Insight into the research frontier of hypoxia in skin health and diseases: a bibliometric analysis

Cancan Huang, Xiang Li, Xingzhu Mou, Wenjun Wang, Wenjun Wang, Jieyu Li, Ni Liu, Xia Xiong, Sha Yi, Guishu Zhong, Yan Chen

Submitted to: JMIR Dermatology
on: June 05, 2024

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Cancan Huang[1*] BMed; Xiang Li[2*] MD; Xingzhu Mou[1*] BMed; Wenjun Wang[2] MM; Wenjun Wang[1] MM; Jieyu Li[1] BMed; Ni Liu[1] BMed; Xia Xiong[1] MM; Sha Yi[1] MM; Guishu Zhong[1] MM; Yan Chen[1] MD

[1]Department of Dermatology, The Affiliated Hospital, Southwest Medical University Luzhou CN
[2]Department of Biochemistry and Molecular Biology, School of Basic Medical Science, Southwest Medical University Luzhou CN
[*]these authors contributed equally

Corresponding Author:
Yan Chen MD
Department of Dermatology, The Affiliated Hospital, Southwest Medical University
No. 25 Taiping Street, Jiangyang District, Luzhou City, Sichuan Province
Luzhou
CN

Abstract

Background: Research has demonstrated that hypoxia, a decrease in intracellular oxygen, is linked to multiple processes in the skin, including metabolic adaptation, cell survival, pathogenic microbe infection, immune response, tumorigenesis, and various diseases.

Objective: This paper aims to perform a thorough bibliometric analysis of studies of hypoxia in skin health and disease to identify the frontiers, hotspots, and evolution of these studies.

Methods: Articles about hypoxia in skin health and disease in the Web of Science Core Collection were gathered as of December 31, 2023. To find bursting keywords and references, VOSviewer was used to look at co-authorship and phrase co-occurrences and make visualizations of them.

Results: A total of 1,511 papers on hypoxia in skin health and disease were examined in this study. China, the United States, and Japan were the top three countries contributing to this topic, while the International Journal of Molecular Sciences was the journal with the most articles. In terms of prolific authors in the publications, Yuesheng Huang from China contributed the most articles. The terms "hypoxia," "angiogenesis," and "wound healing" were the ones that were used the most frequently. In this study, a bibliometric analysis was performed on the last ten years' worth of research on hypoxia in skin health and disease.

Conclusions: The analysis identified the publications, nations, authors, institutions, and journals that were involved in this subject. These data offer a more comprehensive understanding of the area of research that has been conducted on hypoxia in skin health and disease.

(JMIR Preprints 05/06/2024:62925)
DOI: https://doi.org/10.2196/preprints.62925

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Insight into the research frontier of hypoxia in skin health and diseases: a bibliometric analysis

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[1]Department of Dermatology, The Affiliated Hospital, Southwest Medical University, Luzhou 646000, China

[2]Department of Biochemistry and Molecular Biology, School of Basic Medical Science, Southwest Medical University, Luzhou, China

[3]School of Stomatology, Southwest Medical University, Luzhou, Sichuan, Province, China

[+] Co-first authors

*Correspondence should be addressed to Yan Chen; yanchen202110@126.com; 15284067364 and Guishu Zhong; zgshu@swmu.edu.cn

Abstract

Background: Research has demonstrated that hypoxia, a decrease in intracellular oxygen, is linked to multiple processes in the skin, including metabolic adaptation, cell survival, pathogenic microbe infection, immune response, tumorigenesis, and various diseases.

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Keywords

Bibliometrics; CiteSpace; VOSviewer; Hypoxia; Skin

Introduction

Molecular oxygen is crucial for maintaining intracellular bioenergetics and the survival of most species on Earth [1]. Hypoxia, a drop in tissue oxygen supply, triggers metabolic crises and is dangerous for living things [2]. When tissues are hypoxic, various intracellular downstream signals respond in cells, principally hypoxia-inducible factor (HIF), endoplasmic reticulum (ER) stress, energy metabolic pathways such as the mTOR complex 1 (mTORC1), and other O_2 sensing mechanisms [3, 4]. When mammalian cells are exposed to a low-oxygen environment, the expression of hypoxia-inducible transcription factor (HIF) will be triggered [4]. HIF is a central pathway in the hypoxic response, mainly involving three α molecules and one β molecule, integrating the HIF family. Exploration of this pathway can further provide us with a more detailed molecular basis for understanding hypoxia in cell perception, signal transmission, and its potential therapeutic targets in human diseases.

Researchers found that hypoxia is essential in multiple skin biological processes such as angiogenesis, cell metabolism, autophagy, proliferation, cell survival, and immunological response. Among them, angiogenesis is a crucial aspect of skin physiology and is regulated by HIF-1α through modulating factors like fibroblast growth factor-2, Vascular endothelial growth factor-A (VEGF-A) [5, 6], VEGF receptors [7], and other factors [8-10]. In terms of cellular metabolism, to meet the energy demand of the cells during acute anoxia stress, Kierans, S.J., and C.T. Taylor suggested that the metabolic strategy of skin cells can be modulated by HIF-1α [11], specifically by HIF-1-dependent upregulation of genes encoding glycolytic enzymes [12] and glucose transporters [13], as well as the HIF-1-mediated inhibition of oxidative phosphorylation (OXPHOS) to further promote glycolysis [14, 15]. Hypoxia is also found to induce autophagy, and scholars have suggested that autophagy interacts with other cellular pathways in the skin, such as inhibiting the apoptosis of keratinocytes [16] and inducing the proliferation of dermal fibroblasts [17]. And Kim, D., et al. proved that Lysophosphatidic acid/Lysophosphatidic acid receptor 1 (LPA/LPAR1) signaling triggers Phosphoglycerate mutase 1 (PGAM1) expression through the protein kinase B(AKT)/mTOR/HIF-1α

pathway and enhances glycolysis to promote keratinocyte proliferation [18]. Regarding cell survival, the upregulation of HIF-1α in the epidermis, which includes sebaceous gland and bulge epidermal stem cells, can rescue cell death [19]. Researchers also found that HIF-1α assumes a pivotal role in skin immunological responses; for instance, Sobecki, M., et al. reported that HIF-1α in NK cells can keep a balance between antimicrobial defense and overall restoration in the skin [20], and in Manresa, M.C., et al.'s study, they proved that HIF plays a crucial role in neutrophil recruitment to the skin as well as the cytokine production of keratinocytes [21].

Meanwhile, the HIF signal has also been proven to be involved in a variety of skin diseases. There are several dermatoses of metabolism disturbance associated with the HIF signal, such as psoriasis [22], keloid [23], hidradenitis suppurativa [24], and limited systemic sclerosis [25]. Simultaneously, the HIF signal has been demonstrated to play an important role in wound healing [26], various infectious and inflammatory skin diseases [27], including Staphylococcus aureus abscess formation [28], allergic contact dermatitis [29], particulate matter-induced skin inflammation [30], lupus skin disease [31], and atopic dermatitis [32]. Scholars have also suggested that HIF has a close relationship with skin cancer [33], such as melanoma [34], cutaneous squamous cell carcinoma [35], and sporadic cutaneous angiosarcomas [36]. Here, we primarily focused on and summarized the study of hypoxia as associated with skin health and disease.

Bibliometric analysis is a rigorous and popular method used to analyze and explore large amounts of scientific data [37] to describe publishing trends and highlight relationships between publications in a particular field [38]. Bibliometric analysis involves the importance of a research topic, the geography distribution of researches, and quantitative analysis of citations and citation counts [39]. It also identifies different features of authors, institutions, countries, journals, references, and keywords of varied publications in the relevant research field over a period of time [40]. Bibliometric tools such as R package "bibliometrix" [41], VoSviewer [42], and CiteSpace [43] are utilized to enable the visualization of literature analysis, and those tools have been extensively

applied in medical fields including oncology [40, 44], orthopedics [45], cardiology [46, 47], and neurology [48, 49]. Although one scholar has done a bibliometric analysis of hypoxia-inducible factor prolyl hydroxylase inhibitor in anemia [50], studies of hypoxia and skin health and disease have not appeared by means of bibliometry. Related studies in the last few years have shown that hypoxia shows a good prospect in the research of skin health and disease. This study aimed to conduct a bibliometric analysis of research on hypoxia and skin health and disease over the past 10 years (from 2014 to 2023) to clarify current research status and main contributors and to forecast the research tendency and prospects of future development in this field.

Data sources and research methods

Data collection

In this study, a bibliometric analysis of hypoxia and skin health and disease research was conducted based on the Web of Science core collection (WoSCC) database (https://webofscience.clarivate.cn/wos/woscc/basic-search). The Web of Science was chosen as the main database for this study because it covers more than 12,000 academic journals and is frequently used by scholars [51]. Compared to other databases such as PubMed, Scopus, and Medline, Web of Science provides the most reliable and comprehensive bibliometric analysis [52].

We searched relevant studies from WoSCC using accurate keywords,such as “hypoxia” and “skin.” To search the relevant literature comprehensively, we used PubMed’s Medical Subject Headings (MeSH) terms for the retrieval, and the search strategy is as follows #1:(((((hypoxia[MeSH Terms]) OR (Oxygen Deficiency[Title/Abstract])) OR (Oxygen Deficiencies[Title/Abstract])) OR (Hypoxemia[Title/Abstract])) OR (Anoxia[Title/Abstract])) OR (Anoxemia[Title/Abstract]), #2: □skin[MeSH Terms]□ OR □skin[Title/Abstract]□, #3: #1 AND #2. To facilitate further analysis of literature content, only regular articles written in English were included. To capture the latest research trends, the search was restricted to papers published in English from January 1, 2014 to

December 31, 2023, and publication types were set to“articles” and “review articles” (Figure 1). Only research focusing on hypoxia and skin health and diseases was included. The following studies that did not meet the inclusion criteria were excluded: (1). Articles that did not focus on hypoxia and skin health and diseases (2). Retracted articles, conference articles, meta-analyses, expert opinions, correspondences, or guidelines. We extracted data used for bibliometric analysis in articles that met the criteria, including publication trends (e.g., annual number of publications), leading institutions and countries (e.g., the top 10 productive institutions/countries rankings), top research areas (e.g., keyword analysis), most productive authors (e.g., productivity and total citations), and citation analysis (e.g., counts and networks of citations).

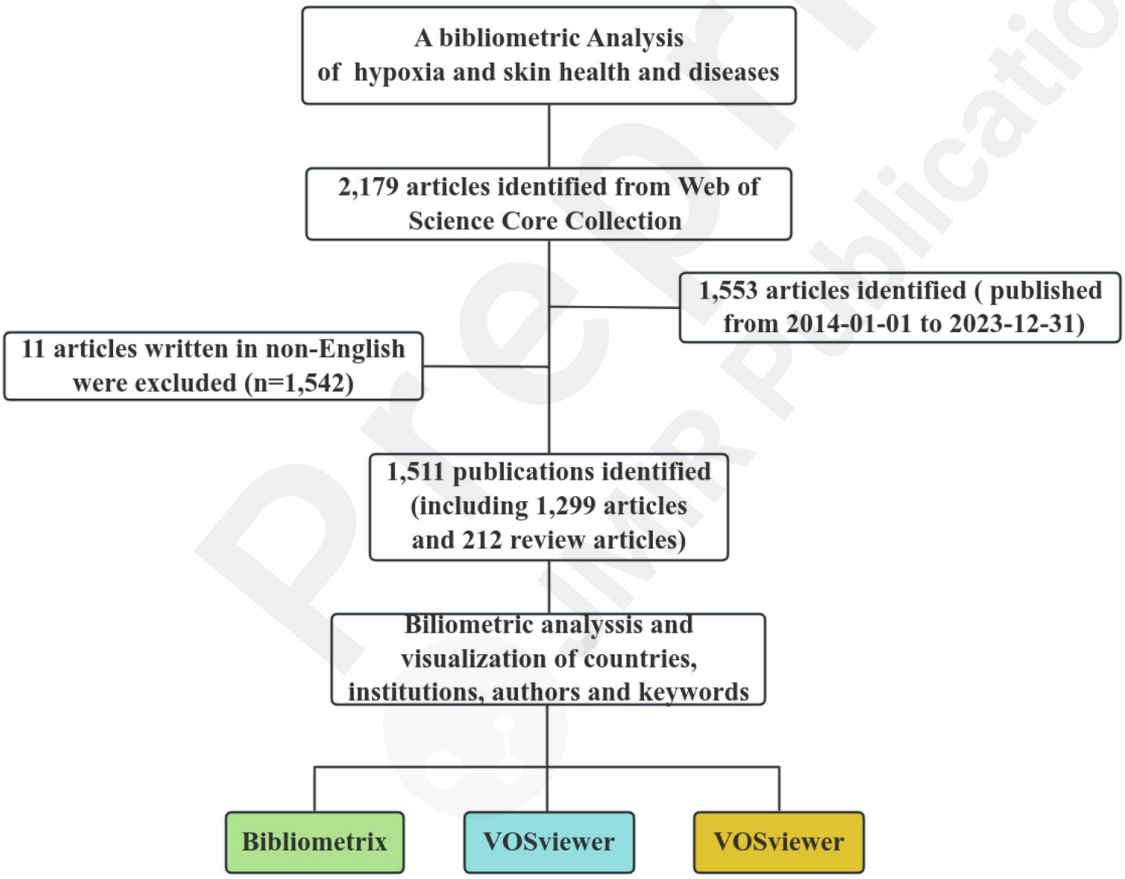


Figure 1. Flowchart for the selection of articles included in this study.

Data analysis methods

We used the Bibliometrix R packages (4.2.3), VOSviewer (1.6.19), and CiteSpace (6.2.R4) to

conduct the analyses. Units of measure were country, institution, journal, author, reference, and keyword.

The R package “bibliometrix” (version 4.2.3) (https://www.bibliometrix.org) was chosen for obtaining the number of annual papers in countries and the total amount of articles issued by countries, institutions, journals, and authors over the years, and trend analysis of topics, and for the establishment of a global distribution grid of articles published in our study.

We used the impact factor [29] and quartile in categories obtained from Journal Citation Reports (JCR) in 2022 as the main evaluation metrics for publications and the quality of scientific information. We also used the H-index [53] to assess the publications and academic influence of researchers and journals. The H-index means that if a scholar’s H-index is h, then at least h papers have been published by him, and each paper has been cited at least h times [54].

VOSviewer (version 1.6.19) was applied for keyword co-occurrence analysis, country and institution analysis, author and co-cited author analysis, and journal and co-cited journal analysis in our study. Nodes in the map produced by VOSviewer represent items such as keywords, authors, journals, institutions, and countries. Node size indicates the number of these items, and node color represents their classification. The co-citation or cooperative relationships of these items were reflected in the line thickness between the nodes [55, 56].

CiteSpace (version 6.2.R4) is a Java-based tool developed by Prof. Chaomei Chen for visualization and bibliometric analysis [57, 58]. CiteSpace was used to analyze references and keywords with the strongest citation bursts.

Results

Trend of publication

A total of 1,511 articles on hypoxia and skin health and disease studies, including 1,299 papers and 212 reviews, were retrieved from the WOSCC database from January 1, 2014, to December 31,

2023. The number of publications and accumulated article number per year are shown in Figure 2.

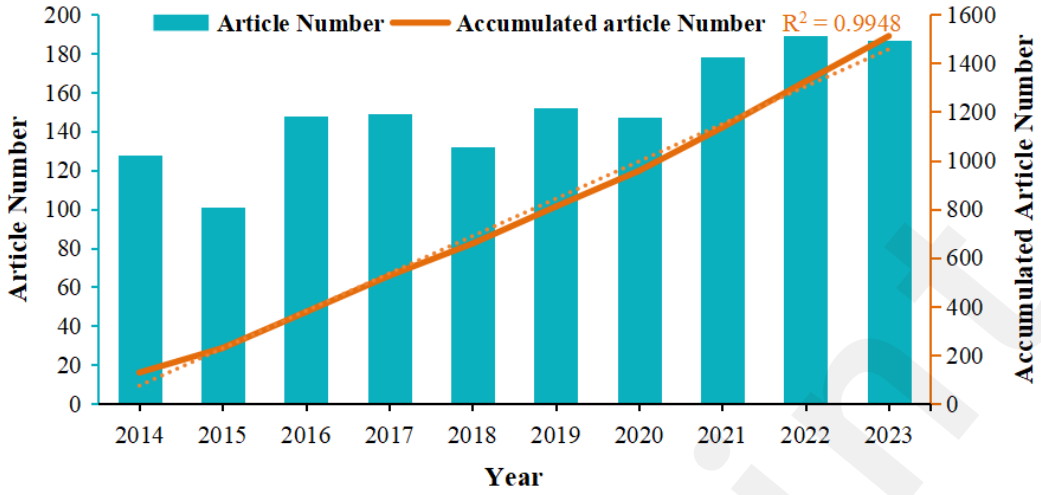


Figure 2. Trend of the number of publications annually and the accumulatd number.

In terms of the number of articles published each year, the whole period could be divided into two parts: Phase I (2014-2018) and Phase II (2019-2023). In Phase I, the average number of articles published per year was about 131.6, which was relatively small. The number of publications in Phase II began to increase observably, with an average annual article count of about 171. The lowest number of published papers was in 2015, with 101 articles, and the highest number was in 2022 (189). A linear growth function was applied to evaluate the relationship between the cumulative number of publications and publication year, which matched the changing trend of the accumulated number of publications ($R^2 = 0.9948$).

Overall, the number of publications indicates the level of attention of scientists to a field and, to some extent, reflects the progress and speed of the field. Thus, the number of articles issued in research is a good indicator of the trends in the field. Based on the phenomenon of the increasing number of papers published annually over the last five years, it can be speculated that research on hypoxia and skin health and disease is expected to maintain academic attention for some time.

Analysis of national publications

To investigate the countries and regions that made the most contributions in this field, we created a map of the geographic distribution, the top ten countries in terms of the number of publications, and a map of collaborative networks in different countries in our study for further analysis.

The geographical distributions of studies on hypoxia and skin health and disease were shown through the map of the world (Figure 3A). Subsequently, Figure 3B shows the top 10 countries with the highest publications of studies related to hypoxia and skin health and disease, and the total citations of these countries are shown in Table S1. Of these countries, China published the largest number of articles at 23.8% (359/1511), followed by the United States (20.1%, 303/1511), Japan (5.9%, 89/1511), and Germany (5.8%, 88/1511). The United States had the most citations (9,674 times), with an average of 31.93 citations per article, followed by China (6,941 times, cited about 19.33 times per paper averagely). The combined number of articles published by the United States and China accounted for nearly half (43.9%) of the total.

Table S1. The top 10 corresponding authors' countries ranked by the number of publications.

Rank	Countries	Number of Articles	Percentages (n/1511)	Total Citations	Average Citation per article
1	China	359	23.8%	6941	19.33
2	the United States	303	20.1%	9674	31.93
3	Japan	89	5.9%	1196	13.44
4	Germany	88	5.8%	1726	19.61
5	Korea	70	4.6%	945	13.50
6	Italy	58	3.8%	1105	19.05
7	England	57	3.8%	1823	31.98
8	Canada	41	2.7%	711	17.34
9	Poland	37	2.4%	558	15.08
10	France	30	2.0%	817	27.23

We also visualized 34 countries based on a threshold of the minimum number of publications of

10, and established a national collaborative network based on the counts and relationships of articles issued in these countries (Figure 3C). This shows that there is a lot of close cooperation among the various countries. For example, China has active cooperation with Germany, the United States, Singapore, Canada, South Korea, and Japan; the United States has close cooperation with China, Germany, England, Canada, Japan, France, and Australia.

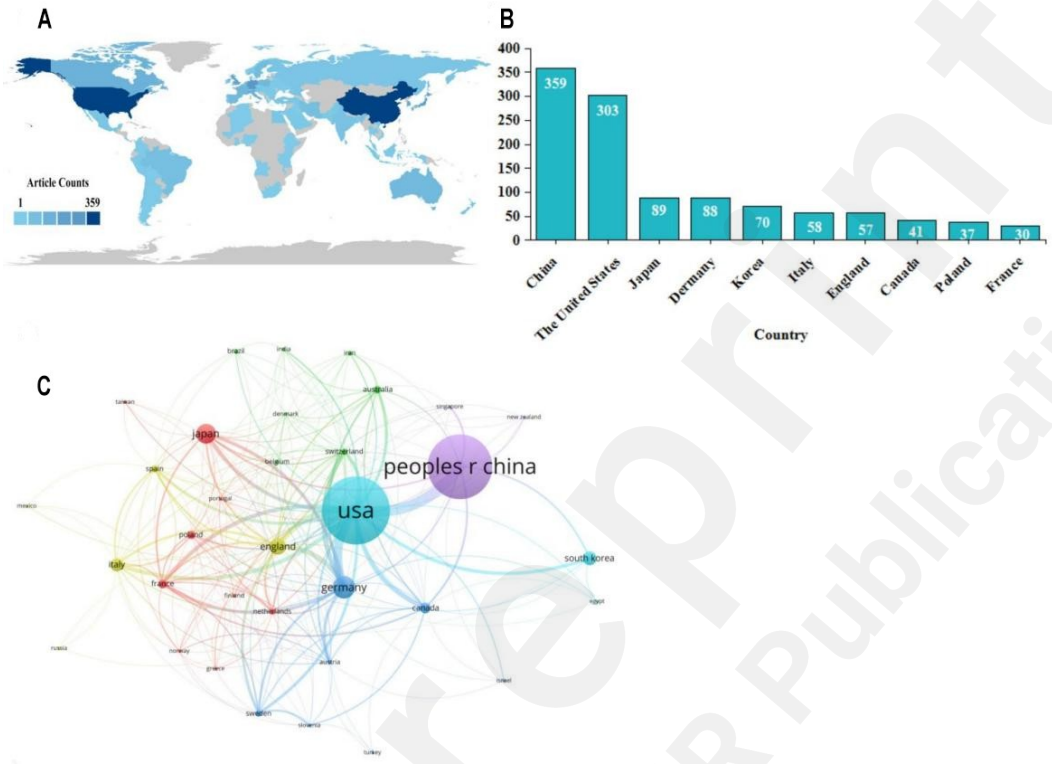


Figure 3. Analysis of national publications. (A) The geographical distribution on hypoxia and skin health and disease research generated by bibliometrix. (B) The top ten countries ranked by the number of publications. (C)The national collaborative network visualization map made by VOS viewer (version 1.6.19).

Analysis of institution publications

To better understand the leading research institutions in the research field, the top ten research institutions by number of publications are listed, and the collaborations among institutions are visualized.

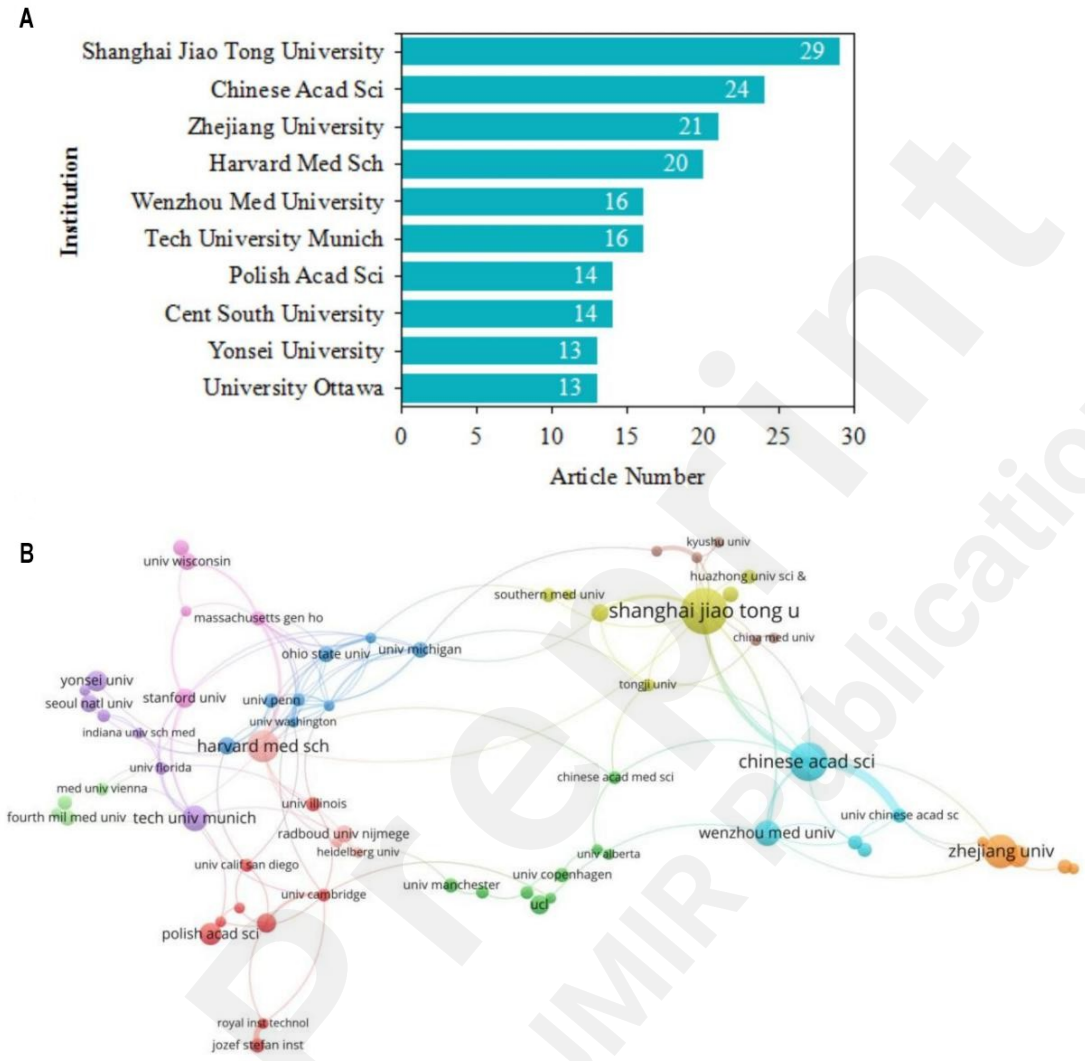
A total of 2,282 institutions published articles on hypoxia and skin health and disease. The top 10 institutions with the largest number of published articles are shown in Figure 4A. And Table S2 lists the total citations of these 10 institutions. According to the results, the top 10 institutions ranked by the number of publications were mainly located in six countries, with five coming from China. The top four organizations with the largest number of published articles were: Shanghai Jiao Tong University (n = 29), Chinese Acad Sci (n = 24), Zhejiang University (n = 21), and Harvard Medical School (n = 20). As is illustrated in Table S2, Tech University Munich from Germany had the most citations, with an average of 63.06 citations per article, followed by Chinese institutions including Chinese Acad Sci (964 citations, with 40.17 citations per article averagely) and Shanghai Jiao Tong University (916 citations, with 31.59 times cited per paper).

Table S2. The top 10 institutions with the largest number of publications.

Rank	Institutions	Countries	Article Counts	Total Citations	Average Citations Per Article
1	Shanghai Jiao Tong University	China	29	916	31.59
2	Chinese Acad Sci	China	24	964	40.17
3	Zhejiang University	China	21	632	30.10
4	Harvard Med Sch	the United States	20	440	22.00
5	Tech University Munich	Germany	16	1009	63.06
6	Wenzhou Med University	China	16	203	12.69
7	Cent South University	China	14	74	5.29
8	Polish Acad Sci	Poland	14	219	15.64
9	University Ottawa	Canada	13	150	11.54
10	Yonsei University	Korea	13	180	13.85

The institutions' collaborative network visualization map is produced by VOS viewer (version

1.6.19). As shown in Figure 4B, there were 68 items and 144 links on the map, and the 68 items were divided into 11 clusters according to color, and the agencies within the same cluster were closely related.



225 Figure 4. Analysis of institution publications. (A) The top 10 institutions with the most publications in the field of hypoxia and skin health and disease. (B) The institutions' collaborative network visualization map made by VOS viewer (version 1.6.19).

Analysis of journal impact

230 To provide a reference for authors to submit their papers, we examined the top ten journals that published articles in this field. There were a total of 680 journals that published articles related to

hypoxia and skin health and disease. The top 10 journals ranked by the number of published papers was shown in Table 1. As illustrated in the table, the top 10 journals currently publish 188 articles, accounting for 12.44% of the total articles. The International Journal of Molecular Sciences (IF 2022 = 5.6) published the largest number of papers (39 articles), followed by Plos One (32 articles, IF 2022 = 3.7), Scientific Reports (30 articles, IF 2022 = 4.6), and the Journal of Investigative Dermatology (19 articles, IF 2022 = 6.5). Nine of the top 10 journals were from the United States, Switzerland, and England with three journals from each of them and one from Denmark. Plos One had the highest H-index (16) and the most total citations (729 times cited), and Stem Cell Research & Therapy had the highest IF (IF 2022 = 7.5) in the top 10 journals ranked by publication number.

Table 1. The top 10 journals of research ranked by publication number.

Rank	Journal Title	Article Counts	Percentage (n/1511)	Total Citations	Countries	IF(2022)	Quartile in Category(2022)	H-Index
1	International Journal of Molecular Sciences	39	2.58%	582	Switzerland	5.6	Q1	11
2	Plos One	32	2.12%	729	the United States	3.7	Q2	16
3	Scientific Reports	30	1.99%	476	England	4.6	Q2	14
4	Journal of Investigative Dermatology	19	1.26%	608	the United States	6.5	Q1	16
5	Experimental Dermatology	15	0.99%	197	Denmark	3.6	Q1	9
6	Stem Cell Research & Therapy	12	0.79%	602	England	7.5	Q1	9
7	Cancers	11	0.73%	67	Switzerland	5.2	Q2	5
8	Journal of Experimental Biology	10	0.66%	190	England	2.8	Q2	8
9	Wound Repair and Regeneration	10	0.66%	310	the United States	2.9	Q2	8
10	Frontiers in Oncology	10	0.66%	135	Switzerland	4.7	Q2	5

Author impact analysis

We identified the leading researchers in this field by analyzing the top ten authors and author collaboration networks. A total of 9,251 authors appeared in the 1,511 articles on hypoxia, and skin health and disease studies. The top 10 most prolific authors in the publications were listed in Table 2, and six of them each published more than 6 papers. Yuesheng Huang from China contributed the most articles (8 articles). But Dominik Duscher from Tech University Munich, Dept. Plast & Hand Surg. had the highest average number of citations per article (47.7 times cited per article), followed by Hans-Guenther Machens from Tech University Munich (34.8 times cited per paper). Table S3 shows the top 10 co-cited authors and total citations on research on hypoxia and skin health and disease.

Table 2. Top 10 authors with the largest number of publications on hypoxia and skin health and disease studies.

Rank	Author	Article Counts	Total Citations	Average Citation Per Article	Institution	Countries	Total link strength
1	Huang, Yuesheng	8	121	15.1	Third Mil Med Univ, Southwest Hosp	China	39
2	Li, Wei	7	188	26.9	Univ So Calif, Keck Med Ctr, Dept Dermatol	the United States	20
3	Zhang, Junhui	7	108	15.4	Third Mil Med Univ, Army Med Univ, Southwest Hosp, Inst Burn Res	China	40
4	Mekjavic, Igor b.	7	77	11.0	Jozef Stefan Inst, Dept Automat Biocybernet & Robot Slovenia	Slovenia	12
5	Kiyatkin, Eugene a.	7	55	7.9	Nih National Institute On Aging [35]	the United States	4
6	Gawronska-Kozak, Barbara	7	44	6.3	Polish Acad Sci Inst Anim Reprod & Food Res	Poland	26
7	Duscher, Dominik	6	286	47.7	Tech Univ Munich, Dept Plast & Hand Surg	Germany	18
8	Machens, Hans-Guenther	6	209	34.8	Tech Univ Munich, Expt Plast Surg, Clin Plast Reconstruct & Hand Surg	Germany	2
9	Chen, Xiang	6	175	29.2	Cent S Univ, Xiangya Hosp, Dept Dermatol	China	13
10	Woodley, David t.	6	158	26.3	Univ So Calif, Labs Investigat Dermatol, Dept Dermatol, Norris Canc Ctr,Keck Med Ctr	the United States	20

Table S3. Top 10 co-cited authors on research of hypoxia and skin health/disease.

Rank	Author	Citations
1	Semenza, Gl	197
2	Sen, Ck	102
3	Rezvani, Hr	75
4	Chen, l	61
5	Liu, y	59
6	Schreml, s	57
7	Wang, y	56
8	Falanga, v	53
9	Gurtner, Gc	51
10	Carmeliet, p	50

We also established a collaborative network map based on the authors with three or more papers, which illustrated the close collaborative relationships among multiple authors (Figure 5). Authors like Roberta Cavalli, Giuliana Giribaldi, and Mauro Prato had an active network of multiple collaborators. For example, Mauro Prato worked closely with Roberta Cavalli, Chiara Magnetto, Giulia Rossana Gulino, and Caterina Guiot; Roberta Cavalli had an active cooperation with Mauro Prato, Giuliana Giribaldi, Chiara Magnetto, Giulia Rossana Gulino, etc.

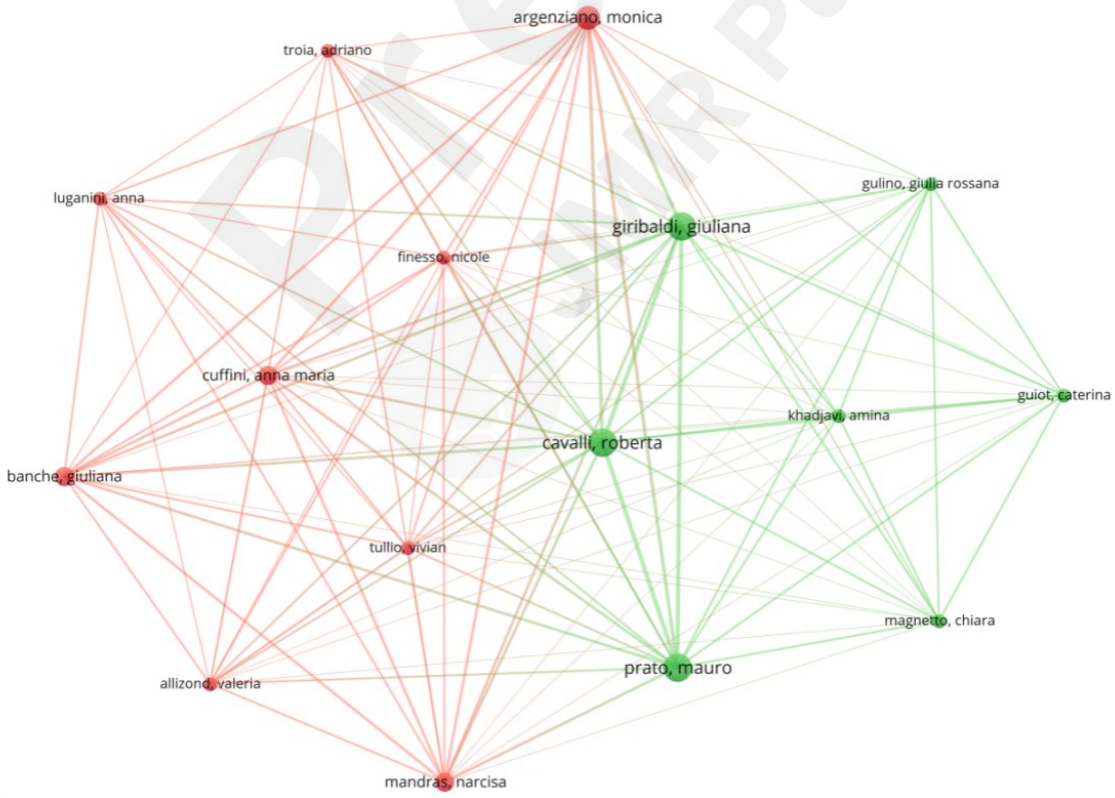


Figure 5. A

collaboration network visualization graph of authors on hypoxia and skin health and disease generated by VOS viewer (version 1.6.19).

Articles and references

The analysis of highly cited articles, references with the strongest citation bursts, and co-cited references can reveal the research hotspots and research basis in this field. Over the last decade, there have been 1,511 articles with 73,632 cited references in our study. We selected articles with greater than or equal to 20 co-citations to establish the co-citation network graph (Figure 6A). As illustrated in Figure 6A, “Gurtner Gc, 2008, Nature” has active co-cited relationships with “Hong Wx, 2014, Adv Wound Care,” “Singer Aj, 1999, New Engl J Med,” “Schreml S, 2010, Brit J Dermatol,” and “Hong Wx, 2014, Adv Wound Care”, etc.

The top 10 co-cited references were listed in Table S4A, which were co-cited at least 26 times, and notably, “Hong Wx, 2014, Adv Wound Care,” was co-cited 49 times and “Gurtner Gc, 2008, Nature” was co-cited 46 times. The top 10 globally cited publications of 1,511 articles on research on hypoxia and skin health and disease are shown in Table S4B. It shows that “Han G, 2017, Adv Ther” is the most globally cited one (1008 times cited) of 1,511 publications in our study, followed by “Carr Ac, 2017, Nutrients,” with 825 times cited by scholars from all over the world.

Table S4A. Top 10 co-cited references on research of hypoxia and skin health/disease.

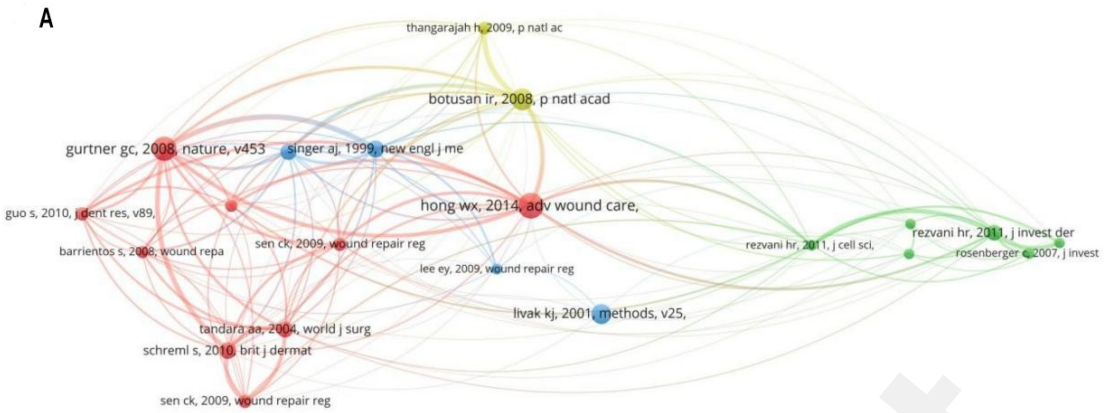
Rank	Cited Reference	Citations
1	Hong Wx, 2014, Adv Wound Care, v3, p390, Doi 10.1089/Wound.2013.0520	49
2	Gurtner Gc, 2008, Nature, v453, p314, Doi 10.1038/Nature07039	46
3	Botusan Ir, 2008, p Natl Acad Sci Usa, v105, p19426, Doi 10.1073/Pnas.0805230105	42
4	Livak Kj, 2001, Methods, v25, p402, Doi 10.1006/Meth.2001.1262	38
5	Singer Aj, 1999, New Engl j Med, v341, p738, Doi 10.1056/Nejm199909023411006	33
6	Schreml s, 2010, Brit j Dermatol, v163, p257, Doi 10.1111/j.1365-2133.2010.09804.x	32
7	Falanga v, 2005, Lancet, v366, p1736, Doi 10.1016/s0140-6736(05)67700-8	31
8	Tandara Aa, 2004, World j Surg, v28, p294, Doi 10.1007/s00268-003-7400-2	31

9	Rezvani Hr, 2011, j Invest Dermatol, v131, p1793, Doi 10.1038/Jid.2011.141	30
10	Guo s, 2010, j Dent Res, v89, p219, Doi 10.1177/0022034509359125	26

Table S4B. Top 10 globally cited articles of 1,511 publications in our study of hypoxia and skin health/disease.

Rank	Articles	Doi	Total Citations
1	Han G, 2017, Adv Ther	10.1007/s12325-017-0478-y	1008
2	Carr Ac, 2017, Nutrients	10.3390/nu9111211	825
3	Dick Kj, 2014, Lancet	10.1016/s0140-6736(13)62674-4	555
4	Baltzis D, 2014, Adv Ther	10.1007/s12325-014-0140-x	350
5	Patel Bk, 2016, Jama-J Am Med Assoc	10.1001/jama.2016.6338	327
6	Stéphan F, 2015, Jama-J Am Med Assoc	10.1001/jama.2015.5213	313
7	Chen Cl, 2017, Biomed Opt Express	10.1364/boe.8.001056	295
8	Gavriatopoulou M, 2020, Clin Exp Med	10.1007/s10238-020-00648-x	286
9	Vozenin Mc, 2019, Clin Oncol-Uk	10.1016/j.clon.2019.04.001	275
10	Lee De, 2016, Stem Cell Res Ther	10.1186/s13287-016-0303-6	273

CiteSpace V (version 6.2.R4) was applied to search for references with citation bursts, which refers to the references frequently cited by scientists in a research field over a certain period of time. Ten references with the strongest citation bursts were exhibited in Figure 6B, and every line segment represents one year, and the red line segment indicates strong citation burstiness [59]. In our study, citation bursts of references appeared as early as 2016 and as late as 2021. Notably, three of the top 10 references with the strongest citation bursts were authored by Dominik Duscher. The latest reference with a citation burst was issued in 2020, and its citation burst is still under way. The strongest citation burst (strength = 5.98, from 2018 to 2019) was from a reference titled “The Role of Hypoxia-Inducible Factor in Wound Healing,” authored by Wanxing Hong et al., followed by the reference titled “Regulation of Wound Healing and Fibrosis by Hypoxia and Hypoxia-Inducible Factor-1,” published in Molecules and Cells by Robin J Ruthenborg et al. with citation burst (strength = 5.58) from 2017 to 2019. Overall, the citation burst strength of these 10 references ranged from 2.53 to 5.98, maintaining 2 to 5 years.



B **Top 10 References with the Strongest Citation Bursts**

References	Year	Strength	Begin	End	2014 - 2023
Semenza GL, 2014, ANNU REV PATHOL-MECH, V9, P47, DOI 10.1146/annurev-pathol-012513-104720, DOI	2014	3.33	2016	2017	
Duscher D, 2015, P NATL ACAD SCI USA, V112, P94, DOI 10.1073/pnas.1413445112, DOI	2015	2.53	2016	2020	
Ruthenborg RJ, 2014, MOL CELLS, V37, P637, DOI 10.14348/molcells.2014.0150, DOI	2014	5.58	2017	2019	
Duscher D, 2015, PLAST RECONSTR SURG, V136, P1004, DOI 10.1097/PRS.0000000000001699, DOI	2015	3.51	2017	2020	
Eming SA, 2014, SCI TRANSL MED, V6, P0, DOI 10.1126/scitranslmed.3009337, DOI	2014	2.74	2017	2018	
Hong WX, 2014, ADV WOUND CARE, V3, P390, DOI 10.1089/wound.2013.0520, DOI	2014	5.98	2018	2019	
Duscher D, 2017, PLAST RECONSTR SURG, V139, P695E, DOI 10.1097/PRS.0000000000003072, DOI	2017	2.76	2018	2020	
Zhao RL, 2016, INT J MOL SCI, V17, P0, DOI 10.3390/ijms17122085, DOI	2016	3.11	2020	2021	
Rodrigues M, 2019, PHYSIOL REV, V99, P665, DOI 10.1152/physrev.00067.2017, DOI	2019	3.06	2021	2023	
Lee P, 2020, NAT REV MOL CELL BIO, V21, P268, DOI 10.1038/s41580-020-0227-y, DOI	2020	2.97	2021	2023	

Figure 6. (A) The visualization of co-cited references on hypoxia and skin health and disease studies. (B) The top 10 references with the strongest citation bursts. (The green bars represent the time interval, and the red bars represent the active time).

Keyword analysis of research hotspots

To precisely discern current research hotspots and possible future research directions, we extracted keywords from 1,511 included articles, visualized the keyword co-occurrence network, and listed the top 20 most frequently used keywords and the top 5 keywords with the strongest citation bursts. Seventy-eight keywords that appeared more than 40 times were used to establish a visual map through the VOS viewer (version 1.6.19) (Figure 7A). Cluster analysis of high-frequency keywords (occurrences more than 40 times) was applied. In the visual map, the high-frequency keywords were sorted into 4 clusters (Cluster 1: Red; Cluster 2: Green; Cluster 3: Blue; Cluster 4:Yellow), with 34 nodes and 502 links. Cluster 1 had the largest number of the four clusters, and the most frequent

keywords were expression (261 times), oxidative stress (105 times), and cells (100 times). For cluster 2, the prominent keywords targeted hypoxia (473 times), skin (216 times), and wound healing (107 times). The main keywords of cluster 3 were angiogenesis (193), in vitro (69), proliferation (64) and hif-1-alpha (58). The most frequent keywords in Cluster 4 are cancer (103 times), therapy (67times), and nanoparticles (46 times).

Subsequently, a time-overlapping co-occurrence network of keywords was generated through the VOS viewer (version 1.6.19) (Figure 7B). The color of the keywords indicates the research hotspots on hypoxia and skin health and disease in recent years. Early-emerging keywords are shown in blue, and recent-appearing keywords are shown in red.

Figure 7C displays the top 20 keywords, sorted by frequency. Keywords with citation bursts refer to those keywords that show a surge trend at a certain stage. The top five keywords with the strongest citation bursts are exhibited in Figure 7D. As shown in figure 7D, citation bursts of keywords appeared as early as 2014 and as late as 2019. The keyword with the strongest citation burst (strength = 3.4, from 2018 to 2019) was “systemic oxygenation,” followed by “vascular endothelial growth factor” (strength = 2.97, from 2014 to 2019). In general, the citation burst strength of the top five keywords ranged from 2.63 to 3.4, with a time duration of 2 to 6 years.

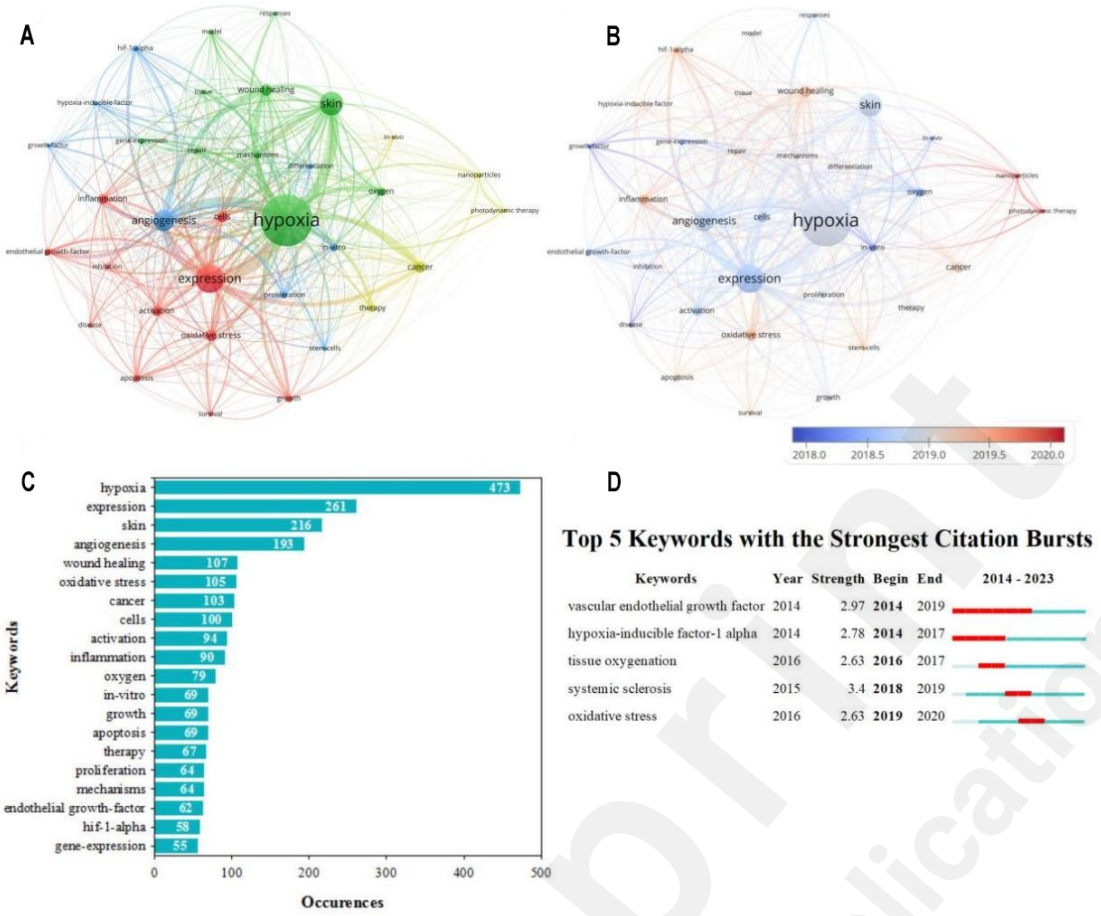


Figure 7. Keywords analysis of research hotspots. (A) The visualization of keyword co-occurrence network generated by VOS viewer (version 1.6.19). (B) The visualization of time-overlapping co-occurrence analysis network generated by VOS viewer (version 1.6.19). (C) The top 20 most frequently used keywords. (D) The top 5 keywords with the strongest citation bursts of articles on hypoxia and skin health and disease.

Discussion

Bibliometric analysis was used to examine the worldwide scientific output of research on hypoxia, skin health, and disease from 2014 to 2023. There are two stages of research growth. The number of articles published in stage I (between 2014 and 2018) was roughly 131.6 on average per year. In contrast, there is an increase in stage II (from 2019 to 2023) with an annual article count of about 171. By 2023, the annual number of publications will be 187, indicating that research on hypoxia and

skin health and disease has entered a stage of rapid development. The underlying reason could be that, with the popularity of hypoxia in various diseases, scientists began to realize that hypoxia may also play an important role in skin health and disease. As a result, research institutions continue to increase their support for research on hypoxia and skin health and disease, and research funding continues to increase, which promotes the rapid development of this field.

There were a total of 1,132 articles published by the top 10 countries, accounting for 74.92% of all articles. According to the analysis for each country, studies of hypoxia and skin health and disease were mainly conducted in China and the United States, with China leading the way. Although China ranked first in the number of publications and Chinese organizations accounted for half of the top 10 productive institutions, the number of citations and articles co-authored with foreign authors was far less than that of the United States. This phenomenon indicates that articles published in the United States have a greater influence and quality, and that Chinese scientists should focus more of their future emphasis on the quality and multinational cooperation of academic essays. The above findings also confirm the United States and China’s critical leading positions and contributions in hypoxia and skin health and disease research, which may result from their national economic conditions and high levels of medical investment. Additionally, we have noticed that China, the United States, Germany, England, and France are five nations that work closely together, signifying this area of research will benefit from extensive international collaboration, which will improve the general standard of research.

Based on international collaborations, seeking broad cooperation between institutions may be critical to improving research competitiveness in situations with limited economics or resources. Results shown five of the top 10 institutions are in China. Despite the United States ranking second in the number of papers published, only one institution makes the top 10. When it comes to the collaboration of research institutions, it can be seen from our results that some scientific institutions have good cooperative relationships with each other, such as Harvard Medical School, the Chinese

Academy of Sciences, and Shanghai Jiao Tong University. However, we also found that such a highly prolific institution as Zhejiang University, while ranking third in the number of papers published, had limited collaboration with other organizations, which will go against the long-term advancement of scientific research. Hence, we strongly recommend that varied scientific institutions conduct extensive communication and collaboration to foster the development of hypoxia, skin health, and disease research.

A peer-reviewed journal is required for scholarly publication. The essential field research is frequently published in core journals. Researchers can find possible journals for submission based on the overall number of periodical articles in the disciplines of hypoxia, skin health, and disease. In our study, the International Journal of Molecular Sciences has the most publications, with 39. Impact factors [29] and JCR are commonly applied to evaluate the impact of journals, and JCR categorizes all journals into four quartiles (Q1 – Q4) based on their impact factors. Among the top 10 journals in our study, there are no journals with an impact factor greater than 10, and Stem Cell Research & Therapy has the highest IF (IF 2022 = 7.5, Q1). Four of the top 10 journals had an IF greater than 5, and Q1 journals account for 40%. From the perspective of the top 10 authors, three were each from China and the United States, two from Germany, and one from Slovenia. Among them, Huang Yuesheng from the Third Military Medical University, Southwest Hospital of China, contributed the most publications. In addition, by assessing the number of co-authored articles and showing the collaborative relationships between various authors marked with the same color. This analysis may be helpful for new researchers in the field to identify influential or potential collaborators, making them more likely to publish more important articles related to hypoxia and skin health or disease. In general, it is still a challenge to publish articles related to hypoxia and skin health or disease in high-IF journals. Additionally, Asian publishers are underrepresented in the top 10 journals, despite significant contributions from China in the fields of hypoxia, skin health, and disease research. Therefore, it is necessary to establish and develop journals with international influence in Asia.

The purpose of this study is to provide an answer to a query about the research hotspots that were extensively investigated by researchers over a specific time frame. One way to measure a publication's foundation and history of research is by looking at its co-cited references [60]. Co-cited references are those cited together by other articles, so that co-cited references could be regarded as the foundation of research and history in a field [61]. To understand the research situation and research hotspots in different stages better, we conducted an analysis of the articles that have been cited and monitoring the progression of research on hypoxia before 2023 as follows:

Back in 1999, the co-cited reference issued by Singer AJ. et al. reviewed traumatic and nontraumatic wound healing and discussed the usage of skin substitutes and growth factors in wound healing [62]. Their review developed a better understanding of wound healing and laid an important foundation for research on the role of hypoxia in wound healing. In the same year, the discovery of HIF provided insight into cellular responses to low oxygen levels, influencing skin disease treatment strategies [63]. Subsequently, an increasing number of studies revealed that hypoxia can impair wound healing, leading to prolonged recovery times and complications [26, 64-67]. In 2001, studies suggested that hypoxia may accelerate skin aging, prompting research into anti-aging treatments and skincare [68]. In 2004, Tandara Andrea A concluded that HIF-1 is essential in the interplay of hypoxia and hyperoxia in wound healing [69]. And the normal biology of wound healing and impaired healing in the diabetic ulcer were reviewed by Falanga Vincent in 2005 [70]. In 2008, the second most co-cited reference produced by Gurtner, Geoffrey C. et al. outlined the stages, molecular mechanisms, and latent regenerative pathways of wound repair [71]. Since 2010, the HIF signal has also been proven to be involved in a variety of skin diseases. The third most co-cited article published by Ileana Ruxandra Botusan et al. proved that impaired modulation of HIF-1 alpha is important for the progression of diabetic wounds [72]. The factors that affect cutaneous wound healing and the potential cellular and/or molecular mechanisms were studied by Guo S. in the same year [73]. And in the next year, Schreml S summarized the role of oxygen in wound healing and

chronic wound pathogenesis [74]. And in Rezvani Hamid R's review, the important function of HIF-1 alpha in cutaneous angiogenesis, skin tumorigenesis, and multiple skin disorders was highlighted [6]. The most co-cited publication was authored by Wanxing Hong in 2014, and this review summarized that hypoxia affects all aspects of wound healing, including fibroblast proliferation, tissue growth, and reconstruction [75]. Although this study only discusses the role of hypoxia in wound healing, it provides the necessary theoretical basis for the study of hypoxia, skin health, and other skin diseases and enhances the confidence of researchers. In general, the top 10 co-cited references focused on the following topics: the mechanisms and influencing factors of wound healing and the role of hypoxia and HIF in skin disorders, especially wound healing, which laid the foundation for the study of hypoxia and skin health and disease.

Since keywords can make it easier for researchers to find a study's core content, "References with citation bursts" reflects the changes in research dynamics and research hotspots in the field, thus helping researchers to quickly grasp the evolution and distribution of hotspots.

In this study, the most frequent keywords were "hypoxia," and "angiogenesis." The frequency of "angiogenesis" was 568 times, and "hypoxia" occurred 473 times. Furthermore, "wound healing" were another frequently appearing keyword. Studies have shown that angiogenesis can promote the formation of epidermal barrier function or the skin cancer progression, and recurrences under hypoxia [76, 77]. However, research on biomarkers related to angiogenesis under hypoxia in skin diseases is rare. Since patients may experience skin disease progression after hypoxia or promote epidermal barrier formation or wound healing, screening for patient groups with potential benefits for angiogenesis under hypoxia is critical. Exploring biomarkers related to the efficacy of angiogenesis under hypoxia through various methods can be an effective tool for maximizing individual treatment outcomes. In conclusion, co-occurrence analysis of highfrequency keywords in research studies can highlight focus areas, such as hypoxia, angiogenesis, and biomarkers. Expanding our understanding of biomarkers related to the efficacy of angiogenesis under hypoxia is

essential for optimizing treatment outcomes. Further research in this area can significantly enhance the effectiveness of personalized skin diseases treatments.

To guide understanding the role of hypoxia in skin function better, we further summarized the differences of hypoxia in angiogenesis of the skin by analyzing the different factors with the highest frequency of keywords. The numerous growth factors and signaling pathways of hypoxia research in cutaneous angiogenesis were discussed, as well as the reasons for these differences.

Cutaneous angiogenesis is crucial for skin physiopathological functions like re-epithelialization, granulation tissue formation, extracellular matrix (ECM) synthesis and remodeling, blood flow, inflammation, the hair follicle cycle, wound healing, and cancer [78-82]. Vessel formation is an intricate yet coordinated process involving numerous growth factors and signaling pathways, influenced by the balance between angiogenic and antiangiogenic factors. Once the balance is disrupted, the vasculature rapidly responds by triggering the expression of angiogenic factors such as Vascular endothelial growth factor (VEGF) [83, 84], VEGF-A [5, 6], VEGF receptors (VEGFRs) [7], stromal cell-derived factor 1 (SDF-1) [85], angiopoietins 1 and 2 (ANG-1 and ANG-2), platelet-derived growth factor (PDGF) [86-88], transforming growth factor-β (TGF-β) [89], connective tissue growth factor (CTGF) [90], insulin-like growth factor binding protein-1 (IGFBP-1) [91], inducible endoplasmic reticulum chaperone oxygen-regulated protein 150 (ORP150), and other factors [8-10], which contribute to vessel growth, neovascularization, and oncogenesis. Among these, angiogenesis- and hypoxia-related pathways, such as VEGF-A and HIF-1α, are most up-regulated in rejuvenated human skin. Numerous earlier investigations have reported that hypoxia can trigger skin angiogenesis. The positive role of HIFs in angiogenesis has been demonstrated, and mice lacking HIF-1α show impaired cytokines Interferon (IFN-γ) and Granulocyte Macrophage-Colony Stimulating Factor (GM-CSF) release, impaired immune response, skin angiogenesis, wound healing, and bactericidal activity, despite promoting skin regeneration and infection prevention [20]. The INT6/HIF-2α pathway, a hypoxia-independent master switch, may be beneficial in treating

ischemic diseases [92]. The mechanism is that the junctional adhesion molecule (JAM-C) regulates vascular permeability and angiogenesis, decreasing basal permeability and preventing VEGF and histamine-induced increases in human dermal microvascular endothelial cell permeability [93]. Junctional adhesion molecule C regulates vascular endothelial permeability by modulating VE-cadherin-mediated cell-cell contacts. In Dmitrieva N. I.’s study, delayed granulation tissue formation and vascularization in autosomal dominant HIES (AD-HIES) patients may affect antiangiogenic therapy in different breast cancer subgroups due to STAT3-controlled transcriptional network deficiencies [94]. These results suggest that differential responses to hypoxia may ultimately help to form new vessels, enhancing the delivery of oxygenated blood to the hypoxic tissues. A comprehensive comprehension of the fundamental factors that contribute to discrepancies in the development of cutaneous angiogenesis under hypoxia can serve as a compass for subsequent investigations, ultimately striving to furnish patients with individualized and efficacious treatment alternatives.

The "burst detection" technique in CiteSpace finds keywords or cited references that have changed significantly over time [57]. Scholars can investigate research hotspots by utilizing keywords and cited references with burst properties. In this study, the first citation burst began in 2016 and was from a paper published by Semenza GL in 2014 [95], which concluded that HIFs play a protective role in the pathophysiology of some diseases and contribute to the pathogenesis of other disorders. The keywords of this article were “bronchiolitis obliterans, cardioprotection, collateral vessels, polycythemia, preconditioning, and retinopathy,” which suggested that the different roles of HIFs in various diseases started to attract the great attention of scholars. The second burst began in 2021 and remain ongoing, which are mainly associated with two publications authored by Melanie Rodrigues in 2019 [96] and Pearl Lee in 2020 [1]. Melanie Rodrigues reviewed the roles of various types of cells and pointed out that single-cell technologies can be applied to decipher cellular alterations in hypertrophic scarring and chronic wounds [96]. And it was illustrated by Pearl Lee that

cells can adapt to hypoxia by regulating metabolism, protein synthesis, and nutrient uptake [1]. We found that the citation bursts of these two references lasted until the end of 2023, which indicated that these research directions had received great attention in recent years and might become directions and hotspots of future research.

Strengths and limitations

Our study has multiple characteristic advantages; above all, for the first time, we conducted a thorough analysis of the research on hypoxia and skin health and disease, identifying the frontiers, status, and evolution of the studies. Secondly, we employed three bibliometric tools at the same time for the analysis, and we followed an objective procedure for analyzing the results. Finally, compared to traditional reviews, our bibliometric approach provides a more comprehensive understanding of the research hotspots and frontiers than do standard reviews. Our study has the following limitations: First, we only gathered data from the WOSCC database, which makes it possible to overlook certain pertinent papers in Embase, PubMed, and other databases. In addition, only English literature was included in this study, and important studies published in other languages might have gone unnoticed. What's more, we just assessed the journals' quartiles in terms of category and IF, and the characteristics of the included articles in the study had not been analyzed.

Conclusion

In this review, we summarized recent ten-year reports and conducted bibliometric analysis of studies of hypoxia in skin health and disease until December 2023. Research on hypoxia in skin health and disease has received more interest in the last few years. The significant annual growth in publications is a sign of the field's increasing importance. This study ranks the top researchers and institutions globally for hypoxia in skin health and disease research. The most active journal is the International Journal of Molecular Sciences, and the most well-known author is Yuesheng Huang. How

angiogenesis adapt to hypoxia by regulating numerous growth factors and signaling pathways in skin and single-cell technologies can study cellular changes in hypertrophic scarring and chronic wounds are current hot issues. Future studies may need to focus on targeted hypoxia to further improve skin function and different skin diseases. This provides a complete picture of the field's evolution and frontiers for new researchers and policymakers.

Acknowledgments

This study was supported by Sichuan Science and Technology Program (2023JDRC0109, 2022YFS0631) and Technology of Traditional Chinese Medicine Administration Project (2020JC0134).

Authors' Contributions

Yan Chen: Conceptualization, Methodology, Writing – original draft, Writing – review & editing, Fund. Cancan Huang: Investigation, Formal analysis, Writing – review & editing. Xiang Li: Data curation, Investigation, Writing – original draft. Wenjun Wang: Data curation, Investigation, Writing – original draft. Xingzhu Mou: Methodology, Visualization. Wuda Huoshen: Investigation, Formal analysis, Writing – review & editing. Jieyu Li: Investigation, Formal analysis. Ni Liu: Formal analysis. Xia Xiong: Conceptualization, Funding acquisition, Project administration, Supervision. Sha Yi: Investigation, Formal analysis. Guishu Zhong: Conceptualization, Supervision, Fund.

Compliance with Ethics Requirements

This review does not contain any studies with human or animal subjects.

Declaration of Competing Interest

The authors have declared no conflict of interest.

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