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Research Trends and Developments in Nanomaterials for Rheumatoid Arthritis: A Comprehensive Bibliometric Analysis

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Background: Rheumatoid arthritis (RA) is one of the common diseases associated with job loss and disability. However, the existing diagnosis and treatment methods are limited by factors such as misdiagnosis, missed diagnosis, and toxic side effects. In recent years, remarkable progress has been made in applying nanomedicine for RA treatment. However, previous studies lack a systematic and comprehensive analysis of the development trajectory of nanomaterials in the diagnosis and treatment of RA, the contributions of key researchers, and the evolution of research focuses. This study aims to fill this gap by providing a detailed bibliometric analysis of the global research landscape on nanomaterial applications in RA diagnosis and treatment, highlighting the significance of this field in advancing therapeutic interventions and identifying future research directions.

Methods: Relevant literature on the application of nanomaterials in RA treatment was searched in the Web of Science Core Collection (WoSCC) database from January 1, 1985 to December 31, 2023. VOSviewer, CiteSpace, "bibliometrix" R-package, and Microsoft Office Excel 2021 were used for bibliometric analysis to evaluate the number of publications, research hotspots, main researchers, and institutions.

Results: A total of 524 articles were included, involving 33 countries or regions, 784 institutions, and 2751 authors, covering 19 disciplines, including biochemistry and molecular biology, chemistry, engineering, immunology, and materials science. Countries with the highest publication output were China, India, and the United States, with China and the United States having the closest cooperation. The University of California at San Diego and CHEN X were the most influential institutions and authors. Journal of Controlled Release had the highest publication output and emerged as the most influential journal in the field. In recent years, research hotspots of nanomaterials in RA included "dexamethasone", "micelle", and "diagnosis".

Conclusion: This study is the first comprehensive bibliometric analysis of nanotechnology in RA application. It highlights the importance of nanomaterials in advancing RA diagnosis and treatment and provides a valuable reference for future research. By identifying key research trends, influential contributors, and emerging hotspots, this analysis offers actionable insights for researchers to build upon, ultimately driving innovation and improving therapeutic outcomes in the field of nanomedicine for RA.

Keywords: bibliometric analysis, rheumatoid arthritis, nanomaterial, research trend

Introduction

Rheumatoid arthritis (RA) is one of the most common chronic inflammatory diseases. Without timely treatment, it can lead to bone damage, joint deformity, and loss of function.[1] RA is one of the main diseases leading to job loss and disability. The global incidence of RA is about 0.4–1.3%, posing a huge economic burden on patients and society.[2] However, due to the lack of early diagnostic methods with high specificity and sensitivity, some RA patients are easily misdiagnosed and miss the best opportunity for treatment.[3] Although non-steroidal anti-inflammatory drugs,

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antirheumatic drugs, glucocorticoids, and other drugs can improve the symptoms of RA to a certain extent, they are limited by drug resistance and serious side effects, and their long-term efficacy remains uncertain.[4,5] These limitations highlight the urgent need for innovative approaches that can address the shortcomings of conventional treatments, such as improving drug delivery efficiency, reducing side effects, and enhancing diagnostic accuracy.

Nanotechnology, which focuses on the properties and applications of nanomaterials with sizes ranging from 1 nm to 100 nm, including polymers, metals, macromolecules, lipids, semiconductors, and chemicals,[6] has emerged as a promising solution to overcome these challenges. Compared to traditional drug delivery methods, nanotechnology offers significant advantages in therapy. It enables targeted drug delivery, enhances local therapeutic efficacy, and significantly reduces systemic toxicity.[7,8] Furthermore, nanotechnology also demonstrates great potential in the diagnostic field. For example, nanosensors can detect RA-related biomarkers with high sensitivity and specificity, while nanoprobe applications in magnetic resonance imaging (MRI) or other imaging techniques enable effective visualization of joint tissue structure and lesions, thus aiding in the early diagnosis of RA.[9] In addition, when compared to other emerging treatment strategies such as biologics and gene therapy, nanotechnology offers a more versatile platform for both diagnostic and therapeutic applications, with the potential to integrate multiple functionalities into a single system. This unique advantage positions nanotechnology as a powerful alternative for addressing the multifaceted challenges of RA management.

Despite the growing interest in nanotechnology for RA diagnosis and treatment, there remains a significant research gap in systematically evaluating the current state of this field. While numerous studies have demonstrated the potential of nanotechnology in various aspects of RA management, a comprehensive understanding of the trends, challenges, and future directions is still lacking. Bibliometric analysis, which combines mathematical, statistical, and data visualization methods to quantitatively and qualitatively analyze the quantity, quality, impact, and structure of academic literature, offers an ideal tool to fill this gap.[10] By assessing the current state of research in a field and emerging trends, bibliometric analysis can provide valuable insights into the development of RA nanotechnology and guide future investigations.

The present study presents the first systematic analysis of the literature on RA nanotechnology using bibliometric methods, providing an objective overview of the application of nanotechnology in diagnosing and treating RA. This research aims to address the existing research gap by identifying key trends, challenges, and future opportunities in this rapidly evolving field, thereby offering valuable insights for future investigations.

Methods

Search Strategy

On April 7, 2024, the relevant literature on the application of nanomaterials in RA treatment was searched in the Web of Science core collection (WoSCC) database (https://webofscience.clarivate.cn/wos/woscc/basic-search) from January 1, 1985 to December 31, 2023, using the search notation TS = (nano*) AND TS = (rheumatoid arthritis). Only English-language publications were included. Eligible study types encompassed original research, reviews, experimental studies, and clinical trials, while conference abstracts, reviews, and non-peer-reviewed articles were excluded. The initial search yielded a large number of results, which were subsequently screened by two authors who independently reviewed the titles and abstracts to exclude publications unrelated to the research topic. Duplicate records were identified and removed using the EndNote reference management software, followed by a manual review to ensure that no duplicates were overlooked. Any discrepancies between the authors regarding the inclusion or exclusion of articles were resolved through consensus discussions with a third author. A total of 524 articles were included in the final analysis. The study workflow is depicted in Figure 1.

Data Analysis

VOSviewer (1.6.18), CiteSpace (6.3 R1), "bibliometrix" R-package (4.4.1), and Microsoft Office Excel 2021 were used for visualization and analysis. VOSviewer was used to analyze countries and regions, institutions, author cooperation, and keyword clustering. CiteSpace was used to analyze citation bursts, keywords, and cited references. The "bibliometrix" R-package was used for quantitative evaluation of basic information such as author, institution, country, and keywords. Microsoft Office Excel 2021 and tidyverse (ggplot2) R-package were used for quantitative analysis and visual

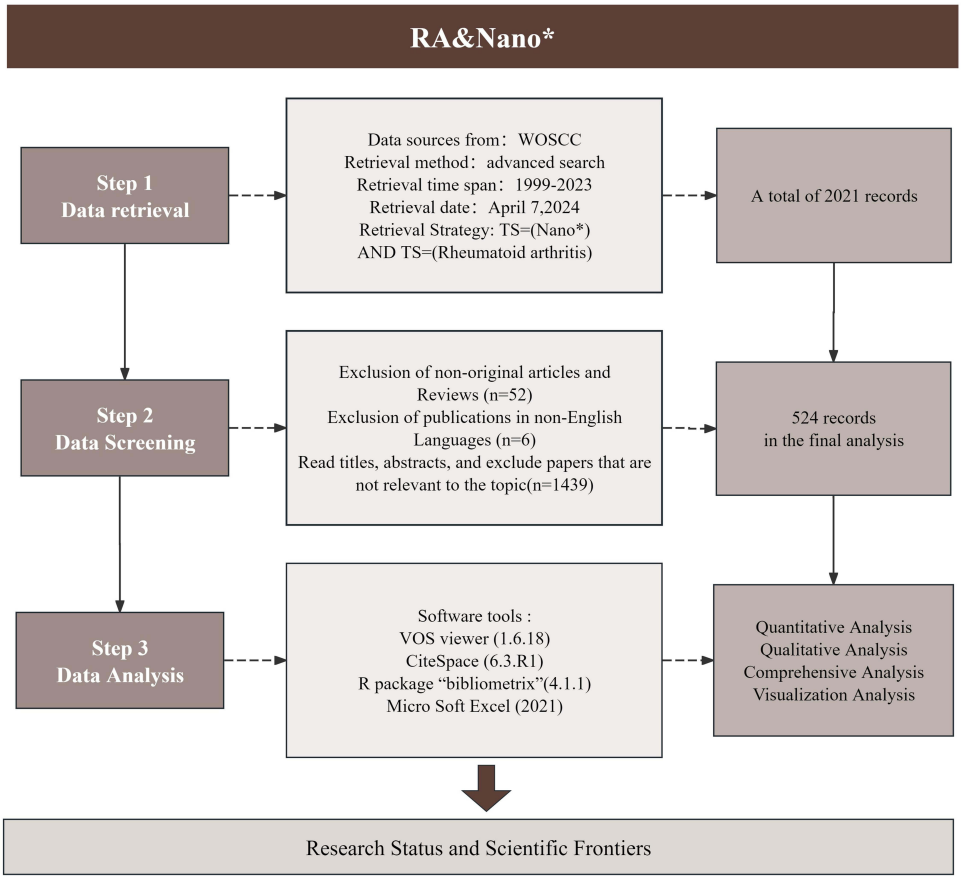

Figure 1 Flowchart of the literature screening process.

drawing. VOSviewer was applied to visualize the cooperation among countries, regions, institutions, and authors (cooperation map) and keyword clustering (co-occurrence map). In the generated plot, each dot represents an element, and the size of the dot indicates the number of publications related to the country, the institution, or the frequency of keywords. The lines connecting these points indicate the number of cooperative relationships or keyword co-occurrences, and the colors indicate different clusters or years. In addition, CiteSpace was employed to further analyze the citation outbreak, keyword time series, and citation bursts, and conduct time series analysis on literature data to show the evolution trend of citations and keywords, which helps understand the development trends in this field.

Result

Descriptive Bibliometric Analysis

A total of 524 articles on nanomaterials and RA were authored by 2751 researchers affiliated with 784 institutions across 33 countries or regions, and published in 199 journals (Table 1). The first study entitled "Suppression of collagen-induced arthritis by single administration of poly (lactic-co-glycolic acid) nanoparticles entrapping type II collagen: a novel treatment strategy for induction of oral tolerance" was published by a Korean scholar Kim WU in Arthritis Rheum in 2002, who developed a nanodrug delivery system named "poly(lactic-co-glycolic acid) nanoparticles encapsulating type II collagen", which was successfully employed for the treatment of collagen-induced arthritis (CIA) mice.[11] In the early stage, there was a low publication rate in this field. However, with the rapid advancements in nanotechnology, the number of published papers has significantly surged since 2015, reaching 95 by 2023, with an average annual growth rate of 27.08%. The polynomial curve analysis demonstrated a positive correlation between the yearly publication count and the publication year ($R^2 = 0.9415$), indicating an upward trend in article numbers (Figure 2). Numerous scholars continue to explore the application of nanotechnology in RA diagnosis and treatment.

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Table 1 Main Information Identified by the Bibliometric Analysis

Rank	Main Information	Results	Rank	Main Information	Results
1	Timespan	2002–2023	9	Author's Keywords (DE)	1254
2	Journal	199	10	Authors	2751
3	Documents	524	11	Authors of single-authored docs	1
4	Annual Growth Rate%	24.22	12	Co-Authors per doc	7.19
5	Document Average Age	4.83	13	International co-authorships%	24.05
6	References	20439	14	Average citations per doc	29.76
7	Keywords Plus (ID)	1287	15	Average citations per year per doc	4.502
8	Country or region	33	16	Institution	784

Research Countries and Institutions

The 524 studies were contributed by authors from 33 countries/regions The top five countries with the highest publication output were China (239), India (69), the United States (36), South Korea (35), and Pakistan (21) (Table 2). Since 2017, China has witnessed exponential growth in the number of publications, establishing itself as the leading country in terms of annual publication count (Figure 3A). Figure 3C represents the publication counts across different countries. Simultaneously, we conducted a comprehensive analysis by tallying the total number of citations received by published papers in each country and calculating their average citation count, as shown in the Figure 3B. The top 10 most cited countries were China (5646), followed by the United States (2231), South Korea (2147), India (1315), Iran (560), Pakistan (457), Portugal (420), Denmark (373), Japan (316), and Germany (234). However, the top 10 countries with the highest average citation frequency were the United States (61.97), South Korea (61.34), Denmark (53.29), Portugal (46.67), Iran (35.00), Germany (33.43), Japan (31.60), China (23.62), Pakistan (21.76), and India (19.06). Figure 3D depicts the cooperation around the world. The United States had the highest level of international research collaborations (63). The most research collaborations were between China and the United States(30).

A total of 784 institutions worldwide were engaged in research related to nanotechnology and RA, of which the institution with the largest output is Jilin University (8), but the total number of citations is only 238 times, failing to enter the top 10 most influential institutions. It is worth noting that although the University of California, San Diego and Stanford University in the United States only published one paper, the total citations were as high as 543 and 361 times, respectively, indicating that

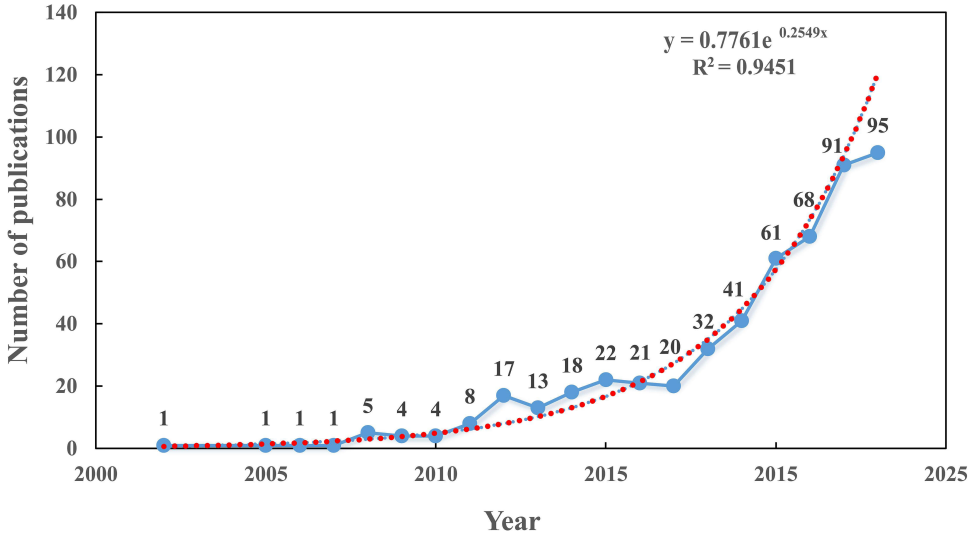

Figure 2 Global publication growth trends from 2002 to 2023.

Table 2 Top 10 Countries with the Most Publications

Rank	Country	Articles	Freq	SCP	MCP	MCP_Ratio
1	China	239	0.4561	204	35	0.146
2	India	69	0.1317	55	14	0.203
3	USA	36	0.0687	24	12	0.333
4	Korea	35	0.0668	27	8	0.229
5	Pakistan	21	0.0401	15	6	0.286
6	Iran	16	0.0305	12	4	0.250
7	Egypt	15	0.0286	10	5	0.333
8	Japan	10	0.0191	10	0	0.000
9	Portugal	9	0.0172	8	1	0.111
10	Brazil	8	0.0153	7	1	0.125

American institutions conducted high-quality research. China, South Korea, India, scholars number is more, total cited frequency is limited, but the quality remains to be improved (Table 3). In addition, the intensity of cooperation between institutions is not high at present, and most institutions conduct related research independently.

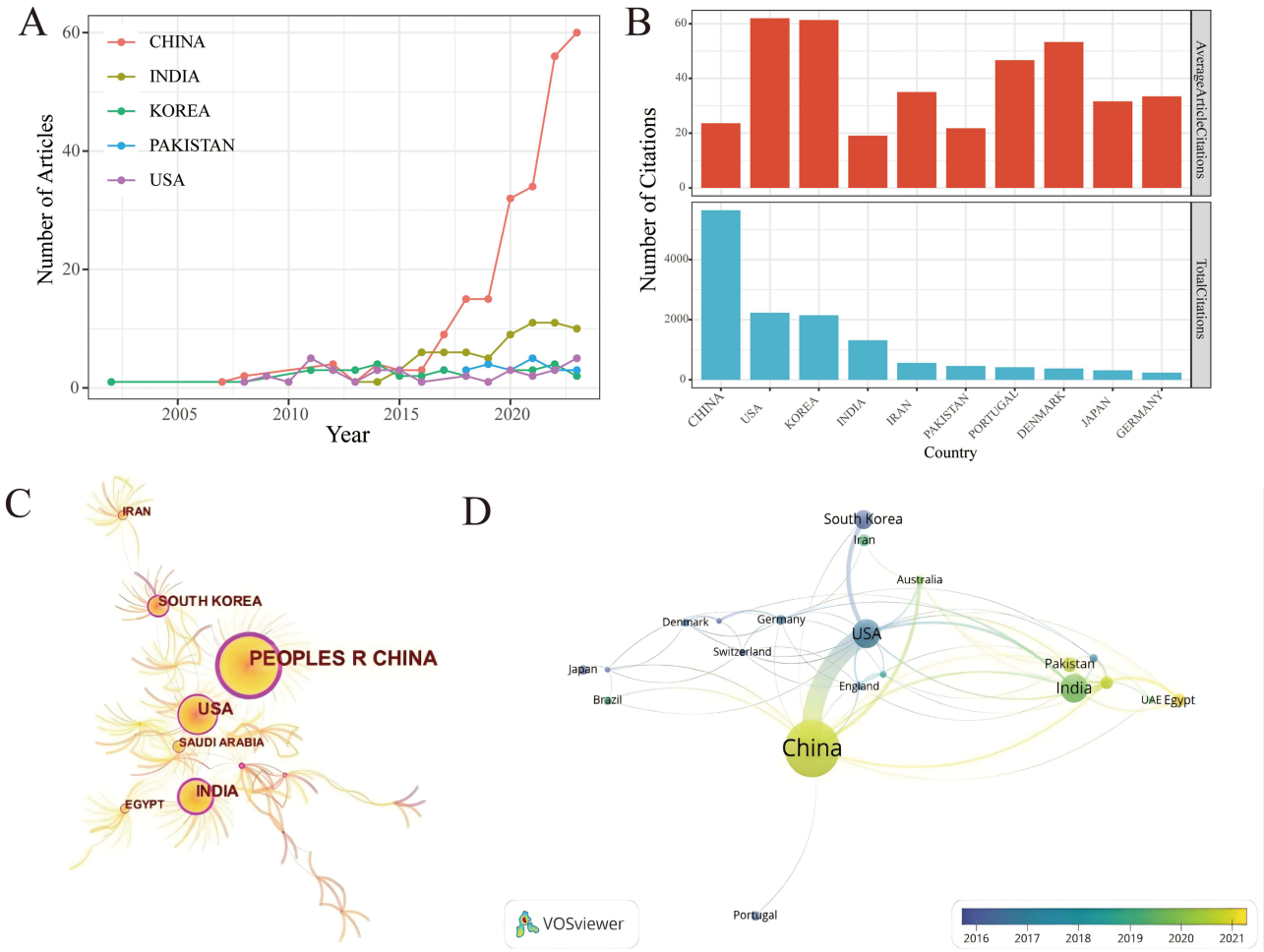

Figure 3 (**A**) Top five countries according to annual scientific production; (**B**) The top 10 countries with the highest cumulative citation count and the average number of citations for these countries; (**C**) Visualization of national scientific productions; (**D**) Visualization of international cooperation.

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Table 3 Top 10 Most Influential Institutions

Rank	Affiliation	Country	Total Cites	Articles
1	University of California at San Diego	USA	543	1
2	Sungkyunkwan University	Korea	406	5
3	Stanford University	USA	361	1
4	Panjab University	India	346	5
5	Yonsei University	Korea	306	2
6	Seoul National University	Korea	298	1
7	Korea Institute of Science and Technology	Korea	251	3
8	Changchun Institute of Applied Chemistry	China	251	2
9	Sichuan University	China	246	5
10	Aarhus University	Denmark	239	1

Analysis of Journals and Co-Cited Journals

The 524 articles were published in 199 academic journals. The Journal of Controlled Release published the highest number of articles and had the highest impact factor. In addition, the International Journal of Pharmaceutics, Biomaterials, International Journal of Nanomedicine, and ACS Nano ranked in the top 10 in terms of the number of publications and co-citations, providing important references in the field of nanometer materials and RA-related research. According to the 2024 journal citation reports (JCR) data, the other cited journals were distributed in the Q1 region, except for Arthritis Research & Therapy and International Journal of Nanomedicine, which were distributed in the Q2 region. Particularly, Advanced Drug Delivery Review, with an impact factor of 98.7, ranked the highest among the most cited journals, and thus research on this topic has a significant influence (Table 4).

Analysis of Authors and Collaboration Networks

The H-index is an important indicator for evaluating the influence of an author based on the quality and quantity of their published papers.[12] Table 5 presents the top 10 authors with the highest H-index, of whom PARK JH and PARK JS were from South Korea, while the remaining authors were from China. It is noteworthy that PARK JS remains the pioneering figure in nanotechnology research in the field of RA, which has greatly contributed to his high H-index and significant academic influence. Despite their relatively late entry into this domain, six Chinese authors, including CHEN X, SUN FY, and TENG LS, managed to publish numerous articles within a short period gaining recognition within the academic community. They represent crucial emerging forces in this particular field. Furthermore, although ZHANG Y had a substantial publication count, her citation numbers were comparatively lower, which resulted in a lower H-index and her absence from Table 5. Figure 4 illustrates author collaborations wherein nodes are sparsely distributed, indicating insufficient closeness in terms of collaborative efforts. This may be attributed to factors such as disciplinary boundaries, geographical concentration, and fragmented research directions. Representative South Korean scholars, such as PARK

Table 4 Top 10 Journals and Co-Cited Journals

Rank	Journal Title	Articles	JCR/IF	Co-Cited Journals	N.LC	JCR/IF
1	Journal of Controlled Release	25	Q1/10.8	Journal of Controlled Release	988	Q1/10.8
2	International Journal of Pharmaceutics	24	Q1/5.8	Biomaterials	734	Q1/14.0
3	International Journal of Nanomedicine	20	Q1/8.0	Annals of the Rheumatic Disease	652	Q1/27.4
4	Biomaterials	15	Q1/14.0	International Journal of Pharmaceutics	575	Q1/5.8
5	ACS Nano	14	Q1/17.1	ACS Nano	565	Q1/17.1
6	Journal of Drug Delivery Science and Technology	12	Q1/5.0	Arthritis & Rheumatology	511	Q1/13.3
7	Colloids and Surfaces B: Biointerfaces	10	Q1/5.8	Nature Reviews Rheumatology	463	Q1/98.5
8	Drug Delivery	10	Q1/6.0	Arthritis Research & Therapy	452	Q2/4.9
9	Chemical Engineering Journal	9	Q1/15.1	International Journal of Nanomedicine	434	Q2/8.0
10	Nanomedicine	9	Q1/5.5	Advanced Drug Delivery Review	305	Q1/98.7

Table 5 Top 10 Most Influential Authors Ranked by the H Index

Author	H Index	G Index	TC	NP	PY_start	Country
CHEN X	8	10	366	10	2018	China
LI CH	8	10	477	10	2017	China
PARK JH	8	9	560	9	2013	Korea
SUN FY	8	11	261	11	2017	China
ZHENG X	8	9	197	9	2021	China
KIM K	7	7	695	7	2011	Korea
LI YX	7	10	216	10	2017	China
LIU Y	7	9	91	9	2012	China
PARK JS	7	8	679	8	2002	Korea
TENG LS	7	9	224	9	2017	China

JH, tend to lead independent research efforts within single institutions. While emerging Chinese authors are highly productive, their collaborations are largely confined to domestic institutions.

WoSCC Research Areas

To facilitate classification, Clarivate Analytics classifies research papers in different research areas in the WoSCC database. Generally, each paper can be classified into at least one research area in the WoSCC database. The statistics on research areas can help grasp the changing focus of research in a particular field.[13] We analyzed the research fields of nanotechnology applied to RA and found that the number of fields covered increased from 1 in 2002 to 19 in 2020, with an overall fluctuating growth trend (Figure 5A). There were 491 papers in the top 10 most active research areas, covering 93.70% of the literature in this field, mainly involving biochemistry and molecular biology, biotechnology and applied microbiology, chemistry, engineering, immunology, materials science, pharmacology and pharmacy, physics, and research and experimental medicine. The annual

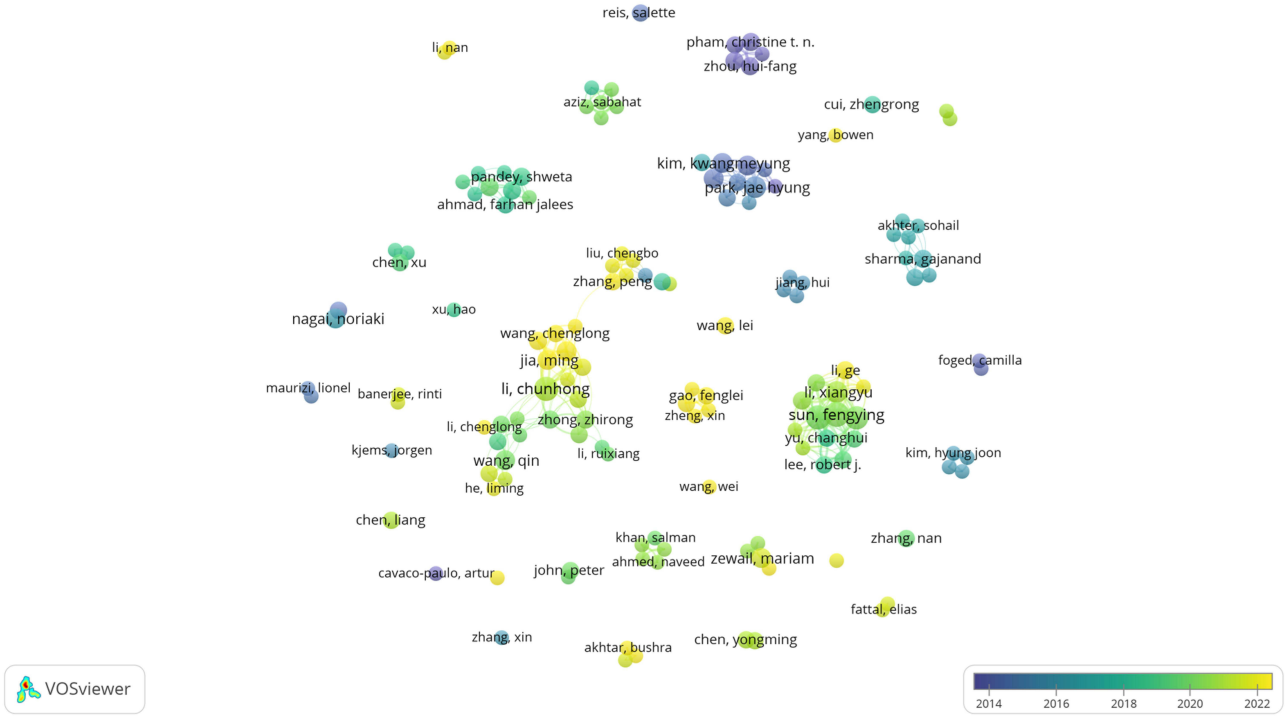

Figure 4 Visualization of author collaboration.

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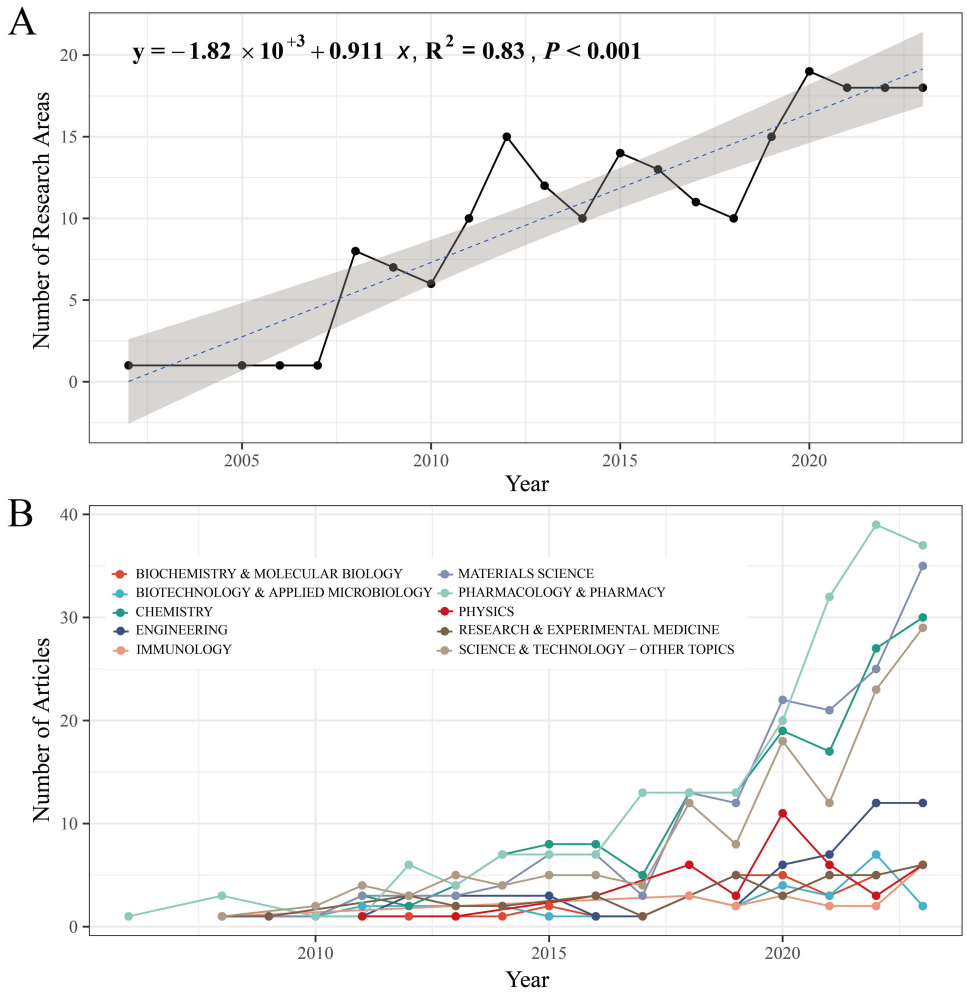

Figure 5 (**A**) Annual changes in the number of WOS research areas; (**B**) Annual Publication Trends in the Top Ten WOS research areas.

changes in the top 10 most productive fields by line plots are displayed in Figure 5B, among which pharmacology had the highest number of publications and remained the research focus in this field.

Analysis of the Most Influential Publications and Citation Bursts

The top ten most cited publications are shown in Table 6. Among them, "Neutrophil membrane-coated nanoparticles inhibit synovial inflammation and alleviate joint damage in inflammatory arthritis"[14] was published in Nature Nanotechnology in 2018 had the highest total number of citations, up to 543, with an average of 77.57 citations per year, indicating its high quality. Another study published in the journal Nano Letters of "Gold nanoparticles: a revival in precious metal administration to patients"[15] was cited 361 times, ranking second, but it was cited 25.79 times per year on average. The corresponding authors of both articles are from the United States, and three of the top ten most cited publications are from China, indicating that both the United States and China provide a certain number of high-quality publications in this field.

The term "citation burst" refers to the time frame in which an academic paper or research result receives a large number of citations, underscoring the academic impact and importance of a publication.[16] Figure 6 depicts the top 15 citation bursts in the literature ranked by citation burst intensity. The earliest citation burst occurred in 2013, the latest occurred in 2021, and the longest burst occurred across four years. The most recent burst was from LI, a scholar at Fudan University in China, who published a study entitled "Route to Rheumatoid Arthritis by Macrophage-Derived Microvesicle-Coated Nanoparticles" in Nano Letters in 2019. This study developed a Macrophage-Derived

Table 6 Top ten Papers According Total Citation

Rank	Paper	DOI	TC	TC per Year	Country
1	ZHANG QZ, 2018, NAT NANOTECHNOL	10.1038/s41565-018-0254-4	543	77.57	USA
2	THAKOR AS, 2011, NANO LETT	10.1021/nl202559p	361	25.79	USA
3	KIM J, 2019, ACS NANO	10.1021/acsnano.8b08785	298	49.67	Korea
4	HOWARD KA, 2009, MOL THER	10.1038/mt.2008.220	239	14.94	Denmark
5	YANG YH, 2021, BIOMATERIALS	10.1016/j.biomaterials.2020.120390	207	51.75	China
6	LEE SM, 2013, ACS NANO	10.1021/nn301215q	201	16.75	Korea
7	LI RX, 2019, NANO LETT	10.1021/acs.nanolett.8b03439	192	32.00	China
8	ABOLMAALI SS, 2013, CANCER CHEMOTH PHARM	10.1007/s00280-012-2062-0	179	14.92	Iran
9	JAIN S, 2015, BIOMATERIALS	10.1016/j.biomaterials.2015.05.028	170	17.00	USA
10	TSAI CY, 2007, ARTHRITIS RHEUM-US	10.1002/art.22401	168	9.33	China

Microvesicle (MMV)-Coated Nanoparticle (MNP) and the targeting effect of MNP in the CIA mice was significantly augmented. The targeting mechanism was revealed by proteomic analysis, and Mac-1 and CD44 were considered to be responsible for the significant targeting effect of MNP. The study also included the model drug tacrolimus, which was encapsulated in MNP (T-RNP) packages and significantly suppressed the progression of RA in mice. This literature is still in the citation explosion stage.[17]

Analysis of Keyword

The core and essence of a paper are encapsulated in keywords. Keyword co-occurrence analysis not only enables the identification of research hotspots within a scientific field but also provides an effective means to comprehend the research direction of a specific topic. The "Most Frequent Words" analysis using the "bibliometrix" R-package revealed that in addition to rheumatoid arthritis and nanoparticles, the most frequent keywords were delivery (97), drug-delivery (77), collagen-induced arthritis (69), inflammation (59), therapy (58), in-vitro (54), methotrexate (54), and cells (40) (Figure 7A).

To present the research hotspots more intuitively, VOSviewer was utilized to create a network visualization of the 524 articles based on the co-occurrence of keywords. The links between articles were established based on the strength of keyword co-occurrence. Forty-one keywords that appeared at least 20 times were selected for visualization purposes. These terms were further divided into four distinct network clusters (Figure 7B), with green and yellow clusters being the largest ones, comprising 19 and 10 terms respectively. The themes within the green cluster primarily revolved around

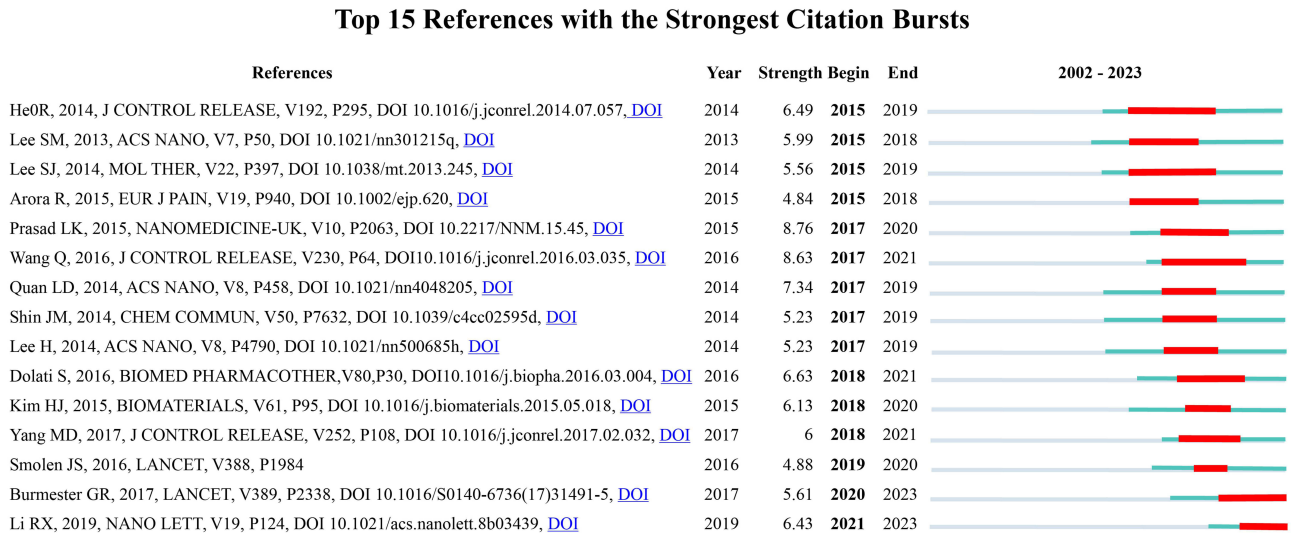

Figure 6 Top 15 references with stronger citation burst.

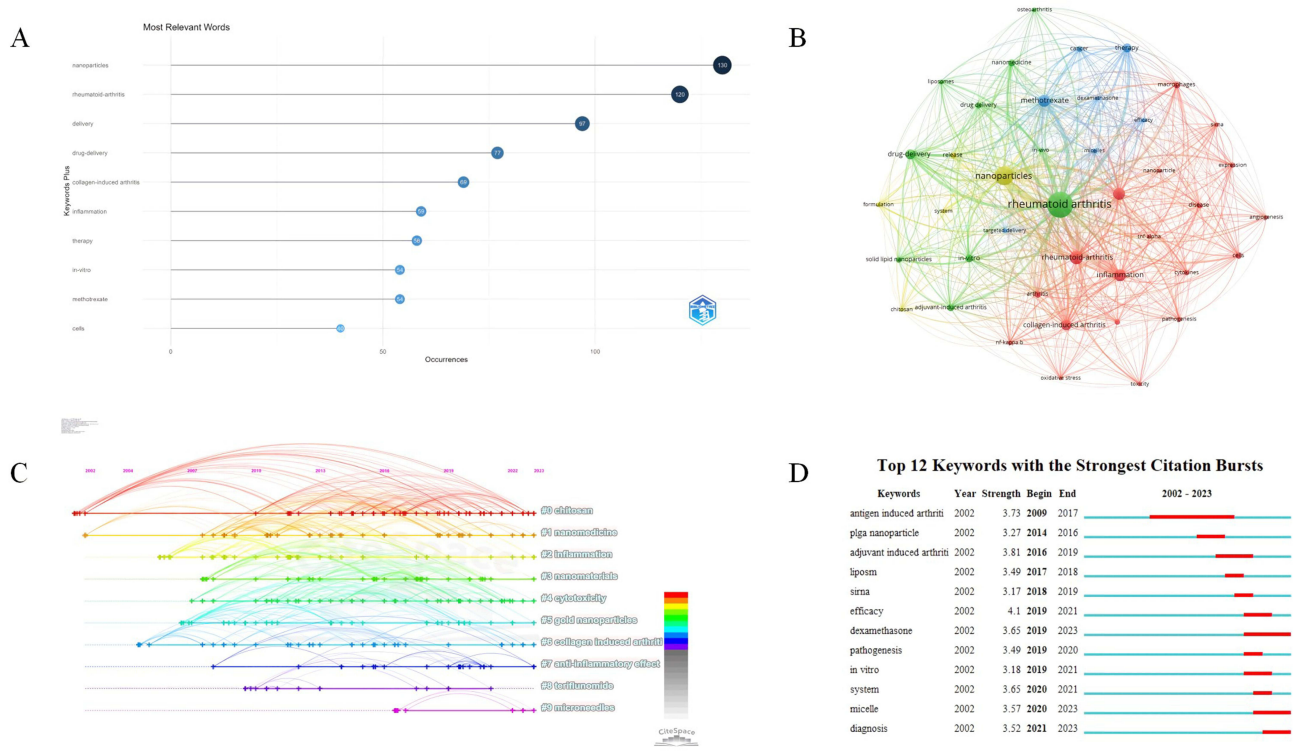

Figure 7 (**A**)Top 10 keywords with the highest frequency; (**B**)Clustering analysis of keywords; (**C**) Keyword co-occurrence clustering map; (**D**)Top 12 keywords with the strongest citation burst.

RA, angiogenesis, cells, collagen-induced arthritis, cytokines, delivery, etc., while topics within the yellow cluster mainly focused on drug delivery aspects such as nanomedicine and drug delivery systems both in vitro and in vivo.

CiteSpace was employed to generate a keyword timeline (Figure 7C). Ten keywords, including "chitosan", "nanomedicine", "inflammation", "nanomaterials", "cytotoxicity", "gold nanoparticles", "collagen-induced arthritis", "anti-inflammatory effect", "teriflunomide" and "microneedles", were clustered. The "chitosan" cluster appeared the earliest and lasted the longest, highlighting its research significance in this field. All other clusters were a hot topic in 2023, except for "teriflunomide".

The 12 keywords with the strongest citation burst are shown in Figure 7D. Among them, "efficacy" was the keyword with the strongest citation burst, indicating that this field paid more attention to the clinical efficacy of nanomaterials in the treatment of RA. In addition, the longest-lasting keyword was "antigen-induced arthritis" (AIA), which refers to animal models in which researchers mimic the pathogenesis and pathophysiology of RA by inducing joint inflammation in mice or rats by injection of specific antigens (such as collagen). This indicates that the application of nanotechnology in RA is still mainly focused on basic research. Additionally, keywords such as "dexamethasone", "micelle", and "diagnosis" continued to attract attention in 2023, implying that these are still hot research topics.

Discussion

Nanotechnology and RA research have developed rapidly in recent years. However, there is still a dearth of bibliometric studies in this field. The present study provides a systematic review of the current research status and potential research hotspots of RA nanotechnology. To the best of our knowledge, this is the first bibliometric analysis of literature in this field between 1985 and 2023. Research trends and changes in this field are summarized as follows.

General Information

Relevant studies on nanotechnology and RA were thoroughly searched in the WoSCC database from 1985 to 2023. A total of 2751 authors from 784 institutions in 33 countries or regions published 524 studies on nanotechnology and RA

in 199 journals. Although the annual number of papers related to nanotechnology and RA showed an overall upward trend, the growth trend was not obvious due to the small number of papers published in the early stage. However, the number of published papers increased rapidly since 2015. The annual number of publications indicates that this is an emerging field and predicts future research prospects. The most influential author was CHEN X from China. Meanwhile, China also emerged as the most productive and cited country. However, the average number of citations of Chinese publications was low because of the low-quality papers. China and the United States had the most research collaborations in this field. Many countries independently conduct research in this field, which suggests that academic barriers—such as competition, intellectual property concerns, discrepancies in global research standards, and limited funding—impede cross-border collaboration among researchers. This underscores the necessity for future collaborative efforts. At present, the related field of nanotechnology for the treatment of RA involves 19 disciplines such as biochemistry and molecular biology, chemistry, engineering, immunology, and materials science, which indicates that the research in this field is extensive. The journal impact factor of the top 10 Q1 journals in JCR partitions was above 5 points, suggesting that high-quality research is being carried out in this field. Moreover, the Journal of Controlled Release was the most prolific and cited journal. The article "Nanotherapeutics alleviate rheumatoid arthritis" garnered 84 citations, serving as a pivotal reference for comprehending the intersection of nanotechnology and RA.[18] Notably, in this journal, almost all RA nano therapy-related publications between 2019 and 2023 were from China, suggesting that the Chinese government is paying close attention to quality issues, thereby gradually improving the quality of research.

Knowledge Base

By consulting highly cited papers, a comprehensive understanding of related research on nanotechnology and RA can be obtained. Gold nanoparticles (AuNPs) are one of the highlights in agro-scientific research in nanotechnology and can more easily penetrate the joint tissue owing to their excellent chemical stability and biocompatibility, as well as their smaller size, inhibiting the inflammatory response to alleviate the symptoms of RA, to relieve pain and swelling of the joints.[19,20] Tsai et al observed the binding of 13 nm AuNPs to vascular endothelial growth factor in human RA synovial fluid, and its effect on RA synovial fluid induced endothelial cell proliferation and migration, demonstrating for the first time that intra-articular administration of AuNPs can improve the clinical course of RA by inhibiting angiogenic factors and reducing macrophage infiltration and inflammation.[21] AuNPs can absorb and convert light energy to generate heat, increasing the local temperature, and thereby causing cell apoptosis, necrosis, or the release of heat-sensitive drugs to achieve therapeutic effects.[22,23] However, AuNP photothermal therapies have mainly been used to treat cancer. Lee et al attempted to explore this property of AuNPs for the treatment of RA. Given that synovial hyperplasia of RA is similar to solid tumors in terms of capillary leakage and other aspects, they developed arginine (R)-glycine (G)-aspartic acid (D) (RGD)-attached gold (gold) half-shell nanoparticles coated with methotrexate (MTX). Under near-infrared irradiation, the gold half-shell generates heat and the drug is rapidly released from the poly (lactic-co-glycolic acid) (PLGA) nanoparticles, thereby achieving photothermally controlled drug delivery. It was found that MTX nanoparticles containing small doses, when used in combination with near-infrared irradiation, showed greater therapeutic effects than conventional MTX solutions in CIA mice.[24] However, the cost of preparation of AuNPs is relatively high, and the long-term safety of treatment remains elusive. Studies have shown that the particle size, surface modification, and particle shape of AuNPs can affect their toxicity in vitro, as well as their blood circulation, biodistribution and accumulation, and the immune system in vivo.[25,26]

Natural biomimetic nanomaterials, such as liposomes, albumin, extracellular vesicles, etc., are also often used in this field. These nanomaterials are usually derived from organisms and have natural biocompatibility and biodegradability and diverse structures and functions, which can simulate complex biological processes in organisms, such as molecular recognition and cell signaling.[27–29] Compared with AuNPs, these nanomaterials are safer and environmentally friendly and have better tissue permeability and targeting, which improves the therapeutic effect.[30] Cell-coated nanoparticles are promising natural biomimetic nanoparticles that use biological methods to wrap cell membranes on the surface of nanoparticles, thereby endowing nanoparticles with characteristics and functions similar to the original cells. This technique combines the advantages of biology and nanotechnology, to overcome challenges posed by the traditional application of nanoparticles, such as immune rejection, biological incompatibility, lack of targeting, etc.[31–33] By fusing

neutrophil membranes to polymer nuclei, Zhang et al developed neutrophil membrane-coated nanoparticles that inherit the antigenic appearance and associated membrane functions of the source cells, making them ideal baits for neutrophil targeting biomolecules to bind immunomodulatory molecules. These nanoparticles have been shown to neutralize proinflammatory cytokines, inhibit synovial inflammation, penetrate deep into the cartilage matrix, and provide strong cartilage protection against joint damage. Neutrophil membrane-coated nanoparticles showed significant therapeutic effects in a CIA mouse model and a human transgenic mouse model of arthritis by improving joint damage and inhibiting the overall severity of arthritis.[14] Li et al developed macrophage-derived microvesicle (MMV)-coated nanoparticles (MNPs) and evaluated the inflammation-mediated targeting ability of MNPs in vitro and in vivo. The results showed that MNPs exhibited stronger binding to inflammatory human umbilical vein endothelial cells (HUVECs) than erythrocyte membrane-coated nanoparticles (RNPs) in vitro and significantly enhanced targeting in vivo in the CIA mouse model. The targeting mechanism was subsequently revealed by proteomic analysis, which showed that Mac-1 and CD44 played a significant targeting role of MNPs. Meanwhile, MNPs encapsulated tacrolimus significantly inhibited the progression of RA in mice, indicating that MNPs may have certain clinical value.[17]

The pathogenesis of RA involves intricate cellular and molecular interactions. Although its mechanism remains unclear, it is closely associated with autoimmune disorders and inflammation.[34,35] The infiltration of synovial tissue by various inflammatory cells, especially macrophages, is one of the important factors in the pathogenesis of RA. Activation of M1 macrophages produces a series of inflammatory cytokines, such as TNF-α/β and IL-6, IL-1, to maintain and increase joint inflammation. Therefore, targeting macrophages and inflammatory states is considered an important therapeutic target for relieving RA symptoms.[36,37] To alleviate synovial inflammation, Yang et al developed folate-modified silver nanoparticles (FA-AgNPs) to eliminate M1 macrophages or convert them to an anti-inflammatory M2 phenotype. Research indicates that M1 macrophages can be specifically targeted by enhancing the expression of folate receptors on their surface. After entering cells, FA-AgNPs dissolve and release Ag+ to cope with intracellular glutathione, thereby promoting the apoptosis of M1 macrophages and scavenging reactive oxygen species (ROS) to promote the polarization of M2 macrophages to achieve therapeutic effects. FA-AgNPs were gradually cleared from the body mainly through feces after treatment, without tissue accumulation and with no obvious long-term toxicity.[38] Jain et al successfully encapsulated the plasmid DNA encoding IL-10 anti-inflammatory cytokine onto alginate nanoparticles and targeted the tuftsin peptide on the surface of the nanoparticle to achieve macrophage activity. 6 days after intraperitoneal injection, 66% of macrophages in the synovium of arthritic rats were in the M2 state. The reduction of proinflammatory cytokines in the whole body and joint tissues indicated that this method could repolarize macrophages from M1 to M2 functional subtype and prevent the progression of inflammation and joint damage.[39] Kim et al developed manganferrite and cerium nanoparticle anchored mesoporous silica nanoparticles (MFC-MNS) that synergistically scavenged ROS and produced O2 to reduce M1 macrophage levels and induce M2 macrophages for RA therapy.[40] Small interfering RNA (siRNA) is a type of short double-stranded RNA molecule, usually composed of about 20–25 bases, with a specific sequence, which can mediate gene silencing by targeting RNA interference pathway. It is one of the natural gene regulatory mechanisms in cells and has certain advantages in the treatment of RA.[41,42] However, it has the characteristics of large volume, strong hydrophilicity, and anionic charge, limiting its ability to enter cells, and thus requires different drug delivery carriers to achieve delivery.[43] Howard et al developed chitosan/siRNA nanoparticles and administered them intraperitoneally to CIA mice and found that chitosan/siRNA nanoparticles reduced the expression of TNF-α in the whole-body macrophages and improved the inflammatory state in CIA mice.[44]

Emerging Topics

Keywords are usually the core concepts of research topics. The study of core keywords in bibliometrics helps to explore important and emerging topics and provides valuable insights for the development of the respective field. By identifying the most significant citation bursts associated with specific keywords through CiteSpace, “dexamethasone” and “micelle” were identified as the main areas of future research.

Dexamethasone (DEX) is a type of long-acting and potent glucocorticoid. Its mechanism of action is that the glucocorticoid receptor binds to the glucocorticoid, and then reaches the nucleus to reduce the activity of nuclear factor-kappa B, thereby reducing the production of inflammatory cytokines to alleviate inflammation. However, due to the

widespread distribution of glucocorticoid receptors in the body, the use of DEX may lead to cardiovascular disease, muscle atrophy, peptic ulcer, osteoporosis, and other toxic side effects.[45–47] The precise delivery of drugs to inflammatory sites by nanotechnology is an important strategy to reduce toxic side effects.[48] The delivery and release mechanisms of DEX have been optimized through nanotechnology. Dextran sulfate (DS)-modified DEX-loaded flexible liposome hydrogel (DS-FLS/DEX hydrogel),[47] N-(2-hydroxypropyl) methacrylamide copolymer nanocellulators,[49,50] Acetone-Based Ketal-Linked Nanomedicine by Dexamethasone Prodrugs (AKP-dexs),[51] 18 amine functional nano diamond (ND-oda),[52] beta CD/PAA nano gel (nanodexa),[53] liposomes (L-Dex), nuclear crosslinked micelles (M-Dex) and slow-release polymer prodrug (P-Dex-missile) and quick release polymer prodrug (P-Dex-fast)[54] have been developed. These carriers can increase the concentration of DEX in the inflammatory area of arthritis, improve the bioavailability of the drug, and reduce systemic exposure, thereby reducing the impact on other organs. Despite these encouraging findings, the application of nanotechnology in the field of DEX drug delivery is still at a relatively nascent stage. Future studies are warranted to address the question of how to achieve the manufacturing, stability, cost-effectiveness, and regulatory approval of these systems in a clinical setting. With more clinical trials and technological development, it is anticipated that nanotechnology will play an important role in improving the efficacy of DEX in the treatment of RA.

Micelle is a nanoscale structure formed spontaneously by amphiphilic molecules in aqueous solution. The formation process involves the outward interaction of the hydrophilic part with water molecules, while the hydrophobic part is oriented inward to form a hydrophobic core. This structure enables the micelle to carry and transport hydrophobic drug molecules within its interior.[55] Micellar drug delivery systems in rheumatoid arthritis offer several advantages. Primarily, micelles enhance the solubility, stability, and bioavailability of drugs. Moreover, they can target drug delivery to inflamed areas, reducing potential side effects throughout the body. For example, Li et al synthesized the microenvironment targeting micelles (PVGLIG-MTX-Que-Ms) by thin film hydration method, and tested the drug-loaded micelles in vitro for their sustained release performance, low cytotoxicity, strong targeting and anti-inflammatory properties. In vivo, the drug-loaded micelles can accumulate in joints for a long time to improve drug availability.[56] Zhou et al, synthesized a micelle named HA@RH-CeO_2 that utilizes HA as a biocompatible carrier and incorporates a cerium oxide nanoenzyme responsive to ROS. The micelle showed precise delivery of the nanoenzyme and RH to M1 macrophages into the inflamed synovial tissue. This targeted delivery system effectively reduced local inflammation in RA. Although micelles can effectively deliver rheumatoid arthritis drugs, their design, cost, biocompatibility, and patient specific conditions need to be optimized for clinical application.[57] Each nanomaterial has advantages and disadvantages, which explains why different nanomaterials have been developed and evaluated, and the appropriate nanomaterials should be selected according to the specific clinical situation.[58]

Traditional diagnostic methods for RA, such as autoantibody detection and imaging, provide valuable information, but their limitations in sensitivity and specificity can lead to missed diagnoses, particularly in atypical cases. This has spurred significant research interest in the potential of nanotechnology for RA diagnosis. The recent advancements in the field of nanotechnology have led to the creation of some new diagnostic methods that combine with traditional RA diagnostic. For example, Veigas et al first reported the target-induced aggregation gold nanoprobe quantitative colorimetric detection of autoantibodies. They found that the detection speed was faster than that of the enzyme-linked immunosorbent assay, with a higher sensitivity, facilitating rapid and reliable RA screening and diagnosis.[59] Chen et al was synthesized with the leukocyte differentiation antigen (cluster of differentiation, CD) 3 monoclonal antibody combining with carboxyl of the polyethylene glycol (peg) - superparamagnetic iron oxide nanoparticles – IOPC - CD3, MRI specific targeted contrast agent, as a marker of T cell markers and tracking the T cells in the body. This approach demonstrates high target specificity in the CIA rat model, suggesting significant potential for applications in immune molecular imaging.[60] Gawne et al encapsulated GC into long-circulating liposomes, synthesized PEG-liposome GC nanoparticles, and conjugated with radioactive zirconia. In an experimental mouse model of inflammatory arthritis, the nanoparticles exhibited high uptake into inflamed joints, but also in the joints with hidden inflammation. Studies in mice have demonstrated that these visible nanomaterials not only accumulate in the target area but also alleviate inflammation within the treatment group. This promising combination of properties suggests broad applicability of these materials in the field of PET imaging.[61]

Looking ahead, several underexplored areas and technological challenges in RA nanomedicine warrant greater attention. The long-term biosafety and biocompatibility of nanomaterials within the body remain unclear, necessitating extensive preclinical and clinical studies to ensure patient safety. Achieving efficient and precise targeting of nanomedicines to RA-affected joints while avoiding unwanted accumulation in other tissues is another critical challenge that requires innovative solutions. The complex pathophysiological environment of RA, characterized by chronic inflammation and tissue remodeling, poses obstacles to the effective delivery and sustained action of nanomedicines, calling for the development of smarter nanosystems that can adapt to these conditions. Moreover, the translation of nanomedicine research into clinical practice is impeded by regulatory hurdles, the need for standardized manufacturing protocols, and the establishment of robust quality control measures. Addressing these issues will require collaborative efforts across academia, industry, and regulatory bodies to bridge the gap between laboratory research and real-world clinical application.

Innovations and Limitations

This study pioneers a systematic bibliometric analysis of the field of nanomaterials in relation to RA. By employing quantitative methods, we provide a comprehensive overview of publication and collaboration patterns, research trends, and hotspots across various levels – countries, regions, institutions, and authors. This analysis sheds light on the evolving landscape of this field, ultimately aiding researchers in navigating and understanding its current development. However, this study has some limitations that need to be acknowledged. First, we only searched publications in English in the WoSCC database and ignored those published in other languages. Therefore, our findings may not be sufficiently comprehensive. Another limitation is the inherent bias in citation analysis based on publication age. Since older cited works have had more time to be referenced, they may appear more influential than recently published high-quality research. This time bias could lead to an underestimation of the impact of newer studies.

Conclusion

In this bibliometric analysis, we describe the application of nanomaterials in the diagnosis and treatment of RA. Current research in this field prioritizes developing nanocarrier systems to target joint inflammation and enhance therapeutic efficacy for rheumatoid arthritis. Notably, micelle-based formulations and dexamethasone delivery are prominent areas of investigation, alongside advancements in diagnostic applications utilizing nanotechnology. These areas show significant potential for development. However, the field is still at its early stages, with most research conducted through animal experiments and challenges in clinical translation, interdisciplinary collaboration, and regulatory approval.

To accelerate progress, we propose the following policy recommendations: 1) Establish interdisciplinary research funding mechanisms to bridge gaps between materials science, medicine, and chemistry, prioritizing grants for joint projects involving clinicians and engineers. 2) Develop standardized regulatory guidelines for RA nanomedicines, including toxicity evaluation criteria and fast-track approval pathways for targeted therapies, drawing from existing FDA nanotechnology guidance. 3) Foster international open science platforms to share preclinical data, animal models, and manufacturing protocols, reducing redundant research and IP disputes. 4) Incentivize industry-academia partnerships through tax breaks or subsidies, encouraging pharmaceutical companies to invest in scalable nanomaterial production. 5) Integrate nanotechnology into RA precision medicine initiatives by supporting biomarker-driven clinical trials.

These findings and policy recommendations significantly contribute to the development of precision medicine for RA, enabling more individualized diagnostic and therapeutic approaches while addressing systemic barriers through policy innovation.

Abbreviations

*, a wildcard symbol to represent variations of the root term “nano”, including nanotechnology, nanomaterials, nanoscience, etc; SCP, Single Country Publications; MCP, Multiple Country Publications; TC, Web of Science Core Collection times cited count; NP, number of scientific productions; PY_start, First year published.

Data Sharing Statement

The data analyzed in this study is included in the article. Further inquiries about the data should be directly to the corresponding author.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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