published in Advanced Materials, was cited 1683 times, which was the greatest cited publication in the field. In relation to investigating topics, five papers investigated advanced tissue engineering, including 3D bioprinting and injectable hydrogels for complex tissue construction and self-healing. Four studies focused on cellular and molecular dynamics in healing, exploring gene expression regulation in WH and the role of macrophages in tissue engineering. Innovative materials for multifunctional WH were tested, such as bioactive glass scaffolds with angiogenesis and osteo-stimulation properties.

3.6. Keyword analysis of research hotspots

Keyword co-occurrence analysis is a frequently employed technique for identifying prevalent study subjects. Fig. 5A and B demonstrate the network and overlay visualization maps of the keywords that appear together. The top ten most commonly utilized keywords were WH, angiogenesis, inflammation, diabetes, hydrogel, VEGF, tissue engineering, tissue regeneration, mesenchymal stem cells, and migration. Fig. 5A illustrates all of the keywords grouped into four clusters. The biggest cluster (green) was linked to the interdisciplinary field of biomedical engineering and tissue engineering, with a specific focus on advanced wound care and healing, particularly in the context of diabetes, including keywords such as "hydrogel," "collagen," "wound dressing," and "diabetic wound." The second largest cluster (red) was connected to cancer biology, including keywords such as "endothelial cells," "proliferation," "invasion and metastasis," and "apoptosis." The third major group (blue) was connected to the field of regenerative medicine, with an emphasis on the healing and regeneration of various tissues and included keywords such as "tissue regeneration," "exosomes," "cytokines," "bone regeneration," and "platelet-rich plasma." The fourth group (yellow) represented diabetes-related complications related to WH and included keywords such as "inflammation," "macrophages," "fibroblasts," and "diabetic foot ulcer." As presented in Fig. 5B, terms marked in purple reveale that their average year of publication was 2018 or earlier, whereas those marked in bright yellow appeared after 2021. Keywords such as "invasion," "neovascularization," "myocardial infarction," and "myofibroblast" were the main topics during the early stage, whereas "antibacterial," "3D bioprinting," "diabetic wound healing," and "hemostasis"

Table 4
Top ten most cited references regarding angiogenesis in wound healing from 2013 to 2023.

Rank	Title	Institution	Authors	Journal	Citations
1	3D bioprinting of vascularized, heterogeneous cell-laden tissue constructs	Harvard University, USA	Kolesky, DB, Truby, RL, Lewis, JA et al.	*Advanced Materials*	1683
2	Antibacterial anti-oxidant electroactive injectable hydrogel as self-healing wound dressing with hemostasis and adhesiveness for cutaneous wound healing	Xi'an Jiaotong University, China	Zhao X, Wu H, Guo BL et al.	*Biomaterials*	1366
3	Antibacterial adhesive injectable hydrogels with rapid self-healing, extensibility and compressibility as wound dressing for joints skin wound healing	Xi'an Jiaotong University, China	Qu J, Zhao X, Liang Yp et al.	*Biomaterials*	1160
4	Metabolic regulation of gene expression by histone acetylation	University Chicago Med, USA	Zhang D, Tang ZY, Zhao YM et al.	*Nature*	1021
5	Adhesive hemostatic conducting injectable composite hydrogels with sustained drug release and photothermal antibacterial activity to promote full-thickness skin regeneration during wound healing	Xi'an Jiaotong University, China	Liang YP, Zhao X, Hu TL	*Small*	846
6	The role of the macrophage phenotype in vascularization of tissue engineering scaffolds	Columbia University, USA	Spiller KL, Anfang RR, Vunjak-Noyakovic G et al.	*Biomaterials*	717
7	Copper-containing mesoporous bioactive glass scaffolds with multifunctional properties of angiogenesis capacity, osteostimulation and antibacterial activity	Chinese Acad Sci, China	Wu CT, Zhou, YH, Xiao Y et al.	*Biomaterials*	608
8	Sequential delivery of immunomodulatory cytokines to facilitate the M1-to-M2 transition of macrophages and enhance vascularization of bone scaffolds	Columbia University, USA	Spiller KL, Nassiri S, Vunjak-Novakovic G et al.	*Biomaterials*	570
9	Exosomes released from human induced pluripotent stem cells-derived MSCs facilitate cutaneous wound healing by promoting collagen synthesis and angiogenesis	Shanghai Jiao Tong University, China	Zhang JY; Guan JJ, Wang Y et al.	*Journal of Translational Medicine*	528
10	Engineering bioactive self-healing antibacterial exosomes hydrogel for promoting chronic diabetic wound healing and complete skin regeneration	Xi'an Jiaotong University, China	Wang Cg, Wang M, Mao C et al.	*Theraostics*	465

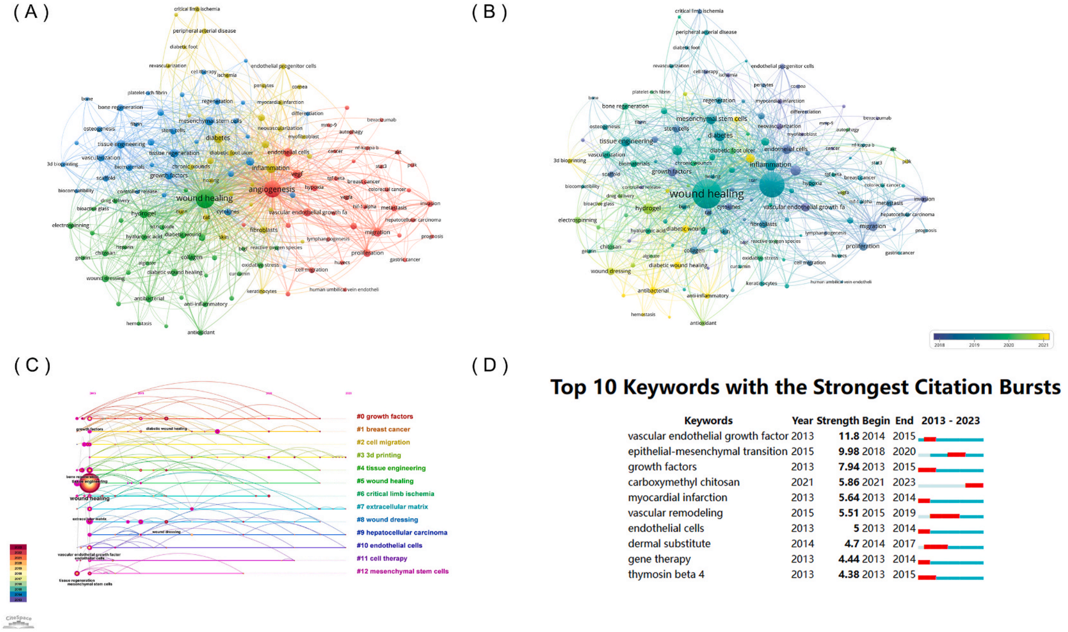

Fig. 5. (A) Network visualization map of co-occurrence and clustering analysis of the keywords; (B) overlay; and (C) timeline and clustering view of keywords. (D) The top ten keywords with the strongest citation bursts.

appeared relatively late in the investigation duration.

A timeline map of co-occurring keywords was generated using CiteSpace (Fig. 5C). This enables an assessment of the duration of every cluster and the growth pattern of a particular cluster. It can be employed to investigate the temporal attributes of the study area represented by every cluster and, therefore, ascertain the trend of hotspot evolution. The Q-value was 0.8201, and the S-value was 0.9561. WH and tissue engineering were the primary hot research keywords during or p 2013. Three-dimensional printing, extracellular matrix, hepatocellular carcinoma, and endothelial cells were hot topics in 2023. The robustness of the keyword bursts served as an additional indicator of the evolving boundaries and hotspots of the investigation throughout time (Fig. 5D). Out of the top ten keywords that saw the most intense citation bursts, VEGF had the greatest burst strength (11.8), followed by epithelial-mesenchymal transition (9.98) and growth factors (7.94). Notably, the term carboxymethyl chitosan showed bursts in 2023, suggesting that this remains a hot topic.

4. Discussion

This is the first investigation to perform a comprehensive bibliometric analysis of publications linked to angiogenesis in WH. Angiogenesis has a vital role in the WH mechanism and interacts with multiple factors to directly affect the outcome of WH. The results revealed a consistent rise in the number of yearly publications on this particular topic, indicating a rising interest in investigating angiogenesis in WH. This may be partly due to a deeper understanding of the molecular mechanisms associated with angiogenesis during WH and the development of novel biological materials.

The impact of various countries, institutions, authors, and journals on this specific research field was examined. Publications from authors and institutions in China were most common. The ten most productive institutions were from China. Among journals, *Acta Biomaterialia*, *Biomaterials*, and *Advanced Healthcare Materials* were especially influential. *PLOS One* stood out as having the most publications and thus the best H-index, while *Biomaterials* had the highest citation count and average citations per paper.

The ten most-cited publications could be considered influential in the field. The leading publication introduced a novel bioprinting method to create 3D tissue constructs that incorporated vasculature, various cell types, and an extracellular matrix [20]. Such 3D micro-engineered environments may be helpful in WH and drug screening, angiogenesis, and stem cell niche studies. Four studies focused on antibacterial injectable hydrogels. One described an injectable hydrogel dressing made from quaternized chitosan, polyaniline, and polyethylene glycol with self-healing, antibacterial, and antioxidant properties [21]. The dressing upregulated growth factors, thickened granulation tissue, and increased collagen deposition to improve *in vivo* WH. A self-healing micelle/hydrogel composite using quaternized chitosan and pluronic F127 upregulated VEGF and increased granulation tissue and collagen deposition [22]. developed. A wound dressing made of hyaluronic acid, dopamine, and reduced graphene oxide outperformed commercial dressings [23]. Four studies examined gene expression regulation and the function of macrophages in tissue engineering for WH. M1 macrophages were noted to activate angiogenesis, whereas M2 macrophages facilitated the maturation of the vessel. Thus, scaffolds designed to sequentially release signals, polarizing infiltrating macrophages first to M1 and then to M2 phenotypes, may augment vascularization [24,25]. Human induced pluripotent stem cell-derived mesenchymal stem cells expedited cutaneous WH by enhancing fibroblast growth, migration, collagen production, and endothelial cell angiogenesis [26]. Zhang et al. [27] Noteworthy was the finding that lactate produced during glycolysis under hypoxic or bacterial conditions triggered histone acetylation. The epigenetic modification stimulated the transcription of WH genes [27]. Lastly, mesoporous bioactive glass scaffolds containing copper with interconnected macro- and mesopores enhanced angiogenesis and osteogenesis [28]. The trend towards new reagents and delivery methods is not unique to WH but can be traced in studies focused on non-WH topics and disease conditions.

Keyword analysis revealed that tissue engineering and inflammation mechanisms were the most prevalent topics. The network visualization categorized keywords into four clusters, comprising biomedical engineering, cancer biology, regenerative medicine, and diabetes-related WH complications. These clusters represent the core themes of this research domain. The overlay map indicated the early emergence of keywords linked to WH and tissue engineering, whereas recent trends focused on 3D printing, extracellular matrix, hepatocellular carcinoma, and endothelial cells.

Understanding of the molecular and cellular mechanisms responsible for normal and pathological WH continues to deepen. Recent studies elucidated the critical roles of various growth factors, notably VEGF and fibroblast growth factor (FGF), in mediating angiogenic responses [29–31]. These discoveries paved the way for the development of targeted therapies. For example, the application of recombinant VEGF in WH models showed promising results, significantly improving healing rates in ischemic and diabetic wounds [32–34]. Use of FGF in clinical trials was associated with better wound granulation and vascularization [35–38]. Beyond growth factors, the role of microRNAs in regulating angiogenesis is an exciting new area of research. microRNAs promoted and inhibited angiogenesis, offering potential novel targets for therapeutic intervention [39]. Angiopoietin-like proteins and their interplay with integrin signaling were found to modulate angiogenesis in response to tissue injury [40]. Extracellular vesicles are also being explored in WH. They carry pro-angiogenic factors and genetic material, influencing the angiogenic process in situ [41]. Furthermore, manipulation of mechano-transduction pathways through material sciences and tissue engineering presents a novel method to enhance angiogenic responses, especially in the mechanically sensitive environments found in chronic wounds [42]. Translating these findings into practical, affordable, clinically applicable treatments with lasting effects remains a challenge. The heterogeneity of wound environments, especially in the context of comorbidities such as diabetes and vascular diseases, supports the use of personalized approaches to therapy. Additionally, understanding the long-term effects and safety of these angiogenic treatments is essential to minimize adverse effects. Thus, while progress in angiogenesis research is undeniable, the possible clinical benefits remain unfulfilled.

Given the complex interplay of cellular, molecular, and environmental factors involved, WH-related angiogenesis is challenging to study. Despite advances in knowledge, clinical translation is slow. For instance, VEGF promotes angiogenesis, and yet exogenous VEGF has not hasten the rate of chronic wound healing in diabetic individuals [43–45]. This is further amplified in the context of aging, where the natural decline in angiogenic response necessitates a delicate balance between promoting angiogenesis and avoiding aberrant vascular growth and tumor growth. In addition, the field of regenerative medicine confronts the challenge of integrating angiogenesis into tissue-engineered products for consistent WH [46–49]. The efficacy of these approaches, as demonstrated in animal models, has not translated to benefits for individuals with aberrant WH. It is clear that a multidisciplinary approach encompassing molecular biology, genetics, pharmacology, and clinical medicine will help overcome these challenges and advance the field of WH.

Our study has certain limitations. Initially, the information was only obtained from the WoSCC database, perhaps leading to an inadequate search. However, the WoSCC database is very vast and internationally thorough, making it a popular choice for bibliometric analysis. The data of WoSCC sufficiently represent the current research landscape in this field. Second, our selection was limited to English-language publications.

In conclusion, using various statistical techniques for bibliometric analysis yielded a thorough assessment of the current status of research papers focusing on angiogenesis in WH. The study uncovered crucial attributes of publications, emphasized the dominant nations, institutions, authors, and journals, and delineated the main investigation hotspots and patterns in angiogenesis within WH. In addition, advances and challenges associated with research in angiogenesis in WH were noted. While much can still be done, investigating the pathophysiological changes in angiogenesis is a reasonable point to start.

Funding

This investigation received some funding from funds provided by the Major Research Plan of the National Natural Science Foundation of China (No. 82272298 and No. 81771933).

Data availability statement

The associated author may provide de-identified data upon a reasonable request.

Institutional review board statement

Institutional approval was not required because this article does not contain any human or animal subjects.

Consent for publication

Not applicable.

CRediT authorship contribution statement

Miao Wang: Writing – original draft, Software, Resources. **Cheng Xu:** Writing – review & editing, Visualization, Validation, Investigation, Funding acquisition. **Di Wang:** Visualization, Validation, Resources, Project administration, Data curation. **Jie Lu:** Writing – review & editing, Visualization, Validation, Methodology, Investigation, Funding acquisition, Formal analysis. **Aizhong Wang:** Project administration, Methodology, Investigation, Funding acquisition. **Quanhong Zhou:** Writing – review & editing, Validation, Supervision, Resources, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgment

We are grateful to CiteSpace and VOSviewer for their free access.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e32311.

References

[1] G.K. Siberry, M.J. Abzug, S. Nachman, et al., Guidelines for the prevention and treatment of opportunistic infections in HIV-exposed and HIV-infected children: recommendations from the national Institutes of health, centers for disease control and prevention, the HIV medicine association of the infectious diseases society of America, the pediatric infectious diseases society, and the American Academy of pediatrics, Pediatr. Infect. Dis. J. 32 (2) (2013) i–KK4, https://doi.org/10.1097/01.inf.0000437856.09540.11. Suppl 2.

[2] C.K. Sen, G.M. Gordillo, S. Roy, et al., Human skin wounds: a major and snowballing threat to public health and the economy, Wound Repair Regen. 17 (6) (2009) 763–771, https://doi.org/10.1111/j.1524-475X.2009.00543.x.

[3] F. Arnold, D.C. West, Angiogenesis in wound healing, Pharmacol. Ther. 52 (3) (1991) 407–422, https://doi.org/10.1016/0163-7258(91)90034-j.

[4] A.P. Veith, K. Henderson, A. Spencer, A.D. Sligar, A.B. Baker, Therapeutic strategies for enhancing angiogenesis in wound healing, Adv. Drug Deliv. Rev. 146 (2019 Jun) 97–125, https://doi.org/10.1016/j.addr.2018.09.010. Epub 2018 September 26. PMID: 30267742; PMCID: PMC6435442.

[5] E. Shaabani, M. Sharifiaghdam, R. Faridi-Majidi, S.C. De Smedt, K. Braeckmans, J.C. Fraire, Gene therapy to enhance angiogenesis in chronic wounds, Mol. Ther. Nucleic Acids 29 (2022) 871–899, https://doi.org/10.1016/j.omtn.2022.08.020. Published 2022 August 17.

[6] P. Orlowski, M. Zmigrodzka, E. Tomaszewska, et al., Tannic acid-modified silver nanoparticles for wound healing: the importance of size, Int. J. Nanomed. 13 (2018) 991–1007, https://doi.org/10.2147/IJN.S154797.

[7] L.A. DiPietro, Angiogenesis and scar formation in healing wounds, Curr. Opin. Rheumatol. 25 (1) (2013) 87–91, https://doi.org/10.1097/BOR.0b013e32835b13b6.

[8] T. Komprda, Z. Sládek, M. Vícenová, et al., Effect of polymeric nanoparticles with entrapped fish oil or mupirocin on skin wound healing using a porcine model, Int. J. Mol. Sci. 23 (14) (2022), https://doi.org/10.3390/ijms23147663.

[9] A. Guerra, J. Belinha, R.N. Jorge, Modelling skin wound healing angiogenesis: a review, J. Theor. Biol. 459 (2018) 1–17, https://doi.org/10.1016/j.jtbi.2018.09.020.

[10] T.N. Demidova-Rice, J.T. Durham, I.M. Herman, Wound healing angiogenesis: innovations and challenges in acute and chronic wound healing, Adv. Wound Care 1 (1) (2012) 17–22, https://doi.org/10.1089/wound.2011.0308.

[11] M. Wang, D.G. Yu, G.R. Williams, et al., Co-loading of inorganic nanoparticles and natural oil in the electrospun janus nanofibers for a synergetic antibacterial effect, Pharmaceutics 14 (6) (2022), https://doi.org/10.3390/pharmaceutics14061208.

[12] Y. Gao, Y. Sun, H. Yang, et al., A low molecular weight hyaluronic acid derivative accelerates excisional wound healing by modulating pro-inflammation, promoting epithelialization and neovascularization, and remodeling collagen, Int. J. Mol. Sci. 20 (15) (2019) null, https://doi.org/10.3390/ijms20153722.

[13] J.J. Roberts, B.L. Farrugia, R.A. Green, et al., In situ formation of poly(vinyl alcohol)-heparin hydrogels for mild encapsulation and prolonged release of basic fibroblast growth factor and vascular endothelial growth factor, J. Tissue Eng. 7 (2016) 2041731416677132, https://doi.org/10.1177/2041731416677132.

[14] P.T. Thevenot, A.M. Nair, J. Shen, et al., The effect of incorporation of SDF-1alpha into PLGA scaffolds on stem cell recruitment and the inflammatory response, Biomaterials 31 (14) (2010) 3997–4008, https://doi.org/10.1016/j.biomaterials.2010.01.144.

[15] M.S. Wietecha, L.A. DiPietro, Therapeutic approaches to the regulation of wound angiogenesis, Adv. Wound Care 2 (3) (2013 Apr) 81–86, https://doi.org/10.1089/wound.2011.0348. PMID: 24527330; PMCID: PMC3623575.

[16] C. Mejia, M. Wu, Y. Zhang, Y. Kajikawa, Exploring topics in bibliometric research through citation networks and semantic analysis, Front Res Metr Anal 6 (2021) 742311, https://doi.org/10.3389/frma.2021.742311. Published 2021 September 24.

[17] P. Kokol, H. Blažun Vošner, J. Završnik, Application of bibliometrics in medicine: a historical bibliometrics analysis, Health Inf. Libr. J. 38 (2) (2021) 125–138, https://doi.org/10.1111/hir.12295.

[18] Y.X. Zhou, X.Y. Cao, C. Peng, Antimicrobial activity of natural products against MDR bacteria: a scientometric visualization analysis, Front. Pharmacol. 13 (2022) 1000974, https://doi.org/10.3389/fphar.2022.1000974.

[19] Y. Zhou, M. Mo, D. Luo, et al., Evolutionary trend analysis of research on 5-ALA delivery and theranostic applications based on a scientometrics study, Pharmaceutics 14 (7) (2022), https://doi.org/10.3390/pharmaceutics14071477.

[20] D.B. Kolesky, R.L. Truby, A.S. Gladman, T.A. Busbee, K.A. Homan, J.A. Lewis, 3D bioprinting of vascularized, heterogeneous cell-laden tissue constructs, Adv. Mater. 26 (19) (2014) 3124–3130, https://doi.org/10.1002/adma.201305506.

[21] X. Zhao, H. Wu, B. Guo, R. Dong, Y. Qiu, P.X. Ma, Antibacterial anti-oxidant electroactive injectable hydrogel as self-healing wound dressing with hemostasis and adhesiveness for cutaneous wound healing, Biomaterials 122 (2017) 34–47, https://doi.org/10.1016/j.biomaterials.2017.01.011.

[22] J. Qu, X. Zhao, Y. Liang, T. Zhang, P.X. Ma, B. Guo, Antibacterial adhesive injectable hydrogels with rapid self-healing, extensibility and compressibility as wound dressing for joints skin wound healing, Biomaterials 183 (2018) 185–199, https://doi.org/10.1016/j.biomaterials.2018.08.044.

[23] Y. Liang, X. Zhao, T. Hu, et al., Adhesive hemostatic conducting injectable composite hydrogels with sustained drug release and photothermal antibacterial activity to promote full-thickness skin regeneration during wound healing, Small 15 (12) (2019) e1900046, https://doi.org/10.1002/smll.201900046.
[24] K.L. Spiller, R.R. Anfang, K.J. Spiller, et al., The role of macrophage phenotype in vascularization of tissue engineering scaffolds, Biomaterials 35 (15) (2014) 4477–4488, https://doi.org/10.1016/j.biomaterials.2014.02.012.
[25] K.L. Spiller, S. Nassiri, C.E. Witherel, et al., Sequential delivery of immunomodulatory cytokines to facilitate the M1-to-M2 transition of macrophages and enhance vascularization of bone scaffolds, Biomaterials 37 (2015) 194–207, https://doi.org/10.1016/j.biomaterials.2014.10.017.
[26] J. Zhang, J. Guan, X. Niu, et al., Exosomes released from human induced pluripotent stem cells-derived MSCs facilitate cutaneous wound healing by promoting collagen synthesis and angiogenesis, J. Transl. Med. 13 (2015) 49, https://doi.org/10.1186/s12967-015-0417-0. Published 2015 Feb 1.
[27] D. Zhang, Z. Tang, H. Huang, et al., Metabolic regulation of gene expression by histone lactylation, Nature 574 (7779) (2019) 575–580, https://doi.org/10.1038/s41586-019-1678-1.
[28] C. Wu, Y. Zhou, M. Xu, et al., Copper-containing mesoporous bioactive glass scaffolds with multifunctional properties of angiogenesis capacity, osteostimulation and antibacterial activity, Biomaterials 34 (2) (2013) 422–433, https://doi.org/10.1016/j.biomaterials.2012.09.066.
[29] K.R. Arya, R.P. Bharath Chand, C.S. Abhinand, et al., Identification of hub genes and key pathways associated with anti- VEGF resistant glioblastoma using gene expression data analysis, Biomolecules 11 (3) (2021), https://doi.org/10.3390/biom11030403.
[30] A. De Zutter, H. Crijns, N. Berghmans, et al., The chemokine-based peptide, CXCL9(74-103), inhibits angiogenesis by blocking heparan sulfate proteoglycan-mediated signaling of multiple endothelial growth factors, Cancers 13 (20) (2021), https://doi.org/10.3390/cancers13205090.
[31] C.K. Nanditha, G.S.V. Kumar, Bioactive peptides laden nano and micro-sized particles enriched ECM inspired dressing for skin regeneration in diabetic wounds, Mater Today Bio 14 (2022) 100235, https://doi.org/10.1016/j.mtbio.2022.100235.
[32] Angiopoietin-like 4 stimulates STAT3-mediated iNOS expression and enhances angiogenesis to accelerate wound healing in diabetic mice, Mol. Ther. 22 (9) (2014) 1593–1604, https://doi.org/10.1038/mt.2014.102.
[33] P. Yang, D. Wang, Y. Shi, et al., Insulin-containing wound dressing promotes diabetic wound healing through stabilizing HIF-1α, Front. Bioeng. Biotechnol. 8 (2020) 592833 https://doi.org/10.3389/fbioe.2020.592833.
[34] E. Węgłowska, M. Koziołkiewicz, D. Kamińska, et al., Extracellular nucleotides affect the proangiogenic behavior of fibroblasts, keratinocytes, and endothelial cells, Int. J. Mol. Sci. 23 (1) (2021), https://doi.org/10.3390/ijms23010238.
[35] M.S. Hu, Z.N. Maan, T. Leavitt, et al., Wounds inhibit tumor growth in vivo, Ann. Surg. 273 (1) (2021) 173–180, https://doi.org/10.1097/SLA.0000000000003255.
[36] Y. Zhu, W. Tan, A.M. Demetriades, et al., Interleukin-17A neutralization alleviated ocular neovascularization by promoting M2 and mitigating M1 macrophage polarization, Immunology 147 (4) (2016) 414–428, https://doi.org/10.1111/imm.12571.
[37] A.V. Kamath, V. Yip, P. Gupta, et al., Dose dependent pharmacokinetics, tissue distribution, and anti-tumor efficacy of a humanized monoclonal antibody against DLL4 in mice, mAbs 6 (6) (2014) 1631–1637, https://doi.org/10.4161/mabs.36107.
[38] K.C. Murphy, J. Whitehead, P.C. Falahee, et al., Multifactorial experimental design to optimize the anti-inflammatory and proangiogenic potential of mesenchymal stem cell spheroids, Stem Cell. 35 (6) (2017) 1493–1504, https://doi.org/10.1002/stem.2606.
[39] J. Wang, Q. Jiang, O.D. Faleti, et al., Exosomal delivery of AntagomiRs targeting viral and cellular MicroRNAs synergistically inhibits cancer angiogenesis, Mol. Ther. Nucleic Acids 22 (2020) 153–165, https://doi.org/10.1016/j.omtn.2020.08.017.
[40] M.B. Morelli, C. Chavez, G. Santulli, Angiopoietin-like proteins as therapeutic targets for cardiovascular disease: focus on lipid disorders, Expert Opin. Ther. Targets 24 (1) (2020) 79–88, https://doi.org/10.1080/14728222.2020.1707806.
[41] E. Ragni, S. Palombella, S. Lopa, et al., Innovative visualization and quantification of extracellular vesicles interaction with and incorporation in target cells in 3D microenvironments, Cells 9 (5) (2020) 1180, https://doi.org/10.3390/cells9051180. Published 2020 May 9.
[42] R. Censi, C. Casadidio, S. Deng, et al., Interpenetrating hydrogel networks enhance mechanical stability, rheological properties, release behavior and adhesiveness of platelet-rich plasma, Int. J. Mol. Sci. 21 (4) (2020) 1399, https://doi.org/10.3390/ijms21041399. Published 2020 February 19.
[43] H. Tanno, E. Kanno, S. Sato, et al., Contribution of invariant natural killer T cells to the clearance of Pseudomonas aeruginosa from skin wounds, Int. J. Mol. Sci. 22 (8) (2021), https://doi.org/10.3390/ijms22083931.
[44] V. Puca, R.Z. Marulli, R. Grande, et al., Microbial species isolated from infected wounds and antimicrobial resistance analysis: data emerging from a three-years retrospective study, Antibiotics (Basel) 10 (10) (2021), https://doi.org/10.3390/antibiotics10101162.
[45] W. Ma, X. Zhang, Y. Liu, et al., Polydopamine decorated microneedles with Fe-MSC-Derived nanovesicles encapsulation for wound healing, Adv. Sci. 9 (13) (2022) e2103317, https://doi.org/10.1002/advs.202103317.
[46] X. Zhu, Y. Shan, M. Yu, et al., Tetramethylpyrazine ameliorates peritoneal angiogenesis by regulating VEGF/hippo/YAP signaling, Front. Pharmacol. 12 (2021) 649581, https://doi.org/10.3389/fphar.2021.649581.
[47] X. He, Y. Yang, L. Mu, et al., A frog-derived immunomodulatory peptide promotes cutaneous wound healing by regulating cellular response, Front. Immunol. 10 (2019) 2421, https://doi.org/10.3389/fimmu.2019.02421.
[48] X. Gong, M. Luo, M. Wang, et al., Injectable self-healing ceria-based nanocomposite hydrogel with ROS-scavenging activity for skin wound repair, Regen Biomater 9 (1) (2022) rbab074, https://doi.org/10.1093/rb/rbab074.
[49] J. Kim, B. Kasukonis, K. Roberts, et al., Graft alignment impacts the regenerative response of skeletal muscle after volumetric muscle loss in a rat model, Acta Biomater. 105 (2020) 191–202, https://doi.org/10.1016/j.actbio.2020.01.024.