Research Article

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Global Landscape Of Bone Tumor Therapy And Biomaterials: A Bibliometric And Citespace Analysis.

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ABSTRACT

Biomaterials possess electrical, optical, and magnetic properties, which make them promising candidates for targeted drug delivery. Moreover, their biocompatibility and low toxicity render them suitable for applications in tumor therapy. We conducted a bibliometric review to investigate trends in biomaterials for bone tumor therapy. Relevant studies published between 2013 and 2024 were identified using the Web of Science database. The Bibliometric R-package and CiteSpace software were used to quantitatively analyze the number of papers, countries, authors, institutions, sources, co-cited literature, and keywords. Papers were categorized according to the main research subject, and those cited at least 10 times annually were qualitatively analyzed. Over the last decade, the number of papers and mean annual citation rate increased. Most papers originated from the USA and China, and the institutions with the highest contributions were the University of California and Harvard University. Among authors, Zhang had the highest number of published articles and maximum citations according to the H-index. The International Journal of Radiation Oncology, Biology, Physics had the highest number of publications. Keyword analysis revealed a focus shift from cells, receptors, and gene therapy to immunological therapy, photothermal therapy, and drugs. Notably, recent research has mainly considered external and internal microenvironmental stimuli-response strategies. This review offers a valuable basis for developing intelligent and versatile biomaterials for bone tumor therapy and regeneration in future investigations.

Keywords : *bibliometric analysis, biomaterials, bone tumor, CiteSpace, therapy.*

INTRODUCTION

Bone tumors can cause major abnormalities in bone tissues, presenting a key challenge in clinical practice and increasing the risk of disability and morbidity.[1][2] With the aging population, the total cost of treating patients with musculoskeletal system diseases has increased by up to 117% in the last 3 years. Moreover, the cost of research is increasing owing to the increasing social demand.

Osteosarcomas, the most common primary malignant bone tumor in children and adolescents,[3] typically necessitates a treatment regimen involving surgical resection alongside preoperative and postoperative neoadjuvant chemotherapy[4] However, bone defects inevitably occur during surgical intervention.[5] Moreover, owing to the complex anatomical structures surrounding tumors, complete tumor excision to prevent recurrence is not always feasible, and reports have suggested that drug concentrations in the postoperative region may be insufficient to remove all remaining tumor cells.[6][7] Notably, local chemotherapy can effectively overcome these limitations by allowing higher concentrations of drugs to be delivered to the tumor microenvironment without major adverse systemic effects.[8, 9] Therefore, functional implants that can replace bone tissue and release chemotherapeutic drugs are of considerable interest for improved treatment and healing of osteosarcomas.

Materials commonly employed as drug carriers encompass natural/synthetic polymers and inorganic minerals. These must be biocompatible, non-immunogenic, and

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inert to facilitate normal bone healing. Examples include hyaluronic acid, collagen, gelatin, calcium monophosphide, hydroxyapatite, β-tricalcium phosphate, polyethylene glycol, and poly(lactic-co-glycolic acid).[11] However, natural polymers are immunogenic, degrade rapidly, and vary between batches, thereby, limiting their utility. Conversely, synthetic polymers are easy to modify and process to achieve the desired properties by changing their molecular weight and functional structure.[12]

Bibliometrics is a scientific method used to quantitatively evaluate the published literature, offering insights for a clear understanding of the current situation and future trends.[13,14] Unlike previous traditional systematic assessments, bibliometric estimation focuses on author collaboration networks, national regions, and relationships between different research institutions and published works.[15] To our knowledge, although bibliometrics has been applied in other areas, such as digestive,[16] nervous,[17] and cancer systems[18], there has been no bibliometric research regarding the application of biomaterials in the treatment of bone tumors. Therefore, we aimed to conduct a bibliometric analysis of the literature published between 2013 and 2024 to visualize the applications of biomaterials in bone tumor therapy, assess their current status, and predict future trends.

MATERIAL AND METHODS

Search strategy

We searched the Web of Science core database for all data in 2024. The search formula was TS=("bone tumor" OR "bone cancer") AND TS=("materials" OR "biomaterials" OR "scaffolds" OR "polymers" OR "cements" OR "hydrogels" OR "gels" OR "nanofibers" OR "nanomaterials" OR "nanosheets" OR "nanoparticles" OR "nanotechnology") AND TS=("drug release" OR "drug delivery" OR "treatment" OR "therapy" OR "local chemotherapy"). Here, TS denotes the topic field. Thorough and repeated screening was conducted to exclude documents that were not articles or reviews, pertinent to the research question, or written in plain English. The data were extracted and saved in the .txt format. The plain text files contained full citations and records that were used to improve bibliometric analysis and visualization (Figure 1). Furthermore, papers cited an average of ≥10 times/year were identified during the qualitative analysis.

The search was limited to a 10-year period (2013–2024). The final anthology included 5323 papers on biomaterials and bone tumors. The extracted data included the journal name, reference type, date of publication, author affiliation and name, and abstract. Our analysis only included original papers and other types of documents were removed through a strict screening process.

Bibliometric analysis and visualization

Bibliometrix is scientific bibliometric software developed by the University of Federico II in Naples, Italy, using the R programming language (Vienna, Austria). Based on past research, R4.0.3 bibliometric procedures were used to automatically convert and evaluate data.[19, 20] The number of articles per year, country, author, institution, and journal, as well as the number of co-cited references and significant search terms, were considered. The indicators used to evaluate the quality of the papers published by an author included the number of papers, number of citations, and H-index of the citations.[20] The H-index is used to evaluate papers published by scientists in a given field.[21] CiteSpace is a scientometric research tool that was created by the School of Computing and Intelligence at Drexel University[20] to conduct co-author analysis for countries, authors, and institutions, co-citation analysis for journals and references, contribution analysis for keywords, and visualization using grids and overlays.

RESULTS

General description

Based on the topic keywords, we identified 7743 papers, including 5546 articles and 915 reviews, published between 1950 and 2024. After applying the filters (**Figure 1**), this number was reduced to 5324 papers, including 3977 articles and 752 reviews, published between 2013 and 2024. During this 10-year period, the cumulative total number of papers increased (**Figure 2A**). Moreover, the number of documents published annually typically increased over time, although there was a minor decrease in 2024 (**Figure 2B**).

The 5324 papers were cited 429.7 times (**Figure 2C**). The average number of citations per year was calculated by dividing the total number of citations by the total number of papers.[19] When the average number of citations per year is high, a paper may be the basis for further research or a research hotspot.[20] The average annual citation rate decreased slightly between 2013 and 2014, exhibited ordinary growth from 2014 to 2017, fluctuated rapidly between 2017 and 2020, and then demonstrated a rapid downward trend from 2020. The highest and lowest average annual citation rates of 6.3 and 0.8 occurred in 2018 and 2024, respectively. These results indicated that biomaterials are slowly developing into a new research hotspot.

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Figure 1. Flowchart of the document search and screening procedure.

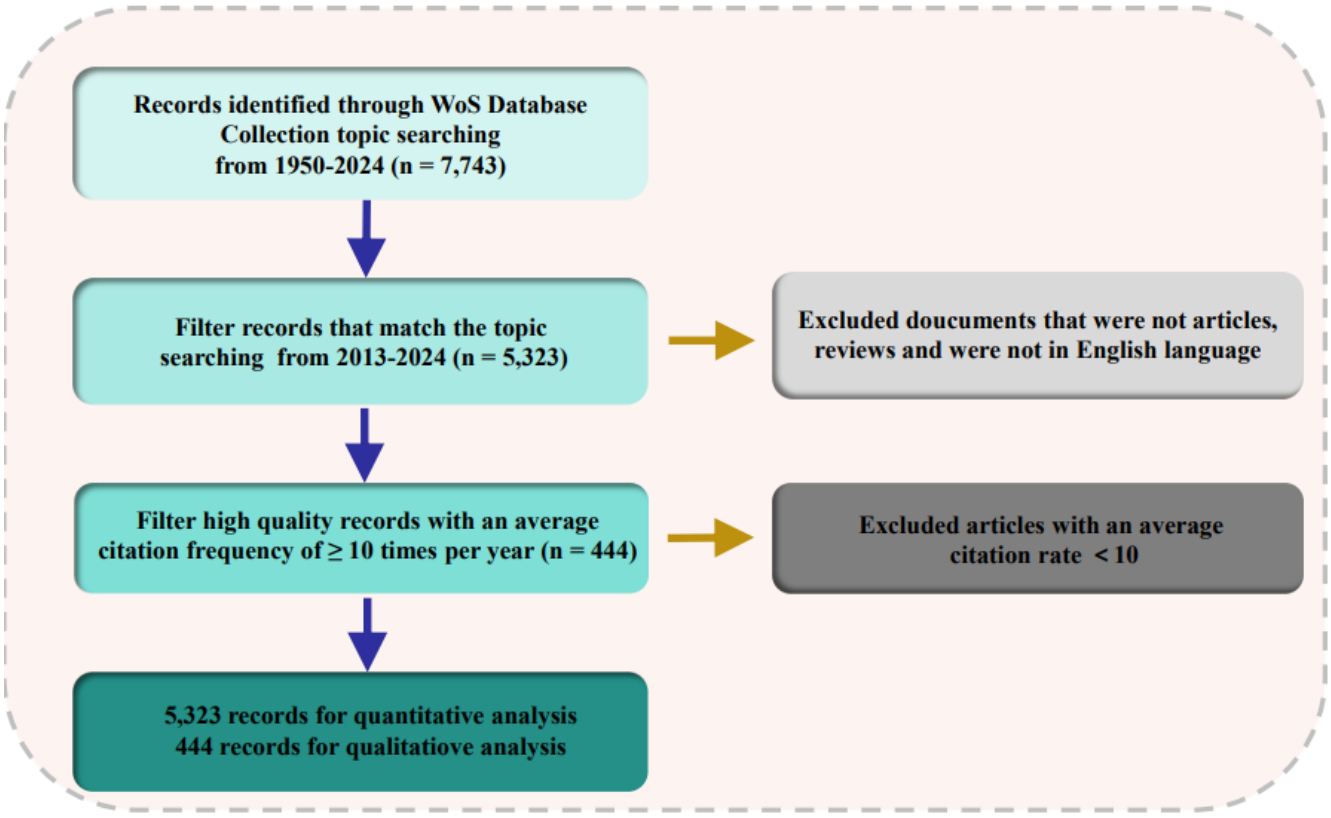
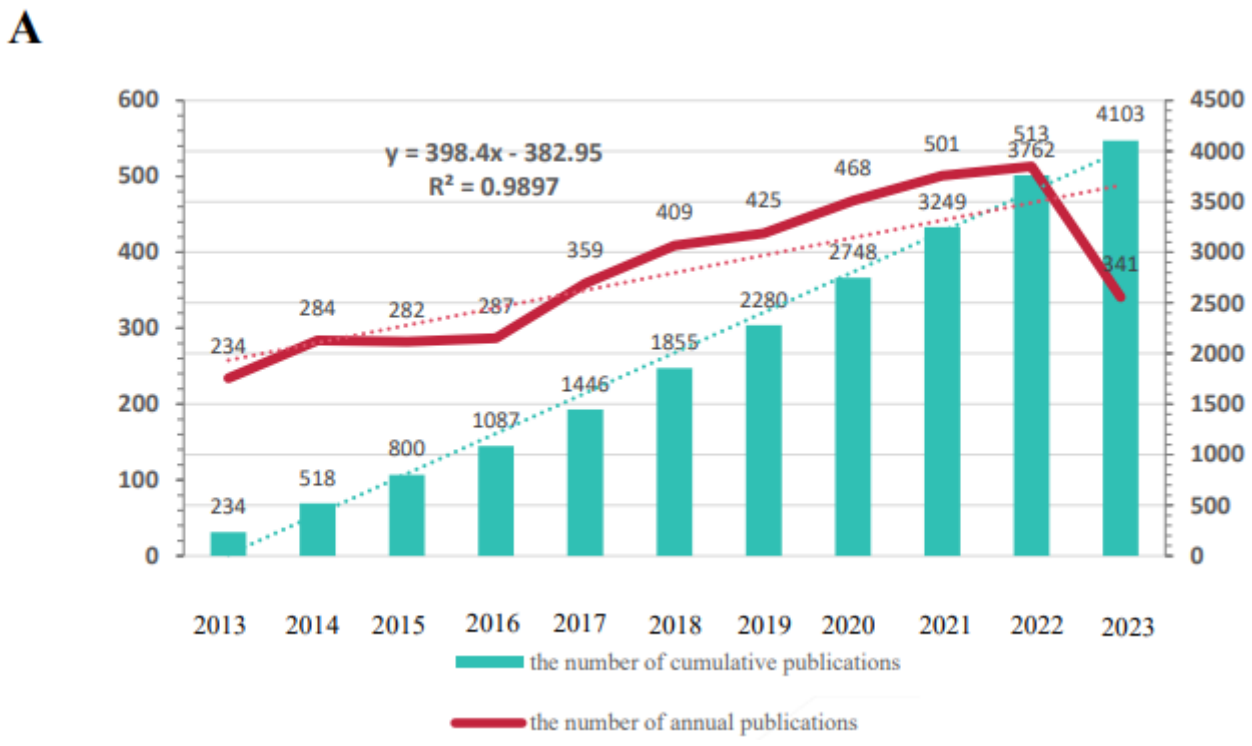
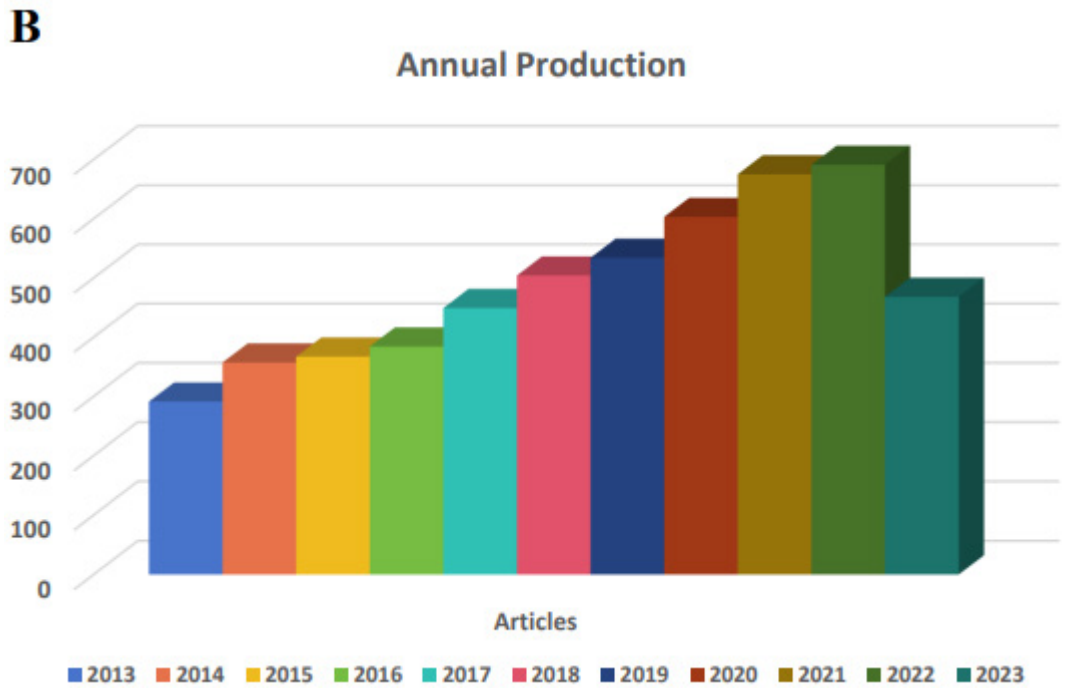


Figure 2. Flowchart of the document search and screening procedure. (A) Diagram showing the number of annual publications and cumulative publications in the past 10 years.

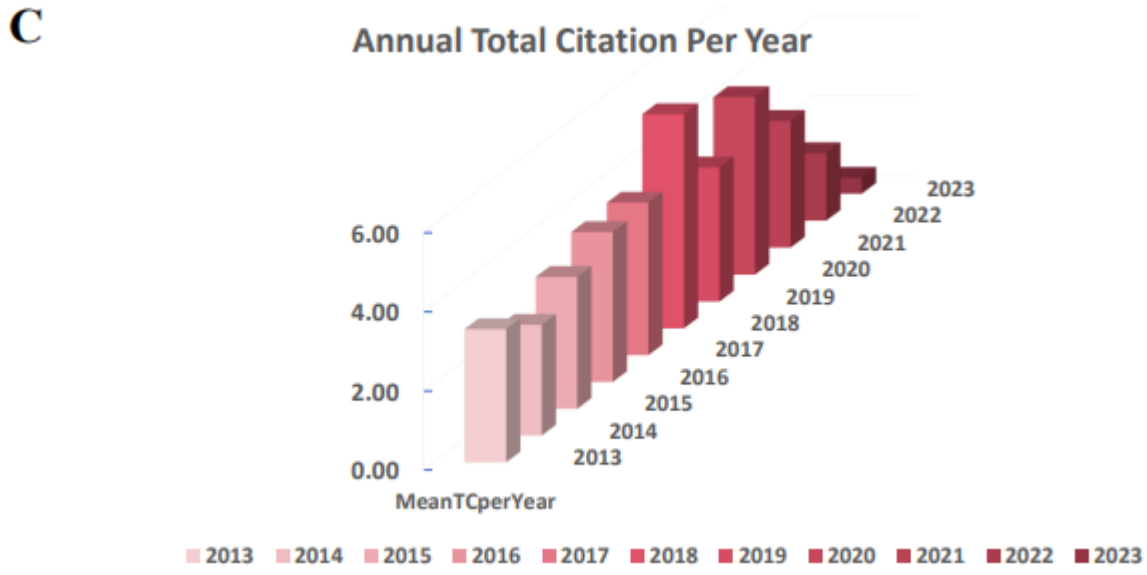


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(B) Diagram of the year-by-year publication growth.



(C) Chart showing the year-by-year citation increase.

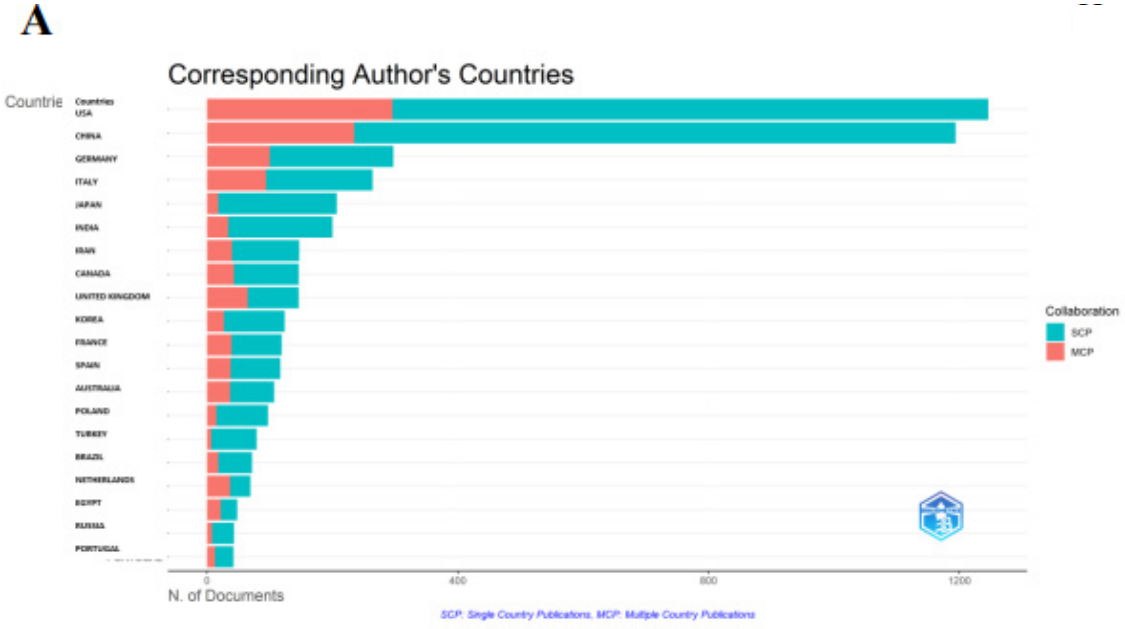


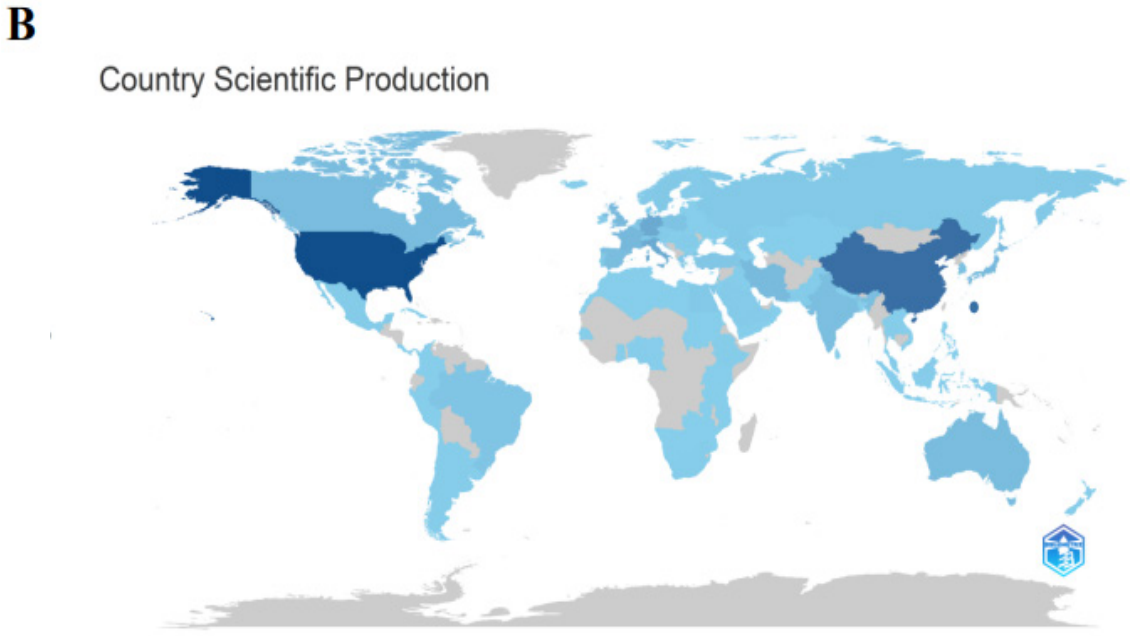
Trends by country and region

The corresponding authors of the 5323 papers were distributed across 74 countries and regions, with the USA and China being the most common (**Figure 3A, 3B, and 3C**). The number of multi-country papers—where the co-authors were from different countries than the corresponding author— was higher for corresponding authors based in the USA than for those based in China. The total number of papers over time for the top five countries is shown in Figure 3C. The total number of papers for China gradually approached that for the USA. Figure 3F shows the average number of citations for papers from the top 10 countries. Papers from the USA (n = 6849) and China (n = 4954) were considerably more prevalent than those from other countries, indicating that these countries are at the forefront of research in this field. Notably, the average citation rate for papers from the USA was similar to that for papers from China, indicating that the papers from the two countries were of similar quality. **Figure 3D and 3E** show the most frequent affiliations. The total citations and the average article citations are exhibited in the **Figure 3F and 3G**.

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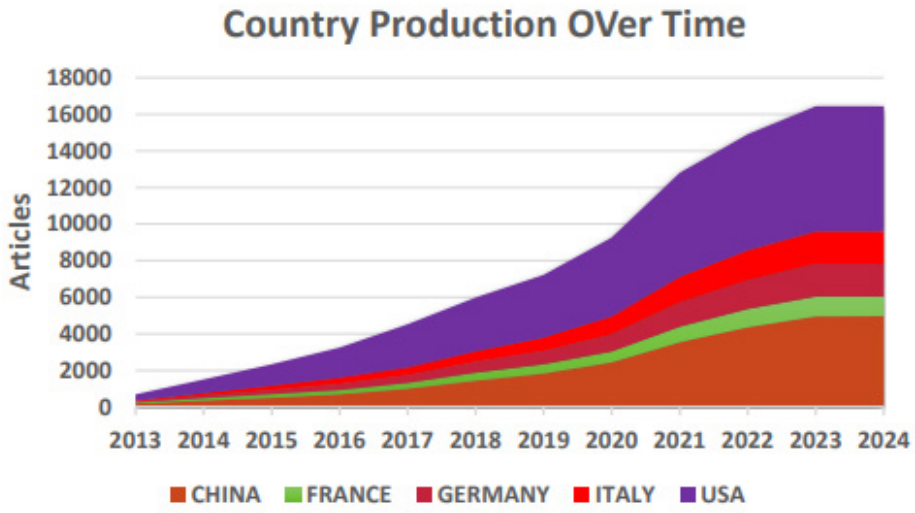
Figure 3. Evaluation of the distribution of state and national publications. (A) Corresponding author's countries. (B) Country scientific production. (C) The variation tendency in the number of publications in the 5 countries with the highest documents from 2013-2024. (D, E) The 10 most evaluation of affiliations. (F) Total citations of the countries. (G) Average article citations of the countries.



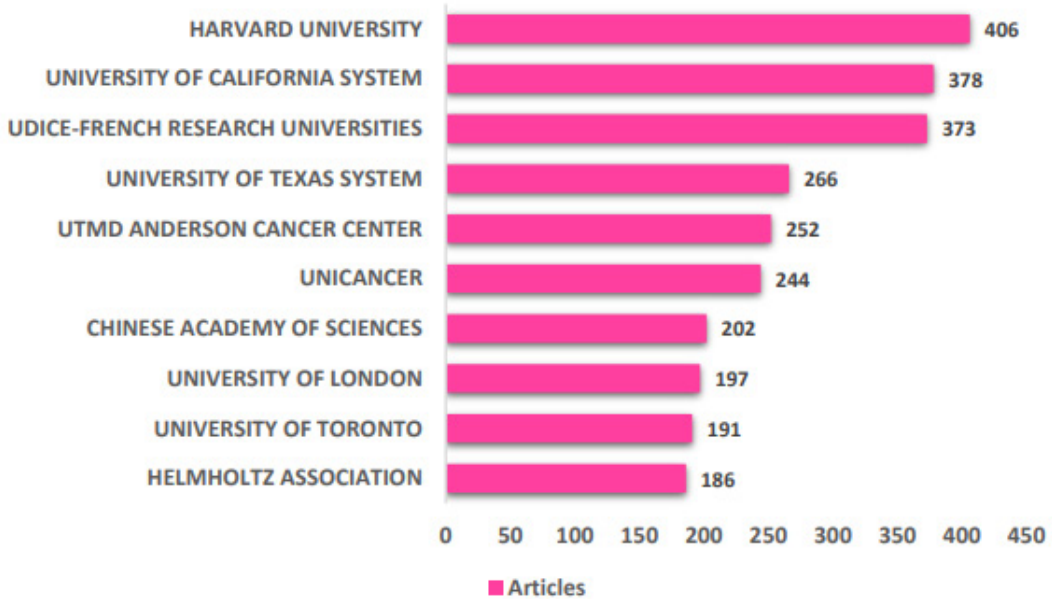


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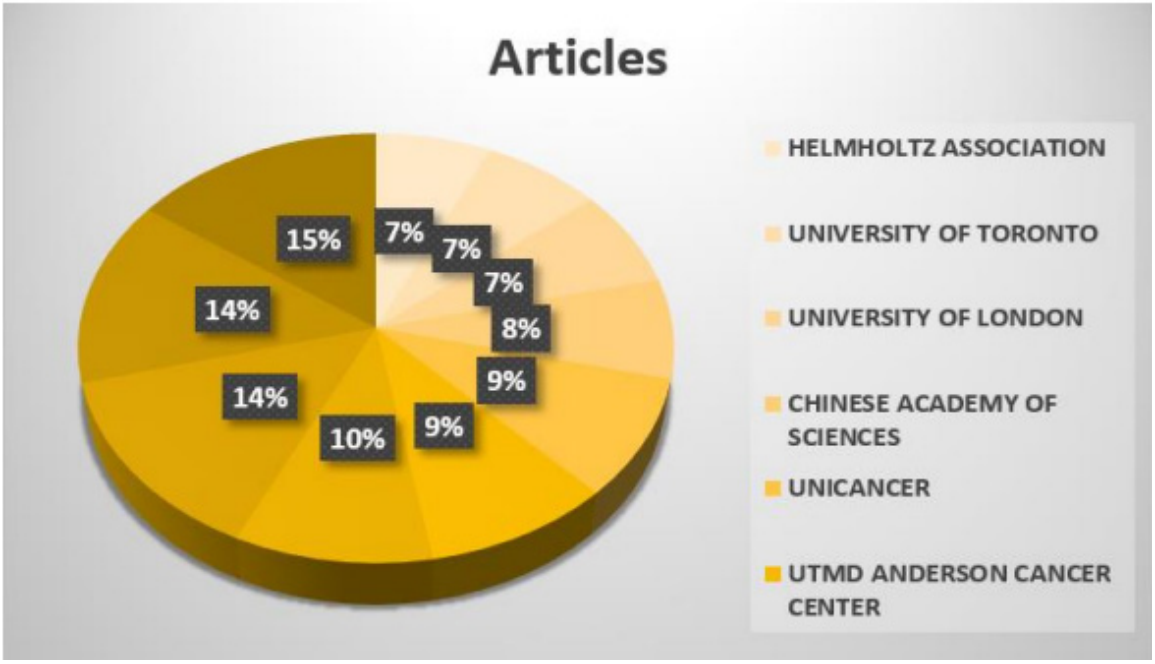
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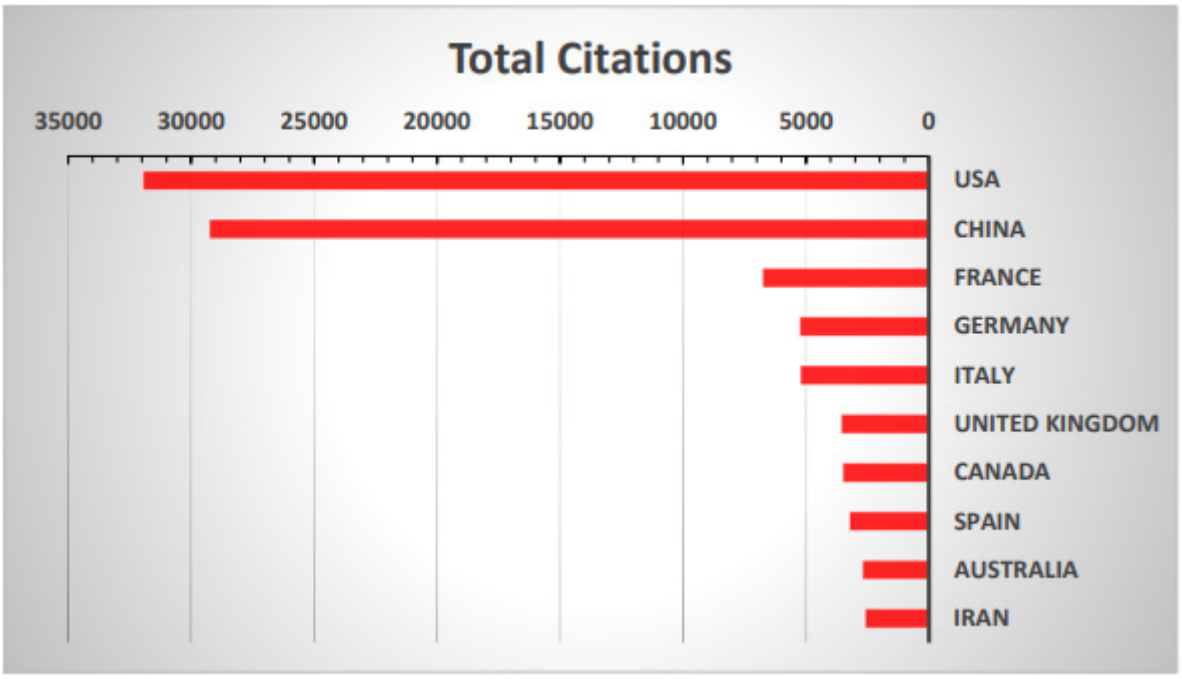


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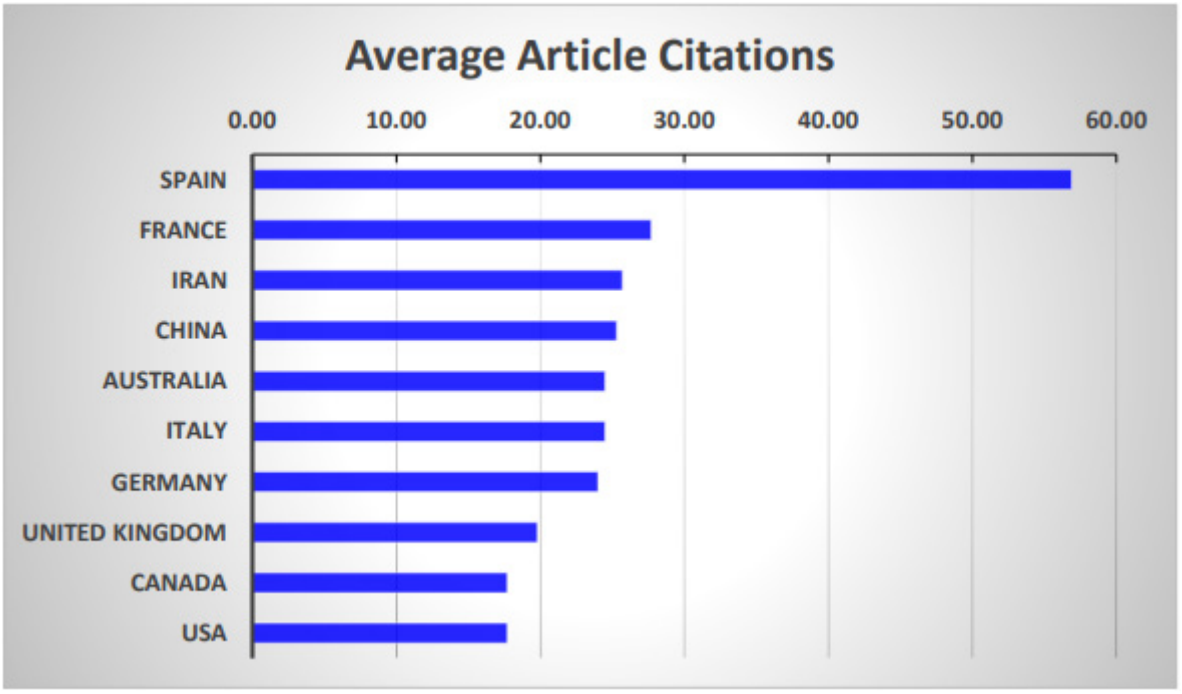


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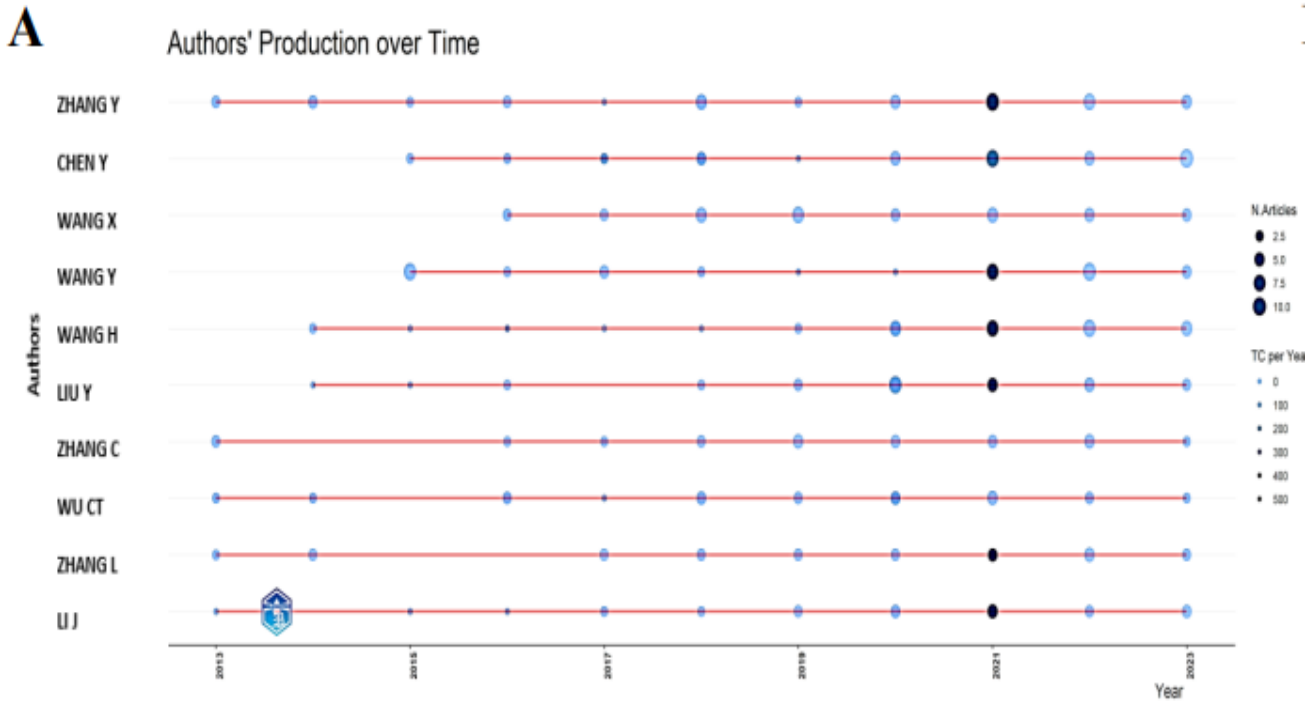


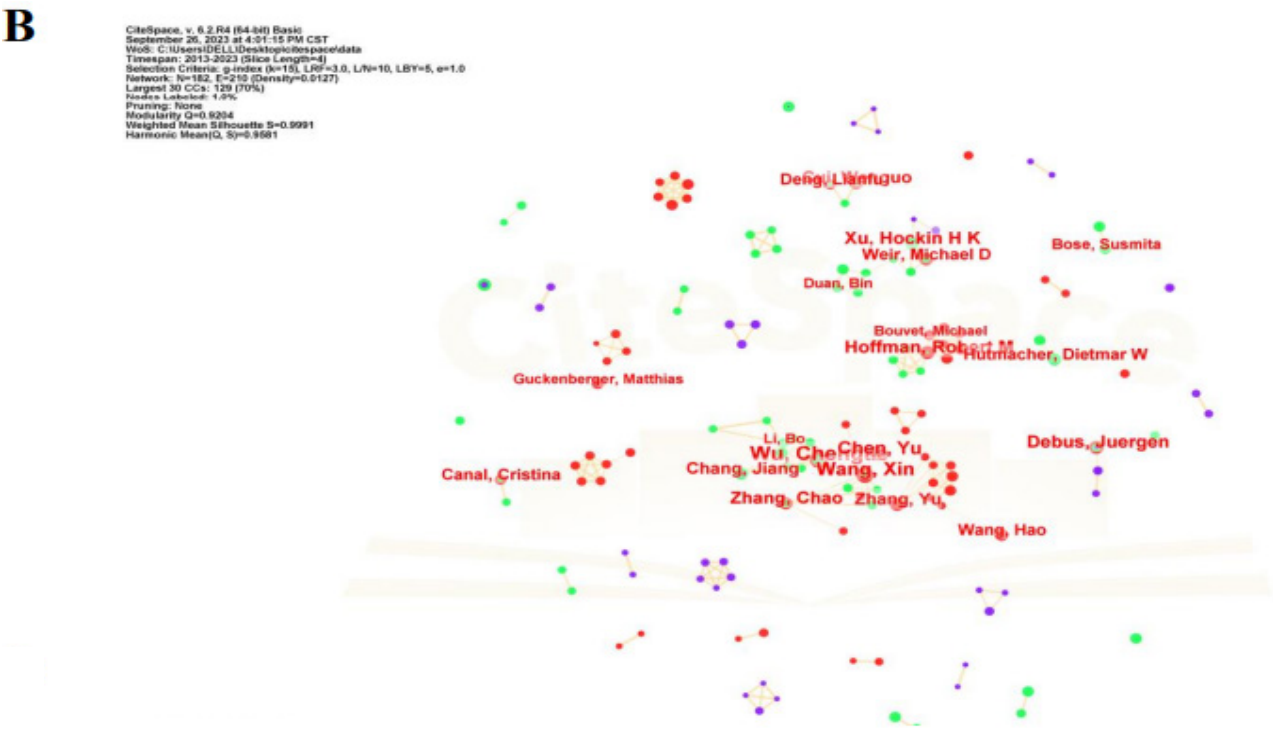
The top 10 authors with the most citations for papers published between 2013 and 2024 are shown in **Figure 4A**. The author with the most papers was Y. Zhang (47 papers, 5.73% of all papers), followed by Chen (39 papers, 5.74% of all papers). Notably, both Y. Zhang and Chen had higher rates of total citations per year (**Figure 4A**, dark blue circles). Y. Zhang also had the highest H-index (19), followed by Chen (18), Y. Wang (18), and Wu (18) (**Figure 4B**). The authors were linked by co-authored papers (**Figure 4C**). Y. Zhang and Chen had centralities of 0.01 and 0.03, respectively.

According to a condensed study using CiteSpace, the University of Miami (centrality=0.54), the Chinese Academy of Sciences (centrality=0.42), and the Memorial Sloan Kettering Cancer Center (centrality=0.31) were the institutions that worked most closely with other universities (**Figure 4D**).

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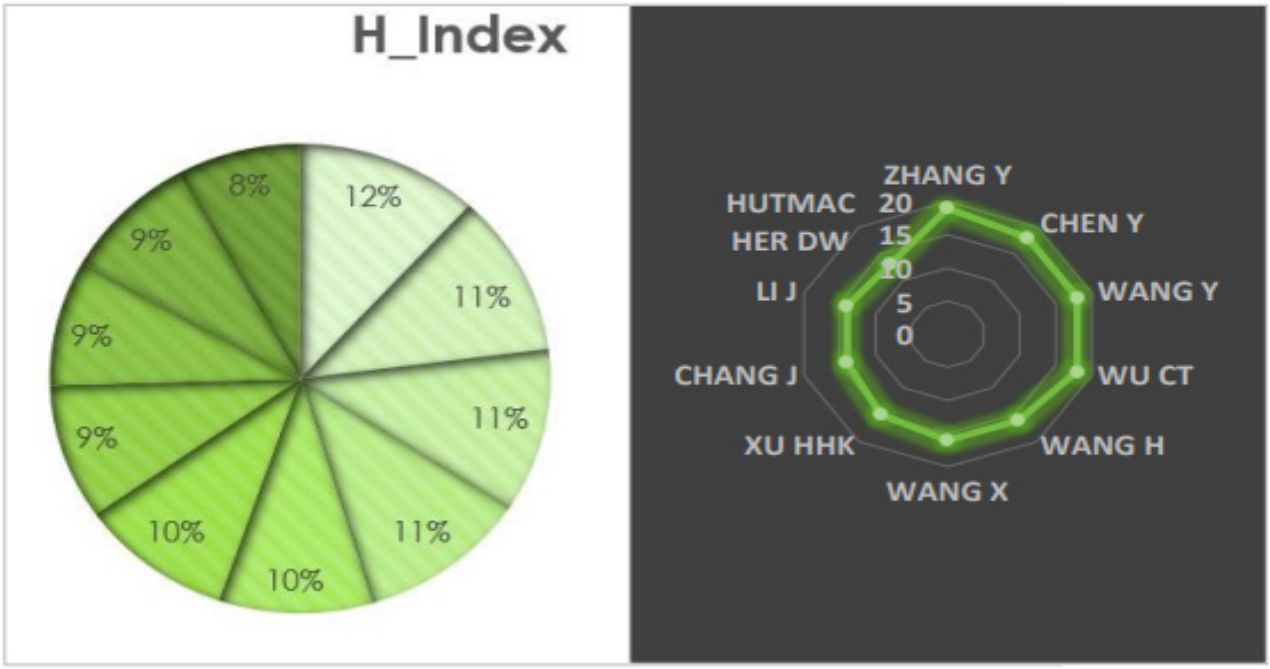
Figure 4. Visualized analysis for active authors and institutes. (A) The timeline degree distribution of the top 10 authors who have publicated the most papers. Red line, temporal distribution of author-related publications; light blue, total citations per year; circle diameter, number of publications. (B) Collaboration chart among authors by cluster analysis. (C) H-index of publications from different authors. (D) Cluster estimation of teamwork institutes.



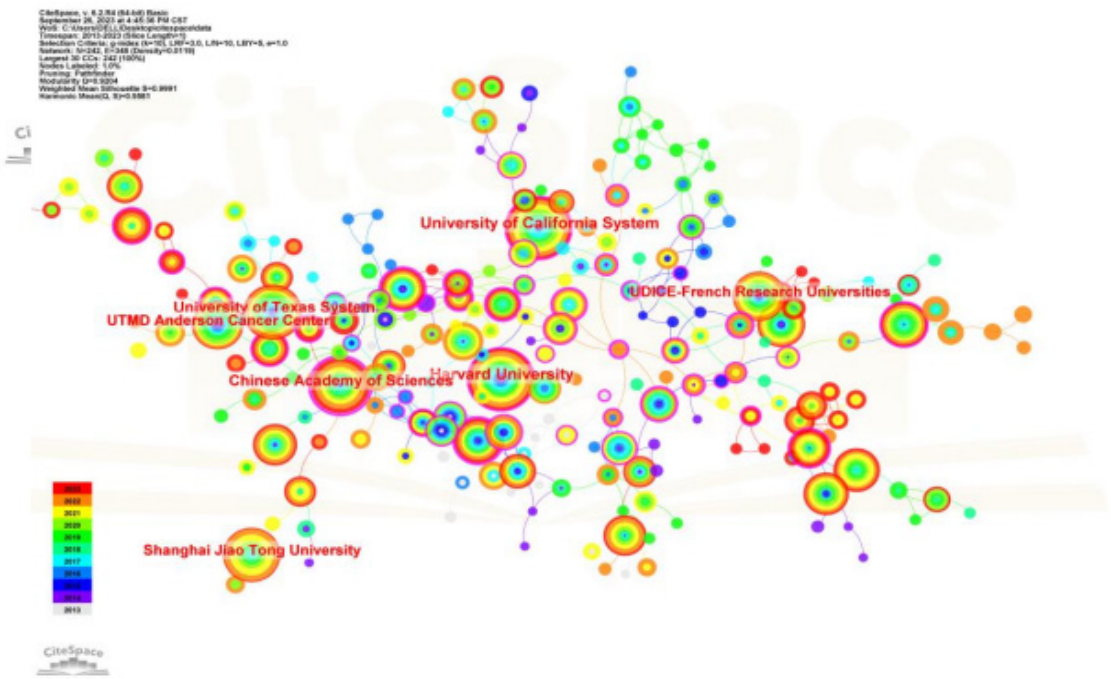


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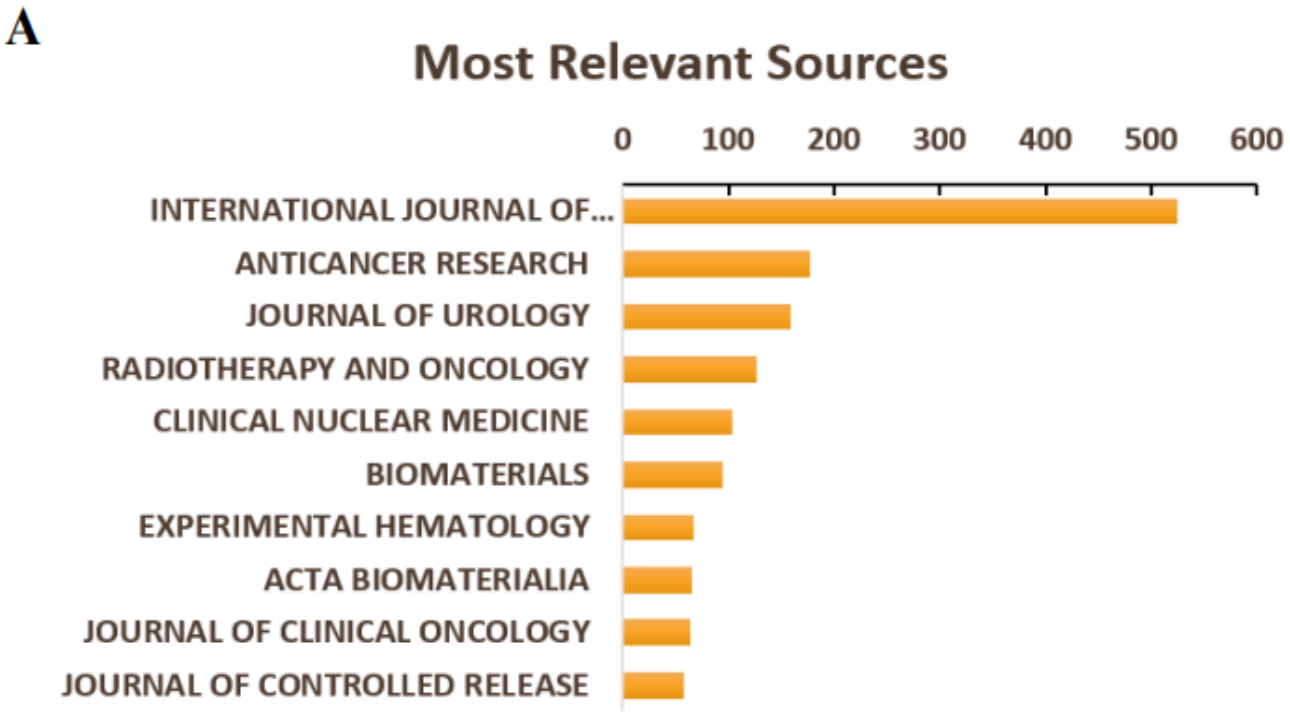
Analysis of publications and affiliated areas

The International Journal of Radiation Oncology, Biology, Physics published the most papers related to biomaterials and bone tumors (187 papers), followed by Anticancer Research (86 papers). Radiotherapy and Oncology, Clinical Nuclear Medicine, and Biomaterials also published a substantial number of papers (**Figure 5A, B**).

Biomaterials was cited most often (10210 citations), followed by the International Journal of Radiation Oncology, Biology, Physics (4573 citations) and Clinical Oncology (4376 citations) (**Figure 5C**). The journal with the highest H-index was Biomaterials (H-index=40), followed by the International Journal of Radiation Oncology, Biology, Physics (H-index=37) and Acta Biomaterialia (H-index=28) (**Figure 5D**). Therefore, target journals should be selected according to their primary areas of interest to provide a good theoretical foundation for the use of biomaterials to treat bone tumors.

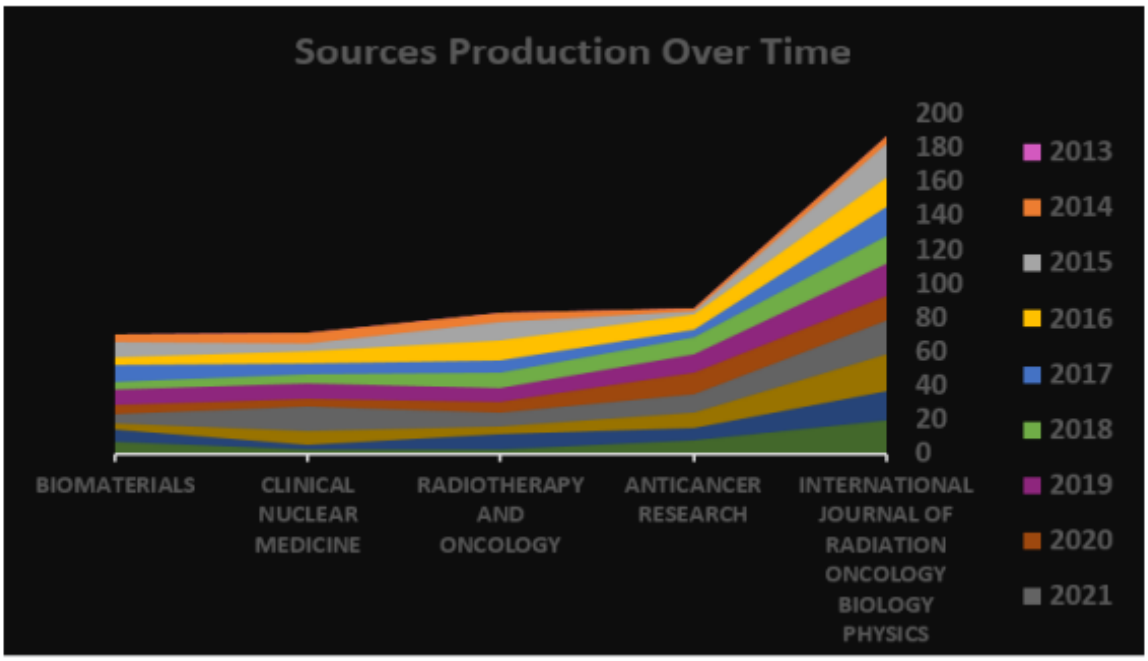
A clustering analysis was conducted using the cited references and journals. Thus, radiotherapy, mesenchymal stem cell therapy, photothermal therapy, and cancer therapy were identified as the four key categories in this study (**Figure 5E**). Furthermore, most quotations for these publications were related to physics, molecular biology, chemistry, immunology, materials, and clinical medicine. Molecular biology, materials chemistry, physics, and immunology are primarily concerned with the use of biomaterials in bone tumor therapy. The growth of these subjects is connected to the development of scientific and biomedical communications.

Figure 5. Analysis of the cited journals and related fields. (A) Top 10 most relevant journals. (B) Rising tendency for the top five most published journals. (C) Most local cited sources. (D) Sources' local impact by H-index. (E) Clustering analysis for the cited references and journals.

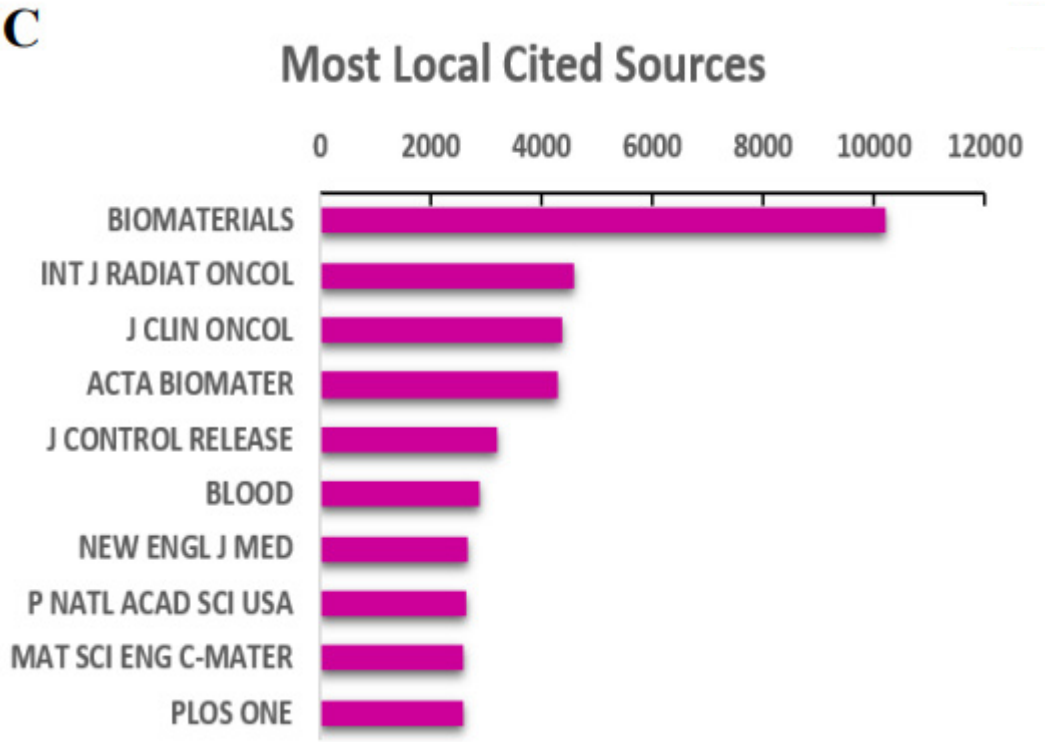


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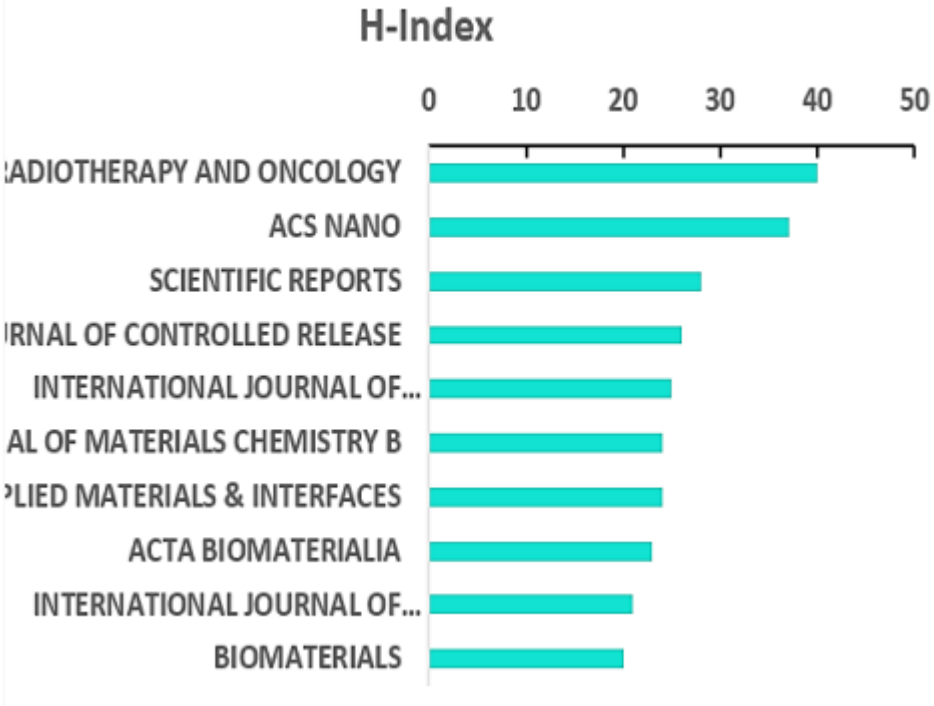


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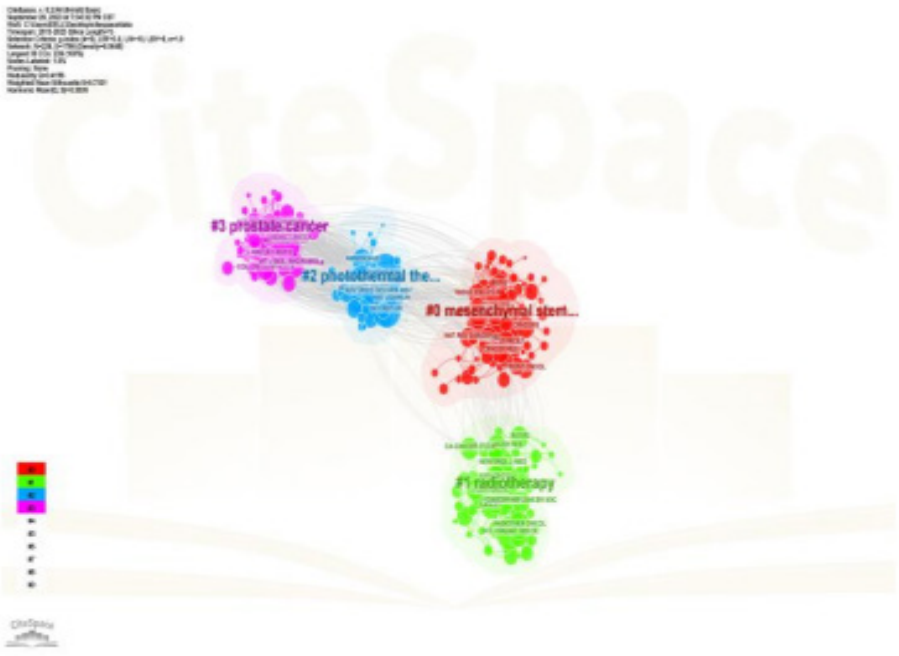


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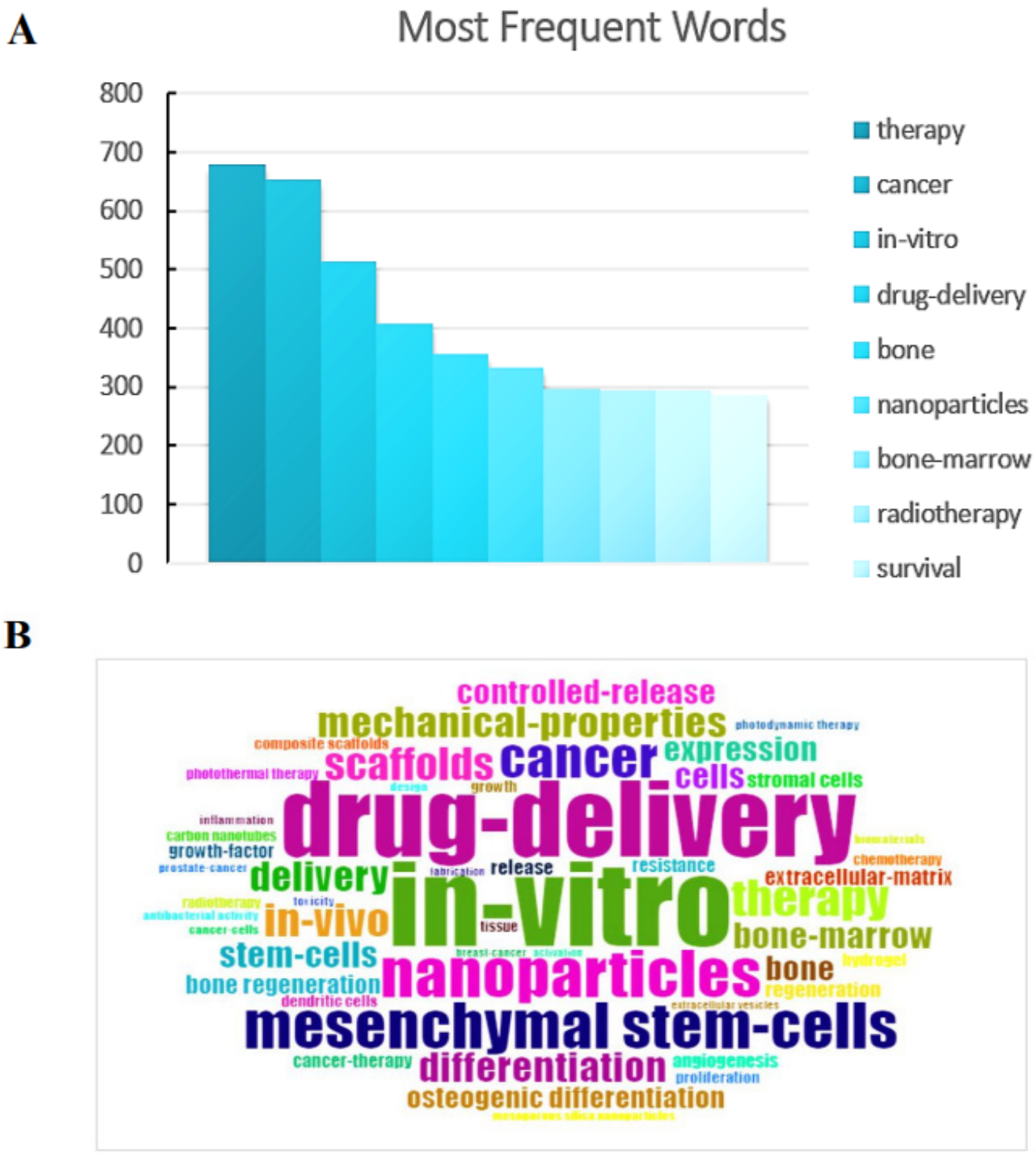


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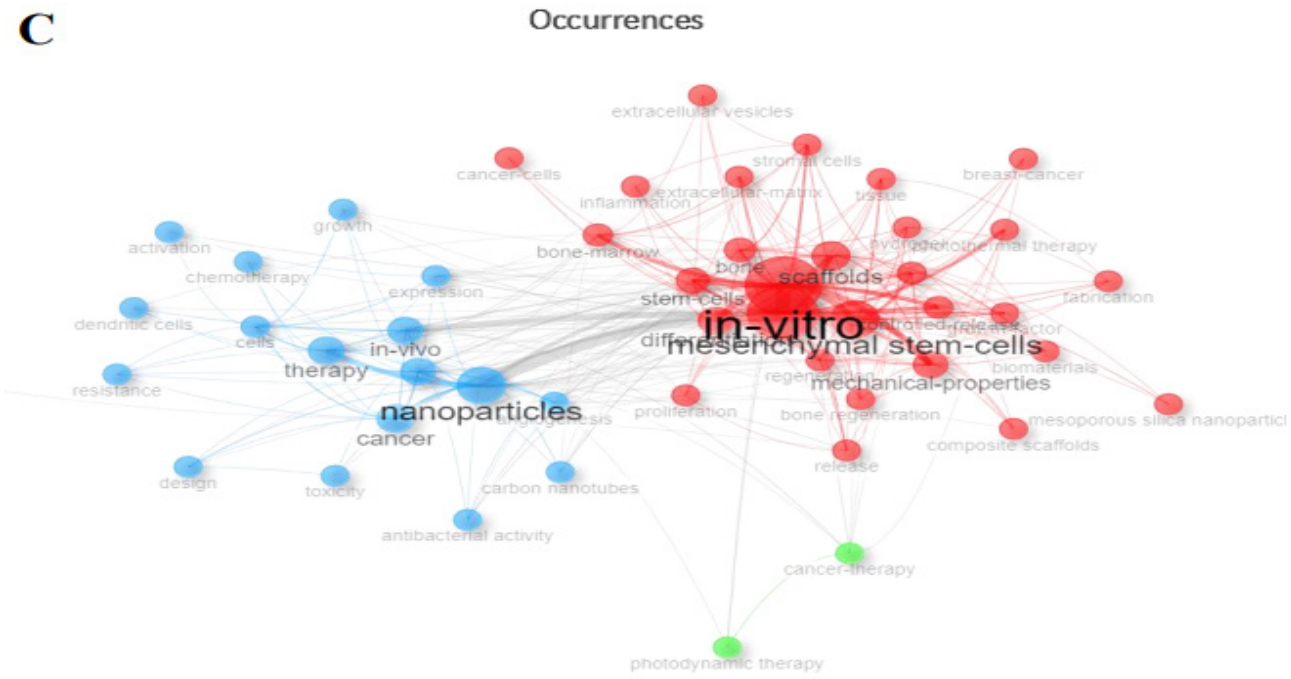
Analysis of the cited references

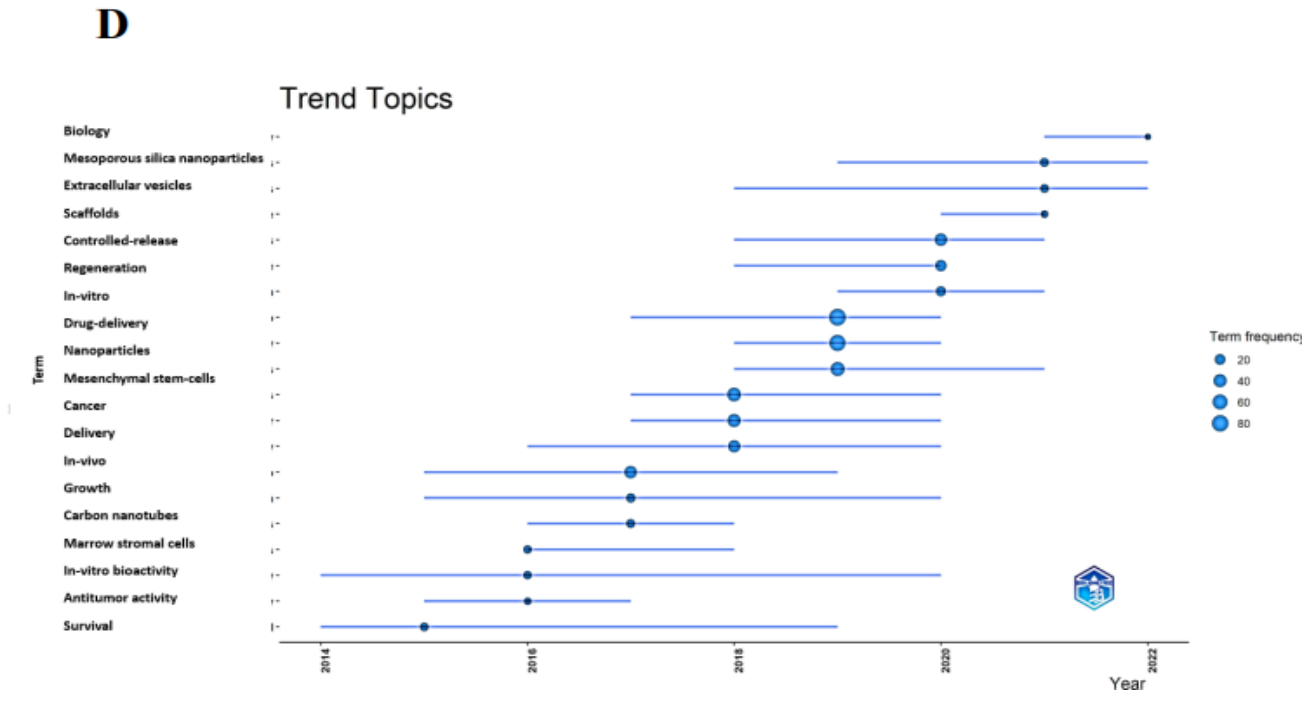
The most frequently mentioned phrases are shown in **Figure 6A**. The main thematic phrases in these publications were as follows: in vitro drug delivery, nanoparticles, mesenchymal stem cells, cancer, therapy, and scaffolds. A word cloud and a co-occurrence network for the phrases are shown in **Figure 6B** and **C**, respectively. In the last 2 years, the keywords "biology," "mesoporous silica nanoparticles," "extracellular vesicles," and "hydroxyapatite" have become increasingly common (**Figure 6D**). Here, we aimed to extend the existing phrases in several ways.

Figure 6. Relevant information for these keywords. (A) Occurrences for the keywords over the past 10 years. (B) The World Cloud for the keywords. (C) The co-occurrence network for these keywords. (D) Term frequency for these keywords from 2013-2024. (E, F) The tree map and the pie chart of key words. (G) Most local cited references of the top 10.



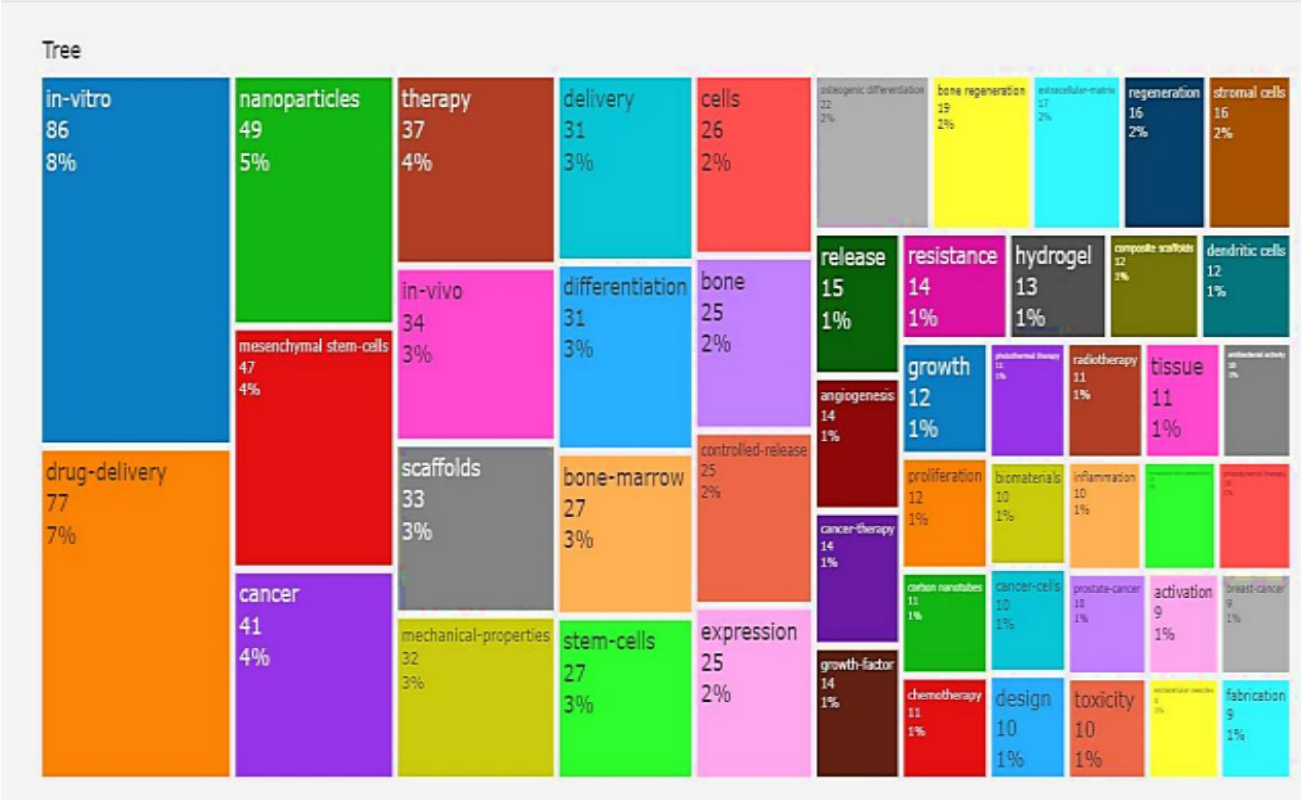
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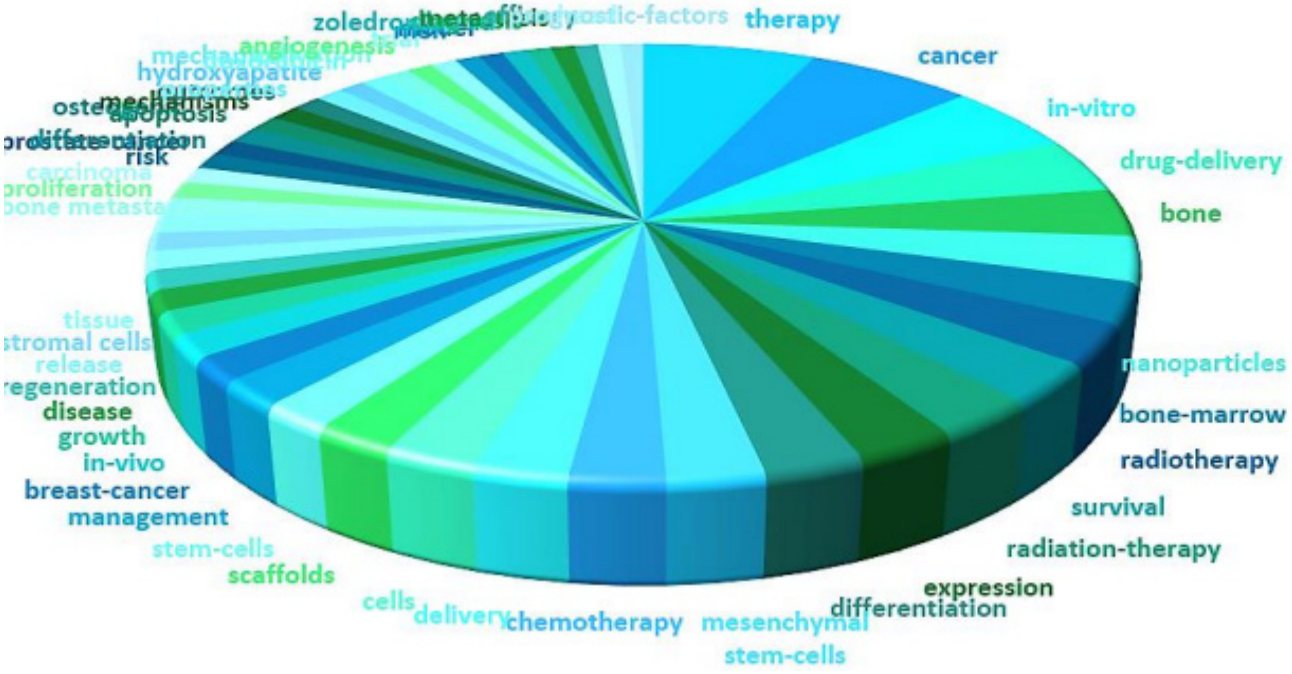


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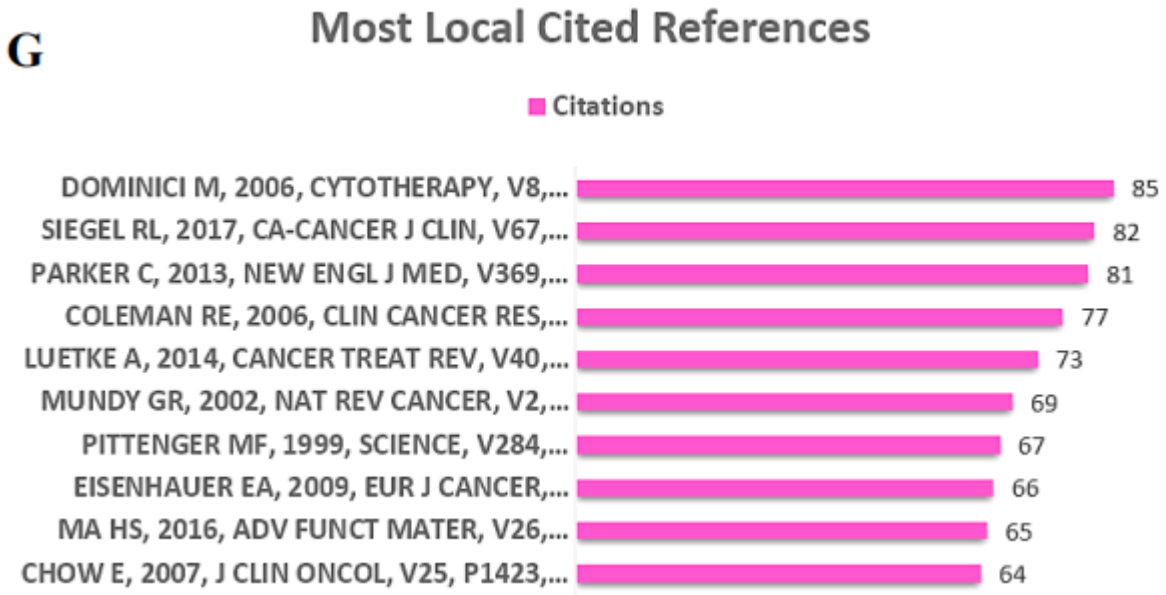
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First, we considered that a paper titled "A Two-Dimensional Biodegradable Niobium Carbide (MXene) for Photothermal Tumor Eradication in NIR-I and NIR-II Biowindows" was the most cited paper in our analysis (861 global citations), while another paper titled "A Biofunctional Biomaterial with Photothermal Effect for Tumor Therapy and Bone Regeneration" was the most locally cited paper (23 local citations) (**Table 1**). Second, the many quotations in this study are important in the field of biologically active materials and bone tumors and serve as a basis for scientific research in this area.

Table 1. Average number of article citations for major participating countries.

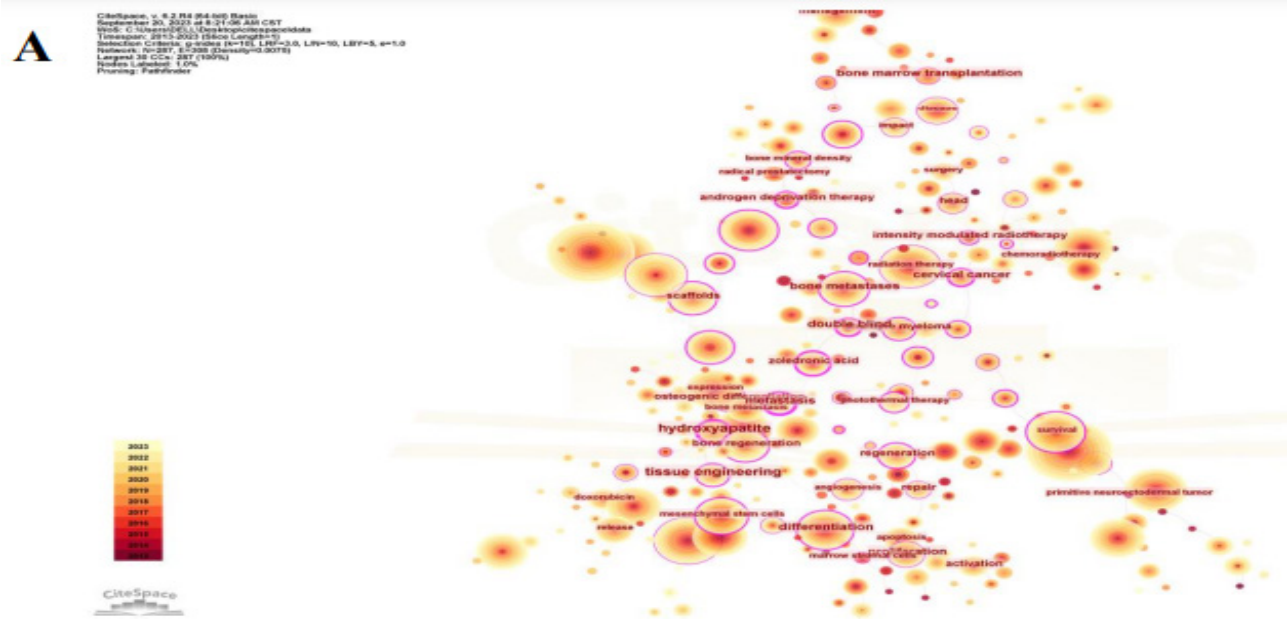
Country	TC	Average Article Citations
USA	31961	25.70
China	29255	24.50
France	6768	56.90
Germany	5261	17.70
Italy	5235	19.80
United Kingdom	3572	24.50
Canada	3508	24.00
Spain	3238	27.70
Australia	2703	25.30
Iran	2603	17.70

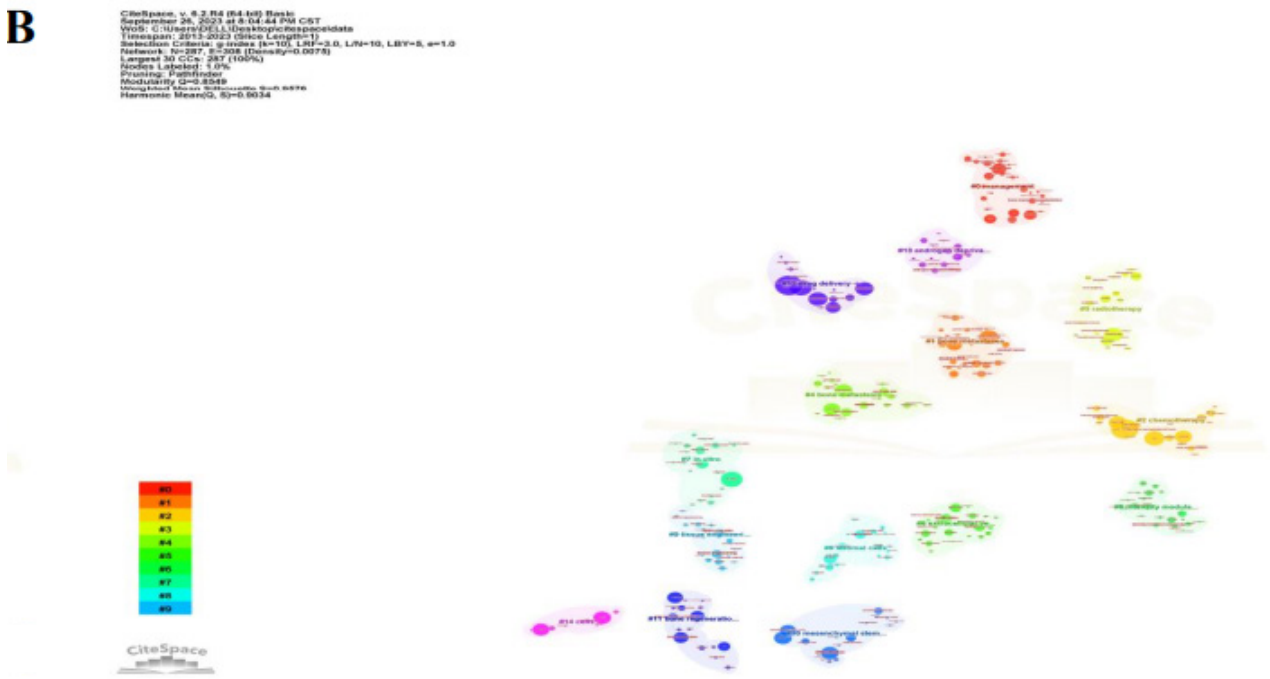
Keyword analysis

We used CiteSpace to identify 14 groups of topic phrases, such as bone, chemotherapy, and radiotherapy. Next, we visualized the keywords graphically (**Figure 7A**), conducted a cluster analysis (**Figure 7B**), and identified the keyword trends from 2013 to 2024 and the top 25 keywords (**Figure 7C, D**). The results indicate that the research hotspots between 2013 and 2024 were stromal cells, receptors, and gene therapy. However, the current hotspots mainly include infusion, photothermal therapy, and drugs, which indicate potential directions for future research.

Figure 7. Visualization of keyword evaluation. (A) Visualization of the keywords. (B) Cluster analysis of the keywords. (C) Trends of the keywords over time from 2013 to 2024. (D) Representative burst keywords among the top 25 keywords with the most powerful citation.

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D Top 25 Keywords with the Strongest Citation Bursts

Keywords	Year	Strength	Begin	End	2013 - 2023
postmenopausal women	2013	8.41	2013	2017	
stromal cells	2013	6.76	2013	2017	
cancer cells	2015	10.46	2015	2018	
drug	2020	8.23	2020	2023	
bone cancer	2020	7.92	2020	2023	
inflammation	2020	7.68	2020	2023	
mice	2014	7.48	2014	2017	
transplantation	2014	7.48	2014	2017	
association	2020	6.54	2020	2023	
randomized trial	2015	6.27	2015	2018	
photothermal therapy	2018	10.26	2021	2023	
stereotactic body radiotherapy	2021	8.66	2021	2023	
palliative radiotherapy	2017	8.64	2017	2019	
phase ii	2016	8.35	2016	2018	
in vivo	2013	8.32	2015	2017	
pathway	2018	7.4	2018	2020	
gene therapy	2014	7.17	2014	2016	
recurrence	2015	6.5	2021	2023	
osteosarcoma	2018	6.46	2021	2023	
adipose tissue	2014	6.36	2014	2016	
positron emission tomography	2014	8.33	2014	2015	
receptor	2013	6.7	2013	2014	
strategy	2018	6.58	2020	2021	
protein	2020	6.53	2020	2021	
chemoradiotherapy	2016	6.38	2016	2017	

Qualitative evaluation

We screened the literature to identify papers with an average citation frequency of ≥10 per year. Overall, we identified 444 highly cited papers, including 259 articles and 175 reviews. The qualitative estimation of a vastly cited document can be used to clarify the progress of scientific research on a subject and to efficiently understand the basis of a study. Based on the specific research objectives, we concluded that neoteric biomaterials have attracted increasing attention in recent years. In the last 5 years, rapid improvements have been made in the synthesis of intelligent stimuli-responsive biomaterials, including the application of external stimuli to enhance therapeutic effects, utilization of smart feedback in the internal microenvironment, and development of synergistic therapies that combine different approaches to enhance treatment efficacy. We reviewed different stimuli-response strategies, including external and local microenvironment stimuli-response strategies, compared

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the advantages and disadvantages of dissimilar strategies, and investigated the current challenges and future insights of these innovative biomaterials. This knowledge may contribute to multifunctional biomaterial development for anti-bone tumor and bone regeneration applications in diverse environments.

External stimuli-response strategies

External stimuli, such as ultrasound, light, electrical spurs, magnetic areas, and suitable automatic stimuli, can generate heat in a scaffold, which stimulates osteoblast adhesion, proliferation, and differentiation, thereby promoting bone healing and formation.[22] Moreover, most biomaterials are composed of nanomaterials, such as photothermal nanoagents and magnetic nanoparticles (NPs), that can act as drug nanocarriers or facilitate magnetic ablation and photothermal treatments.[23-25]

Photoresponsive strategies

Under infrared light, radiation can exhibit photophysical properties that affect the respiratory chain, enhance adenosine triphosphate regeneration, and promote cellular metabolism.[26] Many antitumor and antimicrobial therapies utilize photoresponsive strategies because they are easily amalgamated, and practical photoresponsive nanosystems and components are widely available. Various common photothermal agents have been reported, including transition-metal sulfides, gold nanostructures, single-element nanosheets (e.g., black phosphorus nanosheets), oxides (e.g., CuFeSe2 nanocrystals, Fe3O4 NPs, and copper silicate medisorbs), carbon-based NPs, organic NPs, and graphene.[27-30]

Furthermore, nanohydroxyapatite/graphene oxide particles have been used to produce functionalized chitosan (CS) scaffolds with superior photothermal transformation properties and bone-forming bioactivity.[31] Human osteosarcoma cells are efficiently ablated under near-infrared irradiation when the temperature is elevated to 48°C. Near-infrared irradiation also activates the BMP-2/Smad signaling pathway, which dramatically enhances hBMSC osteogenesis[31]

Magnetothermal strategies

Magnetic NPs, typically Fe3O4 NPs, can be used as magnetic hyperthermic therapeutic agents. They generate heat when exposed to external magnetic fields and may increase osteogenic differentiation. Therefore, magnetic NPs have considerable potential as tissue-regenerative substrates for bone tissue applications.[32,33] Particularly, Fe3O4 NPs irradiated by an external magnetic field can increase the temperature from 42°C to 45°C, which is sufficient to damage or even destroy cancer cells.[34]

Magnetothermal strategies, where NPs serve as an outward-shifting magnetic ground, have a stronger tissue penetration capacity than photoresponsive strategies. Therefore, magnetothermal strategies are better suited for treating deep-tissue lesions, such as bone tumors. Moreover, magnetothermal strategies are noninvasive and controllable, indicating that they can be widely used for bone tumor ablation and bone regeneration.

Many researchers have developed multifunctional biomaterials using magnetothermal strategies that combine bone disease treatment and bone defect repair. For example, magnetic 10Fe5Ca mesoporous bioactive glass scaffolds (Fe3O4-CaO-SiO2-P2O5 systems) generate heat when they are exposed to external magnetic fields.[33] Furthermore, alkaline phosphatase activity, osteoblast proliferation, and osteogenic differentiation can increase owing to the reduced ionolysis rate and favorable pH. For example, drugs, such as gentamicin, can be extracted in lower pH microenvironments, which provides the corresponding therapeutic effects.

Zhu et al.[30] used three-dimensional printing technology to combine CaO2 and Fe3O4 NPs with akermanite (AKT) scaffolds (called AKT-Fe3O4-CaO2) to facilitate magnetic hyperthermia and bone formation. The loaded Fe3O4 NPs triggered magnetic hyperthermia, rapidly increasing the temperature, and acted as nanocatalysts for the Fenton reaction. Furthermore, under the acidic tumor conditions, the loaded CaO2 NPs also generated H2O2, which compensated for the depletion of H2O2 and released Ca2+, inducing further restoration of the bone defects.

Future research should aim to improve the uniformity of heating to reduce the risk of unexpected damage to healthy tissues in the irradiation field.

Local microenvironmental stimuli-reactive strategies

Oxidative species-reactive strategy

Reactive oxygen species (ROS), such as superoxide, peroxides, monoclinic oxygen, and alpha-oxygen, are chemically reactive molecules that contain oxygen.[35,36] The overexpression of ROS in biological systems has been observed in various pathological conditions, such as aging, neurodegenerative disorders, cardiovascular disease, physical injury, inflammation, and cancer.[37,38] Therefore, endogenous ROS overloading is commonly used as a trigger to stimulate a therapeutic response for bone treatment and regeneration. Many recent studies have focused on these strategies and the synthesis of multifunctional biomaterials.

Zhu et al.[39] constructed a composite scaffold with a local microenvironmental response using simple hydrothermal therapeutics. A Ni-Ti layered double hydroxide membrane inserted with butyrate released cytotoxic butyrate by exploiting the overexpression of H2O2 in the microenvironments surrounding tumors and infections, which inhibited tumor

metastasis and increased osteogenesis. Albarrán et al.[40] developed maximized Fe-CaSiO3 synthesized scaffolds (30CS) with three-dimensional printing and gluing. These innovative stents exhibited high mechanical strength and were suitable for ROS treatment of tumors and photothermal therapy.

Specific ionic concentration-response strategy

New biomaterials have good biocompatibility, extraordinary drug encapsulation ability, low cell toxicity, low Ca2+ concentrations, and low pH values around bone tumors, which can trigger the release of 5-fluorouracil to achieve an antitumor effect.

Although there has been relatively limited research on materials sensitive to ionic concentrations, electrolyte levels could serve as significant markers for diagnosis and treatment. Therefore, advanced materials sensitive to ionic concentrations may yield promising results for enhancing precision in bone therapy and promoting bone regeneration in the future.

Multi-response strategies

Owing to the synergistic effects of multi-treatment modalities, combination therapies generally yield better outcomes than single-treatment modalities.[41] Moreover, multiple combinations of bone tumor-therapy methods can be considered. Particularly, researchers have attempted to combine external and internal stimuli-response strategies, yielding remarkable results.

Tan et al.[42] synthesized a multi-responsive "gated scaffold." This scaffold can combine the effects of the Ca2+ concentration related to osteolysis, low pH around bone tumor cells, and hyperthermia therapy, which had a collaborative effect on bone tumor therapy and bone regeneration. Similarly, Dong et al.[29] designed AKT-Fe3O4-CaO2 scaffolds for multifunctional treatment of bone tumors and bone tissue regeneration. In these intelligent stimuli-response platforms, Fe3O4 NPs act as a medium for therapy by rapidly increasing the temperature when they are exposed to an alternating magnetic field. Furthermore, loading CaO2 NPs into the smart platform yielded sufficient H2O2 at the osteolysis site under low pH conditions to trigger the Fenton response, which ultimately induced oxidative tumor therapy.

These novel intelligent stimuli-responsive scaffolds demonstrate significant potential in treating bone tumors and facilitating the regeneration of bone defects caused by surgery.

DISCUSSION

This study quantitatively and qualitatively analyzed 5323 papers in the field of bone tumor therapy using the Web of Science database between 2013 and 2024. The quantitative analysis revealed that the total number of papers and mean annual citation rate in this discipline are increasing. The authors predominantly hailed from the USA and China, with the former playing an important role in global cooperation. The number of papers published in China has been increasing since 2013, although the number of citations in China remains lower than that in the USA. This result indicates that research in China is developing rapidly, although the best papers continue to originate from the USA. The qualitative analysis was based on 444 papers that had an annual citation rate of ≥10. Based on the citation frequency and publication date, we confirmed that biomaterials are an attractive field in bone tumor research. Intelligent stimuli-responsive biomaterials differ significantly from traditional biomaterials because they can respond to stimuli or triggers from their surroundings (both internal and external).[43,44] Therefore, these new biomaterials have attracted increasing attention from researchers in recent years.

This study had some limitations. First, quantitative and qualitative analyses were based on papers from the Web of Science database, and the sample data from 2013 to 2024 were small. Second, qualitative analyses are considerably more subjective than quantitative analyses, and different perspectives may lead to different results. Nevertheless, this study revealed the current trends in bone-tumor therapy using biomaterials, especially intelligent stimuli-responsive biomaterials, and provides a theoretical basis and direction for future research.

CONCLUSIONS

In recent years, studies on intelligent stimuli-responsive biomaterials using small animal models, such as subcutaneous tumor formation in nude mice and orthotopic transplantation tumors, have demonstrated promising results. However, intelligent biomaterials are in their initial stages, and there remain challenges that must be addressed. Consequently, these studies have not led to clinical trials and complete treatments. This study provides a summary of the current research in this field and is a valuable resource for forecasting future trends in bone tumor therapy using intelligent stimuli-responsive biomaterials and bone regeneration after surgery.

Abbreviations

AKT, akermanite; CW, chitosan; NP, nanoparticle; ROS, reactive oxygen species.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors.

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Conflict of Interest

The authors have no conflict of interest.

Ethics Statement

This study did not require approval from the Committee on Ethical Medicine.

Informed Consent: N/A.

Registry and the Registration No. of the study/trial: N/A.

Animal Studies: N/A.

Author Contributions

YP conceptualized the study, developed the methodology. JL utilized the software and conducted data curation, conducted validation. YP and WG performed formal analysis. YP wrote the original draft. JL wrote reviewed, and edited the manuscript. WG and YP supervised the study and acquired funding. All authors have read and agreed to the published version of the manuscript.

REFERENCES

1. Zhang Y, Yu T, Peng L, Sun Q, Wei Y, Han B. Advancements in hydrogel-based drug sustained release systems for bone tissue engineering. Front Pharmacol. 2020;11:622. doi:10.3389/fphar.2020.00622

2. Wang P, Zhao L, Liu J, Weir MD, Zhou X, Xu HH. Bone tissue engineering via nanostructured calcium phosphate biomaterials and stem cells. Bone Res. 2014;2:14017. doi:10.1038/boneres.2014.17

3. Ward E, DeSantis C, Robbins A, Kohler B, Jemal A. Childhood and adolescent cancer statistics, 2014. CA Cancer J Clin. 2014;64(2):83-103. doi:10.3322/caac.21219

4. Isakoff MS, Bielack SS, Meltzer P, Gorlick R. Osteosarcoma: current treatment and a collaborative pathway to success. J Clin Oncol. 2015;33(27):3029-3035. doi:10.1200/JCO.2014.59.4895

5. Altaf F, Weber M, Dea N, et al. Evidence-based review and survey of expert opinion of reconstruction of metastatic spine tumors. Spine (Phila Pa 1976). 2016;41:S254-S261. doi:10.1097/BRS.0000000000001819

6. Quraishi NA, Rajabian A, Spencer A, et al. Reoperation rates in the surgical treatment of spinal metastases. Spine J. 2015;15:S37-S43. doi:10.1016/j.spinee.2015.01.005

7. Konishi M, Tabata Y, Kariya M, et al. In vivo anti-tumor effect through the controlled release of cisplatin from biodegradable gelatin hydrogel. J Control Release. 2003;92(3):301-313. doi:10.1016/s0168-3659(03)00364-x

8. Walter KA, Tamargo RJ, Olivi A, Burger PC, Brem H. Intratumoral chemotherapy. Neurosurgery. 1995;37(6):1128-1145.

9. Ning S, Yu N, Brown DM, Kanekal S, Knox SJ. Radiosensitization by intratumoral administration of cisplatin in a sustained-release drug delivery system. Radiother Oncol. 1999;50(2):215-223. doi:10.1016/s0167-8140(98)00134-0

10. Santoro M, Tatara AM, Mikos AG. Gelatin carriers for drug and cell delivery in tissue engineering. J Control Release. 2014;190:210-218. doi:10.1016/j.jconrel.2014.04.014

11. Wang Y, Li M, Li P, et al. Progress and applications of polyphosphate in bone and cartilage regeneration. BioMed Res Int 2019;2018:5141204. doi:10.1155/2019/5141204

12. Zeng Y, Hoque J, Varghese S. Biomaterial-assisted local and systemic delivery of bioactive agents for bone repair. Acta Biomater. 2019;93:152-168. doi:10.1016/j.actbio.2019.01.060

13. Chen C. Searching for intellectual turning points: progressive knowledge domain visualization. Proc Natl Acad Sci U S A. 2004;101 Suppl 1(Suppl 1):5303-5310. doi:10.1073/pnas.0307513100

14. Xing D, Zhao Y, Dong S, Lin J. Global research trends in stem cells for osteoarthritis: a bibliometric and visualized study. Int J Rheum Dis. 2018;21(7):1372-1384. doi:10.1111/1756-185X.13327

15. Pu QH, Lyu QJ, Su HY. Bibliometric analysis of scientific publications in transplantation journals from Mainland China, Japan, South Korea and Taiwan between 2006 and 2015. BMJ Open. 2016;6(8):e011623. doi:10.1136/bmjopen-2016-011623

16. Huang X, Fan X, Ying J, Chen S. Emerging trends and research foci in gastrointestinal microbiome. J Transl Med. 2019;17(1):67. doi:10.1186/s12967-019-1810-x

17. Martynov I, Klima-Frysch J, Schoenberger J. A scientometric analysis of neuroblastoma research. BMC Cancer. 2020;20(1):486. doi:10.1186/s12885-020-06974-3

18. Zhang T, Yin X, Yang X, et al. Research trends on the relationship between microbiota and gastric cancer: A bibliometric analysis from 2000 to 2019. J Cancer. 2020;11(16):4823-4831. doi:10.7150/jca.44126

19. Huang Y, He K, Fang D, et al. A bibliometric of research trends in acupuncture for spinal cord injury: Quantitative and qualitative analyses. Front Neurol. 2022;13:936744. doi:10.3389/fneur.2022.936744

20. Xiong W, Wang S, Wei Z, et al. Knowledge domain and hotspots predict concerning electroactive biomaterials applied in tissue engineering: A bibliometric and visualized analysis from 2011 to 2021. Front Bioeng Biotechnol. 2022;10:904629. doi:10.3389/fbioe.2022.904629

21. Brähler E, Decker O. [The H-index]. Psychother Psychosom Med Psychol. 2005;55(11):451. doi:10.1055/s-2005-915263

22. Lui YS, Sow WT, Tan LP, Wu Y, Lai Y, Li H. 4D printing and stimuli-responsive materials in biomedical aspects. Acta Biomater. 2019;92:19-36. doi:10.1016/j.actbio.2019.05.005

23. Jin A, Wang Y, Lin K, Jiang L. Nanoparticles modified by polydopamine: Working as "drug" carriers. Bioact Mater. 2020;5(3):522-541. doi:10.1016/j.bioactmat.2020.04.003

24. Glyn-Jones S, Palmer AJ, Agricola R, et al. Osteoarthritis. Lancet. 2015;386(9991):376-387. doi:10.1016/S0140-6736(14)60802-3

25. Zhang H, Fan T, Chen W, Li Y, Wang B. Recent advances of two-dimensional materials in smart drug delivery nano-systems. Bioact Mater. 2020;5(4):1071-1086. doi:10.1016/j.bioactmat.2020.06.012

26. Rosso MPO, Buchaim DV, Pomini KT, et al. Photobiomodulation therapy (PBMT) applied in bone reconstructive surgery using bovine bone grafts: A systematic review. Materials (Basel). 2019;12(24):4051. doi:10.3390/ma12244051

27. Yang B, Yin J, Chen Y, et al. 2D-Black-Phosphorus-Reinforced 3D-Printed Scaffolds:A Stepwise Countermeasure for Osteosarcoma. Adv Mater. 2018;30(10). doi:10.1002/adma.201705611

28. Koski C, Vu AA, Bose S. Effects of chitosan-loaded hydroxyapatite on osteoblasts and osteosarcoma for chemopreventative applications. Mater Sci Eng C Mater Biol Appl. 2020;115:111041. doi:10.1016/j.msec.2020.111041

29. Dong S, Zhang YN, Wan J, et al. A novel multifunctional carbon aerogel-coated platform for osteosarcoma therapy and enhanced bone regeneration. J Mater Chem B. 2020;8(3):368-379. doi:10.1039/c9tb02383f

30. Zhu C, He M, Sun D, et al. 3D-Printed multifunctional polyetheretherketone bone scaffold for multimodal treatment of osteosarcoma and osteomyelitis. ACS Appl Mater Interfaces. 2021;13(40):47327-47340. doi:10.1021/acsami.1c10898

31. Sarkar N, Bose S. Controlled release of soy isoflavones from multifunctional 3D printed bone tissue engineering scaffolds. Acta Biomater. 2020;114:407-420. doi:10.1016/j.actbio.2020.07.006

32. Cao Z, Wang D, Li Y, et al. Effect of nanoheat stimulation mediated by magnetic nanocomposite hydrogel on the osteogenic differentiation of mesenchymal stem cells. Sci China Life Sci. 2018;61(4):448-456. doi:10.1007/s11427-017-9287-8

33. Zhu Y, Shang F, Li B, et al. Magnetic mesoporous bioactive glass scaffolds: preparation, physicochemistry and biological properties. J Mater Chem B. 2013;1(9):1279-1288. doi:10.1039/c2tb00262k

34. Zhang J, Zhao S, Zhu M, et al. 3D-printed magnetic Fe3O4/MBG/PCL composite scaffolds with multifunctionality of bone regeneration, local anticancer drug delivery and hyperthermia. J Mater Chem B. 2014;2(43):7583-7595. doi:10.1039/c4tb01063a

35. Hayyan M, Hashim MA, AlNashef IM. Superoxide Ion: Generation and chemical implications. Chem Rev. 2016;116(5):3029-3085. doi:10.1021/acs.chemrev.5b00407

36. Jiang S, Lin K, Cai M. ZnO Nanomaterials: Current advancements in antibacterial mechanisms and applications. Front Chem. 2020;8:580. doi:10.3389/fchem.2020.00580

37. Sun C, Wang Z, Yue L, Huang Q, Lu S, Wang R. ROS-initiated chemiluminescence-driven payload release from macrocycle-based Azo-containing polymer

nanocapsules. J Mater Chem B. 2020;8(38):8878-8883. doi:10.1039/d0tb01475c

38. He Q, Yang J, Pan Z, et al. Biochanin A protects against iron overload associated knee osteoarthritis via regulating iron levels and NRF2/System xc-/GPX4 axis. Biomed Pharmacother. 2023;157:113915. doi:10.1016/j.biopha.2022.113915
39. Zhu L, Liu J, Qiu M, et al. Bacteria-mediated metformin-loaded peptide hydrogel reprograms the tumor immune microenvironment in glioblastoma. Biomaterials. 2022;288:121711. doi:10.1016/j.biomaterials.2022.121711

40. Albarrán V, Villamayor ML, Chamorro J, et al. Receptor tyrosine kinase inhibitors for the treatment of recurrent and unresectable bone sarcomas. Int J Mol Sci. 2022;23(22):13784. doi:10.3390/ijms232213784

41. Kim J, Kim J, Jeong C, Kim WJ. Synergistic nanomedicine by combined gene and photothermal therapy. Adv Drug Deliv Rev. 2016;98:99-112. doi:10.1016/j.addr.2015.12.0

42. Tan LL, Song N, Zhang SX, Li H, Wang B, Yang YW. Ca2+, pH and thermo triple-responsive mechanized Zr-based MOFs for on-command drug release in bone diseases. J Mater Chem B 2016;4:135-140

43. Kumar S, Nehra M, Kedia D, Dilbaghi N, Tankeshwar K, Kim KH. Nanotechnology-based biomaterials for orthopaedic applications: Recent advances and future prospects. Mater Sci Eng C Mater Biol Appl. 2020;106:110154. doi:10.1016/j.msec.2019.110154

44. Fu Q, Li Z, Fu F, Chen X, Song J, Yang H. Stimuli-responsive plasmonic assemblies and their biomedical applications. Nano Today. 2021;36:101014. doi:10.1016/j.nantod.2020.10101