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Article

Highly cited papers on biological products: A bibliometric study

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Abstract: The clinical application of biological products is increasingly extensive, bringing good therapeutic effects for patients with a variety of immune diseases. We searched the Science Citation Index Expanded (SCI-E) database in the Web of Science Core Collection (WOSCC) and selected the highly cited papers based on biological products. The literature was analyzed based on journals, countries/regions, institutions, authors, and keywords, using VOSviewer, SCImago Graphica, and CiteSpace software to generate knowledge maps and identify hotspots and trends. The 193 highly cited papers appeared in 124 journals from 59 different countries/regions. Nature Reviews Rheumatology published most of the articles, while Nature Reviews Drug Discovery had the highest number of citations. The United States had the highest number of publications, and the top institution and author was the University of California San Diego and Fabbrocini, Gabriella. The top 5 co-occurrence keywords included drug delivery, double blind, in vitro, monoclonal antibody, and in vivo. Biological products are important adjunctive therapies for the treatment of immune-mediated inflammatory diseases. Lowering the nanotoxicity of biological products, reducing adverse events due to immunogenicity, therapeutic drug monitoring (TDM) the efficacy of biological products, and producing new substances with intrinsic antimicrobial activity may be the focus and trends for future biological products research.

Keywords: bibliometric analysis; biological products; CiteSpace; VOSviewer; trends

1. Introduction

The main categories of biological products include extractions of a living organism (e.g., blood or blood derivatives), products from recombinant DNA (e.g., monoclonal antibodies), vaccines, and cellular and gene therapy [1]. The number of biological products development and approvals rises each year, some of them, e.g., etanercept and adalimumab, have been in clinical use for decades [2,3]. The European League Against Rheumatism (EULAR) recommends that any biological (b) DMARDs (TNFi, IL-6Ri, Co-stimulation-I, anti-B-cell (CD20)) must be added if conventional synthetic (cs) DMARDs for rheumatoid arthritis (RA) do not improve at 3 months or do not achieve target at 6 months and if there are poor prognostic factors [4]. And the EULAR recommends add-on therapy with belimumab should be considered for patients with inadequate response to standard-of-care (HCQ and GC with or without immunosuppressive agents) [5]. The bvacizumab increased the 42-month progression-free survival of ovarian cancer patients from 22.4 months to 24.1 months ($p < 0.05$) [6], and compared with traditional therapy, the biological products (etanercept (73.2%) and adalimumab (19.7%), etc.) increased the 5-year survival rate of pediatric psoriasis from 35.9% to 57.1% [7].

The first article about biological products was published in 1912 [8]. Over the past 110 years, researchers have made significant progress in biological products for clinical therapy.

However, understanding the overall progress and research trends in the field of biological products is challenging, so using bibliometric techniques for scientific analysis is essential. Getting to know the top 193 cited articles on biological products will give the researcher a more in-depth view of the current research focus. Bibliometric analysis may assist researchers adequately in a certain current research field [9]. Unfortunately, we found no similar studies in our search of the previous literature. We used bibliometric analysis to examine the research focus and trends in the field of biological products after finding 193 highly cited papers. We believe this study will accelerate the development of the biological products research field and encourage academics to generate new discoveries in this field.

2. Materials and methods

2.1. Data sources and search strategies

Data were obtained from the Science Citation Index Expanded (SCI-E] database in the Web of Science Core Collection (WOSCC). The following was the framework for the literature search: TS = (“Biological Products” OR “Biological Product” OR “Biologic Product” OR “Biologic Products” OR Biopharmaceuticals OR Biopharmaceutical OR “Biologic Pharmaceuticals” OR “Biologic Drug” OR “Biologic Drugs” OR “Biological Drug” OR “Biological Drugs” OR “Biologic Agents” OR “Biological agent”). The range of publication dates was set from inception of the database to 30 March 2024.

2.2. Bibliometric software

To conduct the bibliometric analysis, three primary tools were employed: CiteSpace 6.1.R6, VOSviewer 1.6.19, and SCImago Graphica 1.0.36. Each tool played a distinct role in analyzing and visualizing the data.

CiteSpace 6.1.R6 was used to identify key trends and influential nodes within the citation network. This tool is grounded in citation analysis theory, where the centrality of a node indicates its importance within the network. Nodes with high centrality are highlighted by purple rings, signifying pivotal points in the literature. Keywords with high centrality and citation frequency were categorized as "hotspots" of the research field, while nodes exhibiting strong citation bursts were recognized as "frontiers," representing emerging areas of study.

VOSviewer 1.6.19 was employed to visualize collaboration patterns among authors, institutions, and countries. In these visualizations, node size represented the frequency of co-occurrence, and different colors were used to indicate clusters of closely related items. This tool was particularly useful for mapping collaborative networks and identifying major contributors to the research field.

Lastly, SCImago Graphica 1.0.36 was used as a complementary visualization tool to explore and communicate the data more effectively. Its advanced graphical

capabilities allowed for clearer representation of the complex relationships and trends discovered during the analysis.

2.3. Inclusion and exclusion criteria

The language of publication is limited to English and the category of publication is limited to articles and reviews. The quick filters were used to limit highly cited papers. Ultimately, 193 records were identified (**Figure 1**).

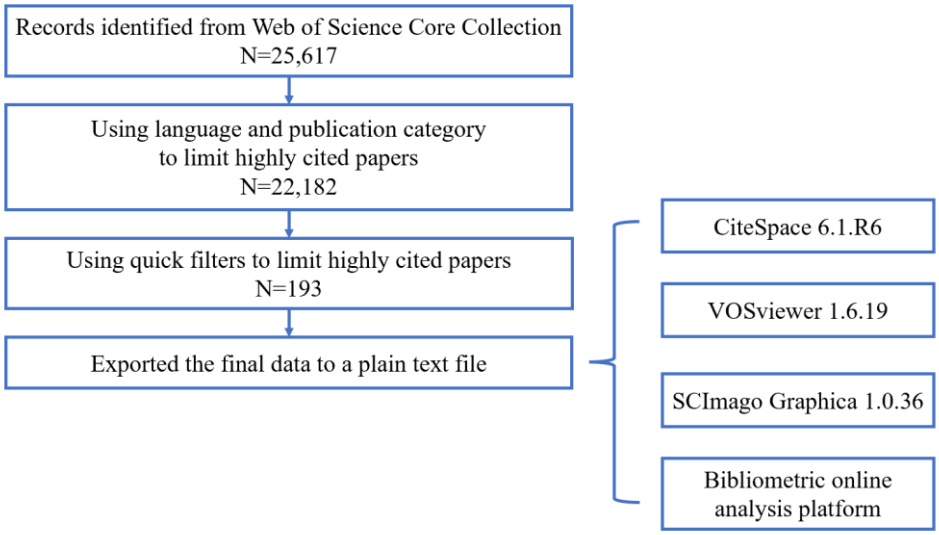


Figure 1. The flowchart for the search strategy and selection process in this study.

2.4. Data analysis

CiteSpace 6.1.R6 was used for visual analysis of journals, countries/regions, institutions, authors, and keywords, and it set Pruning (Pathfinder, pruning sliced networks), Selection Criteria (the value of King-index is changed to 25), and other parameter settings follow the initial software settings. CiteSpace 6.1.R6 was carried out to decode keyword-term frequency and co-occurrence, detect keyword terms with the strongest citation burst, and construct visualization maps, thereby uncovering Biological Products' hotspot bursts. Using VOSviewer 1.6.19 and SCImago Graphica 1.0.36, we completed studies on journals, countries/regions, institutions, and authors.

3. Results

3.1. Citation characteristics and publications

A total of 22182 documents were initially retrieved from the Web of Science Core Collection (WOSCC). After a thorough screening process, 193 highly cited papers were selected, consisting of 60 original research articles and 133 reviews. **Table 1** lists articles that have been cited more than 500 times. These papers, published between 2013 and 2023, accumulated 46,858 citations, with an average of 242.8 citations per paper, ranging from 7 to 1,491 citations. (**Figure 2**) The 2023 year encompassed the greatest number of citations (9977) and encompassed the greatest number of articles (28, 14.51%) in the highly cited papers. Furthermore, the year with

the highest average number of citations was 2022 (1 paper, 454 citations). The most cited article frequently cited articles included "Trends in GPCR drug discovery: new agents, targets and indications", which was published in 2017 in Nature Reviews Drug Discovery by Hauser, AS et al, with 1491 citations. Followed by "2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis" (1282 citations), "Overcoming the challenges in administering biopharmaceuticals: formulation and delivery strategies" (1164 citations), "Diagnosis and Management of Rheumatoid Arthritis A Review" (1126 citations) and "Osteosarcoma: Current Treatment and a Collaborative Pathway to Success" (1037 citations). The above-mentioned articles have been cited more than 1000 times.

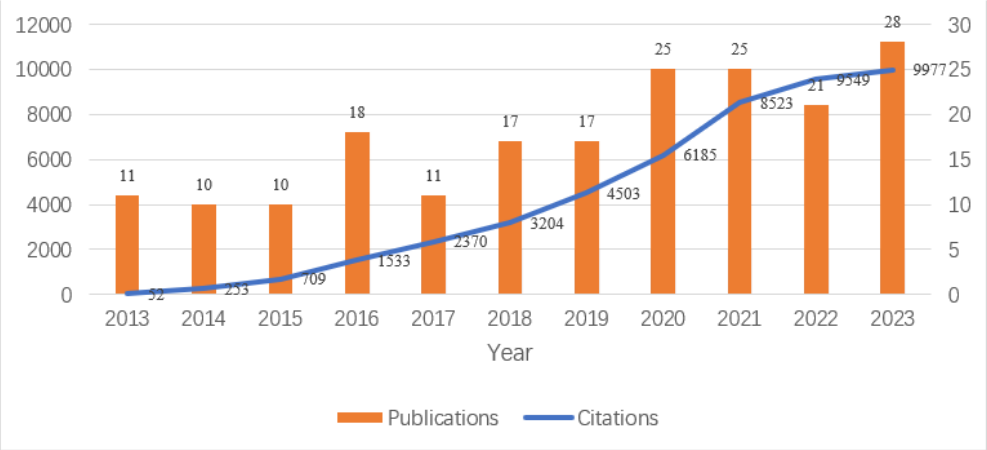


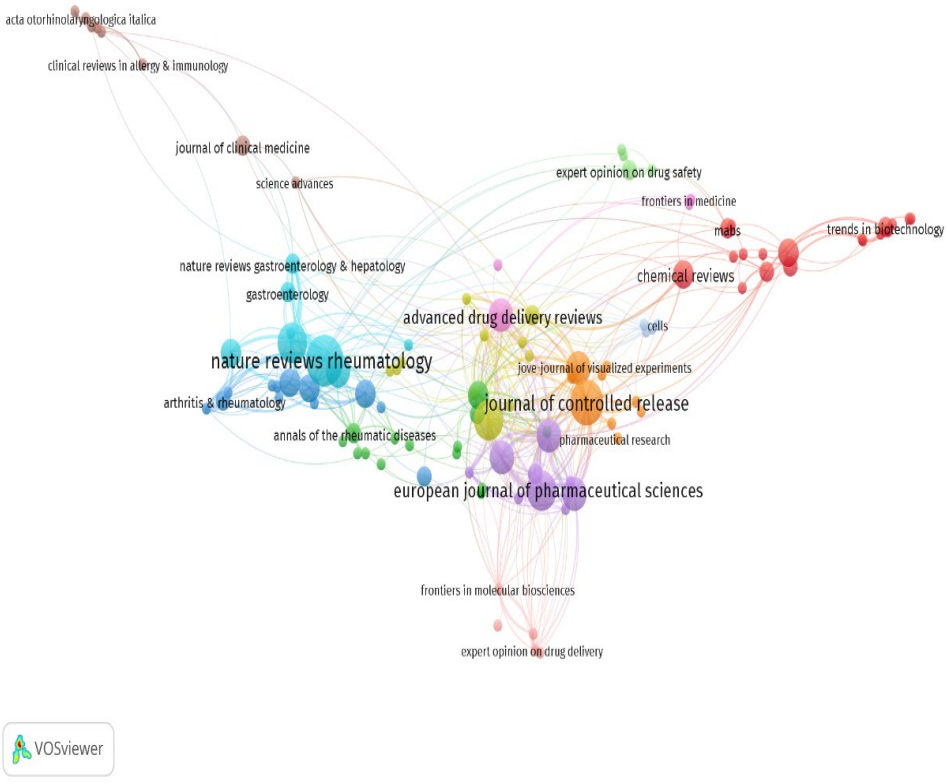
Figure 2. Frequency distribution of publications and citations by year.

Table 1. The top 22 cited papers in biological products until 2024.

Rank	Title	First Author	Citations	Journal	Year
1	Trends in GPCR drug discovery: new agents, targets and indications	Hauser AS	1491	Nature Reviews Drug Discovery	2017
2	2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis	Singh JA	1282	Arthritis & Rheumatology	2016
3	Overcoming the challenges in administering biopharmaceuticals: formulation and delivery strategies	Mitragotri S	1164	Journal of Nanobiotechnology	2014
4	Diagnosis and Management of Rheumatoid Arthritis A Review	Aletaha D	1126	Jama-journal of the American Medical Association	2018
5	Osteosarcoma: Current Treatment and a Collaborative Pathway to Success	Isakoff MS	1037	Journal of Clinical Oncology	2015
6	The Human Gene Mutation Database: building a comprehensive mutation repository for clinical and molecular genetics, diagnostic testing and personalized genomic medicine	Stenson PD	998	Human Genetics	2014
7	The promising future of microalgae: current status, challenges, and optimization of a sustainable and renewable industry for biofuels, feed, and other products	Khan MI	979	Microbial Cell Factories	2018
8	The therapeutic monoclonal antibody market	Ecker DM	949	MABS	2015
9	Repair and tissue engineering techniques for articular cartilage	Makris EA	839	Nature Reviews Rheumatology	2015
10	Mesenchymal Stem Cell Secretome: Toward Cell-Free Therapeutic Strategies in Regenerative Medicine	Vizoso FJ	758	International Journal of Molecular Sciences	2017
11	Head and Neck Squamous Cell Carcinoma: Update on Epidemiology, Diagnosis, and Treatment	Marur S	753	Mayo Clinic Proceedings	2016
12	Biopharmaceutical benchmarks 2014	Walsh G	708	Nature Biotechnology	2014
13	Renal cancer	Capitanio U	700	Lancet	2016
14	Emerging Frontiers in Drug Delivery	Tibbitt MW	690	Journal of the American Chemical Society	2016
15	Polymeric Amorphous Solid Dispersions: A Review of Amorphization, Crystallization, Stabilization, Solid-State Characterization, and Aqueous Solubilization of Biopharmaceutical Classification System Class II Drugs	Baghel S	640	Journal of Pharmaceutical Sciences	2016
16	Biopharmaceutical benchmarks 2018	Walsh G	625	Nature Biotechnology	2018
17	Protein expression in Pichia pastoris: recent achievements and perspectives for heterologous protein production	Ahmad M	618	Applied Microbiology and Biotechnology	2014
18	Understanding Asthma Phenotypes, Endotypes, and Mechanisms of Disease	Kuruvilla ME	614	Clinical Reviews in Allergy & Immunology	2019
19	Therapeutic miRNA and siRNA: Moving from Bench to Clinic as Next Generation Medicine	Chakraborty C	552	Molecular Therapy-Nucleic Acids	2017
20	Estimated Research and Development Investment Needed to Bring a New Medicine to Market, 2009–2018	Wouters OJ	547	Jama-journal of the American Medical Association	2020
21	The role of biomass and bioenergy in a future bioeconomy: Policies and facts	Scarlat N	505	Environmental Development	2015
22	PEGylation of Biopharmaceuticals: A Review of Chemistry and Nonclinical Safety Information of Approved Drugs	Turecek PL	502	Journal of Pharmaceutical Sciences	2016

3.2. Analysis of journals

A total of 124 journals were identified in the 193 highly cited papers. The journal with the most publications was Nature Reviews Rheumatology (N = 7), followed by Journal of Controlled Release (N = 6) (**Table 2**). Nature Reviews Drug Discovery acquired the most citations (N = 3422). **Figure 3a** shows the journals involved in 193 highly cited articles in the field of biological products. The dual journal graph overlay (**Figure 3b**) shows 3 major citation pathways. Green pathways show that papers published in Medicine/Medical/Clinical journals frequently cite those from Molecular/Biology/Genetics and Health/Nursing/Medicine journals, reflecting the translation of basic biological research into clinical practice. Orange pathways demonstrate that papers from Molecular/Biology/Immunology journals often reference Molecular/Biology/Genetics and Chemistry/Materials/Physics journals, indicating the integration of molecular insights with material sciences. Pink pathways illustrate that papers from Physics/Materials/Chemistry journals tend to cite work from Molecular/Biology/Genetics and Chemistry/Materials/Physics, emphasizing the growing synergy between these fields. These citation patterns provide valuable guidance for new researchers in biological products, offering clear references to foundational research across disciplines.



(a)

(b)

Figure 3. (a) Network visualization for journal coupling analysis of 193 highly cited papers; **(b)** CiteSpace-based dual map overlay of journals connected to the field of biological products.

Table 2. Top 10 journals in the 193 highly cited papers on biological products.

Rank	Journal	Publications	Citations	Citations per publication	IF	JCI
1	Nature Reviews Rheumatology	7	2779	397	33.7	4.40
2	Journal of Controlled Release	6	618	103	10.8	2.09
3	European Journal of Pharmaceutical Sciences	5	984	196.8	4.6	1.38
4	Pharmaceutics	5	899	179.8	5.4	1.31
5	Clinical Gastroenterology and Hepatology	5	684	136.8	12.6	2.46
6	Nature Reviews Drug Discovery	4	3422	855.5	120.1	12.45
7	Jama-journal of the American Medical Association	4	1912	478	120.7	11.17
8	Journal of Pharmaceutical Sciences	4	1349	337.25	3.8	0.88
9	International Journal of Pharmaceutics	4	1099	274.75	5.8	1.65
10	Acta Pharmaceutica Sinica B	4	768	192	14.5	3.30

3.3. Distribution of countries/regions and institutions

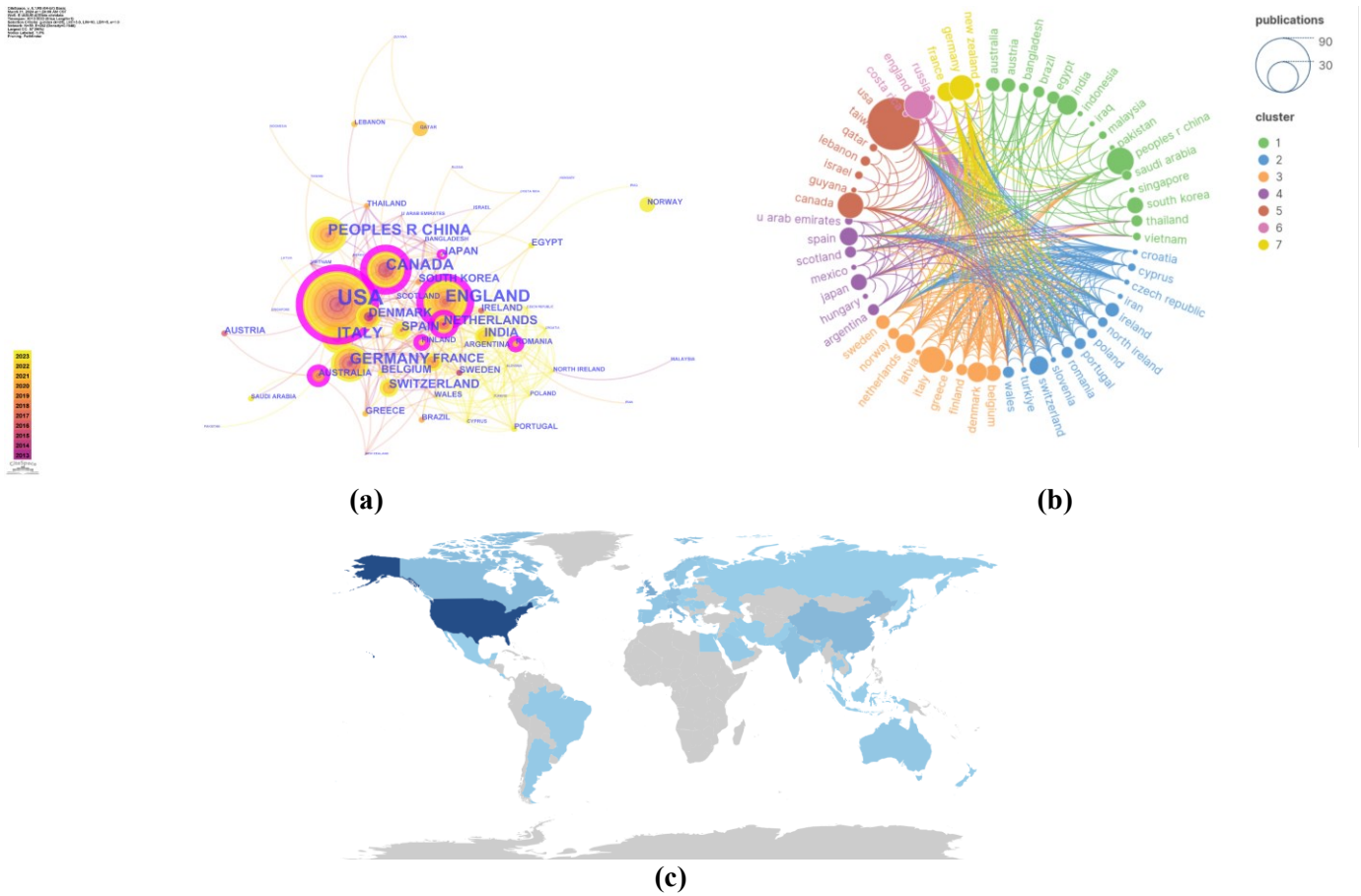
Countries/regions.

A total of 556 institutions in 59 countries/regions did research on the 193 highly cited papers. The USA contributed the most publications (N = 81, 41.97%), followed by England (N = 24, 12.44%) and People R China (N = 22, 11.40%) (**Table 3**). As shown in **Figure 4a**, of these 59 countries/regions, England has the strongest centrality (0.35), followed by Canada (0.27) and USA (0.24). The bibliometric map (**Figure 5b**) highlighted the close relationship between countries/regions. The bibliometric analysis identified a map of 58 countries and regions, forming seven major clusters that reflect strong international collaborations. The United States led the largest cooperative network, partnering with 46 countries, followed by England with 36 and Germany with 30. The clusters revealed distinct research focuses: the red cluster, led

by the USA, concentrated on rheumatoid arthritis; the pink cluster, led by England, collaborated with Russia and Costa Rica on a study related to multisystem inflammatory syndrome in children; the yellow cluster, led by Germany, focused on treatment strategies for liver metastases from colorectal cancer; the green cluster, led by China, emphasized drug delivery; and the orange cluster, led by Italy, centered on drug selection for disease treatment.

Table 3. Top 10 countries in the 193 highly cited papers on biological products.

Rank	Country/Region	Publications	Centrality	Year
1	USA	81	0.24	2013
2	ENGLAND	24	0.35	2013
3	PEOPLES R CHINA	22	0.01	2013
4	ITALY	21	0.01	2014
5	CANADA	20	0.27	2013
6	GERMANY	19	0.04	2013
7	INDIA	12	0.02	2013
8	DENMARK	12	0.05	2013
9	FRANCE	11	0.07	2014
10	SWITZERLAND	11	0.01	2014



(a) **(b)**

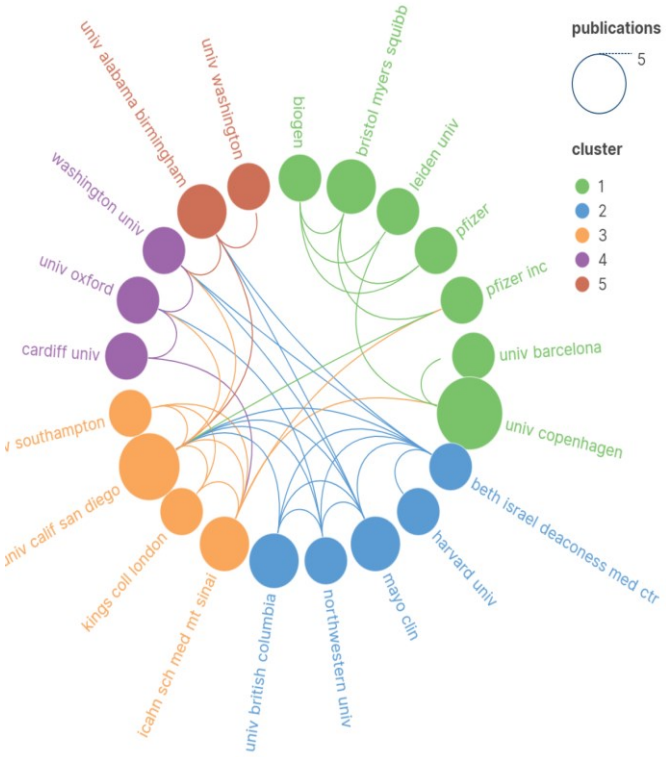
(c)

Figure 4. (a) Network visualization of authors collaborations analysis of 193 highly cited papers; **(b)** network visualization of the clustering countries/regions analysis of the 193 highly cited papers; **(c)** geographic visualization of the countries/regions analysis of the 193 highly cited papers.

3.4. Institutions

In terms of the total number of publications, the Univ Calif San Diego contributed the most papers ($N = 6$), followed by Univ Naples Federico II ($N = 5$), Univ Alabama Birmingham ($N = 5$), Harvard Med Sch ($N = 5$), and Icahn Sch Med Mt Sinai ($N = 5$). Of these 556 institutions, the Cardiff Univ has the strongest centrality (0.10), followed by the Stanford Univ (0.07) and the Tufts Med Ctr (0.07) (**Table 4**). The largest institutional cooperation network, covering 55 institutions, was formed by the Univ Calif San Diego, followed by the Univ Copenhagen and Mayo Clin, with 46 and 41 institutions, respectively (**Figure 5a**). The top 68 cooperating institutions were organized into 10 major clusters (**Figure 5b**). The analysis highlighted significant research contributions from leading institutions, particularly the University of California, San Diego (UCSD) and the University of Copenhagen. UCSD is actively engaged in developing comprehensive treatment guidelines for rheumatoid arthritis and psoriasis, alongside assessing the efficacy and safety of various drug therapies for inflammatory bowel disease, ulcerative colitis, and non-alcoholic steatohepatitis. In contrast, the University of Copenhagen focuses on the development of new drugs and conducts risk analyses to evaluate adverse drug events, thereby contributing valuable insights into drug safety and innovation in therapeutic strategies.

(a)



(b)

Figure 5. (a) Network visualization of institutions collaborations analysis of the 193 highly cited papers; **(b)** network visualization of the clustering institutions analysis of the 193 highly cited papers.

Table 4. Top 10 institutions in the 193 highly cited papers on biological products.

Rank	Institution	Publications	Centrality	Year
1	Univ Calif San Diego	6	0	2019
2	Univ Naples Federico II	5	0	2022
3	Univ Alabama Birmingham	5	0.04	2015
4	Harvard Med Sch	5	0	2016
5	Icahn Sch Med Mt Sinai	5	0.04	2016
6	Univ Calif San Francisco	4	0.01	2019
7	Duke Univ	4	0.02	2016
8	Univ Copenhagen	4	0	2013
9	Bristol Myers Squibb	4	0	2018
10	Mayo Clin	4	0.04	2015

3.5. Analysis of authors

The 193 highly cited publications were contributed by 1066 different authors. Fabbrocini, Gabriella authored the greatest number of papers (N = 5), followed by Ruggiero, Angelo (N = 4) (**Table 5**). The network has no obvious core and there was active collaboration within the group of authors of 2 different clusters (**Figure 6**). Gabriella Fabbrocini, Angelo Ruggiero, and Matteo Megna et al. are emerging writers in recent years, who focus on biologic treatment of psoriasis. Akl, Elie A et al. focus on guideline for the Treatment of Rheumatoid Arthritis.

Table 5. Top 10 authors in the 193 highly cited papers on biological products.

Rank	Author	Publications	Centrality	Year
1	Fabbrocini, Gabriella	5	0	2022
2	Ruggiero, Angelo	4	0	2022
3	Megna, Matteo	3	0	2023
4	Akl, Elie A	3	0.01	2016
5	Battista, Teresa	3	0	2023
6	Camela, Elisa	3	0	2022
7	Potestio, Luca	3	0	2023
8	Martora, Fabrizio	3	0	2023
9	Weinblatt, Michael E	2	0	2021
10	Johnson, Sindhu R	2	0	2021

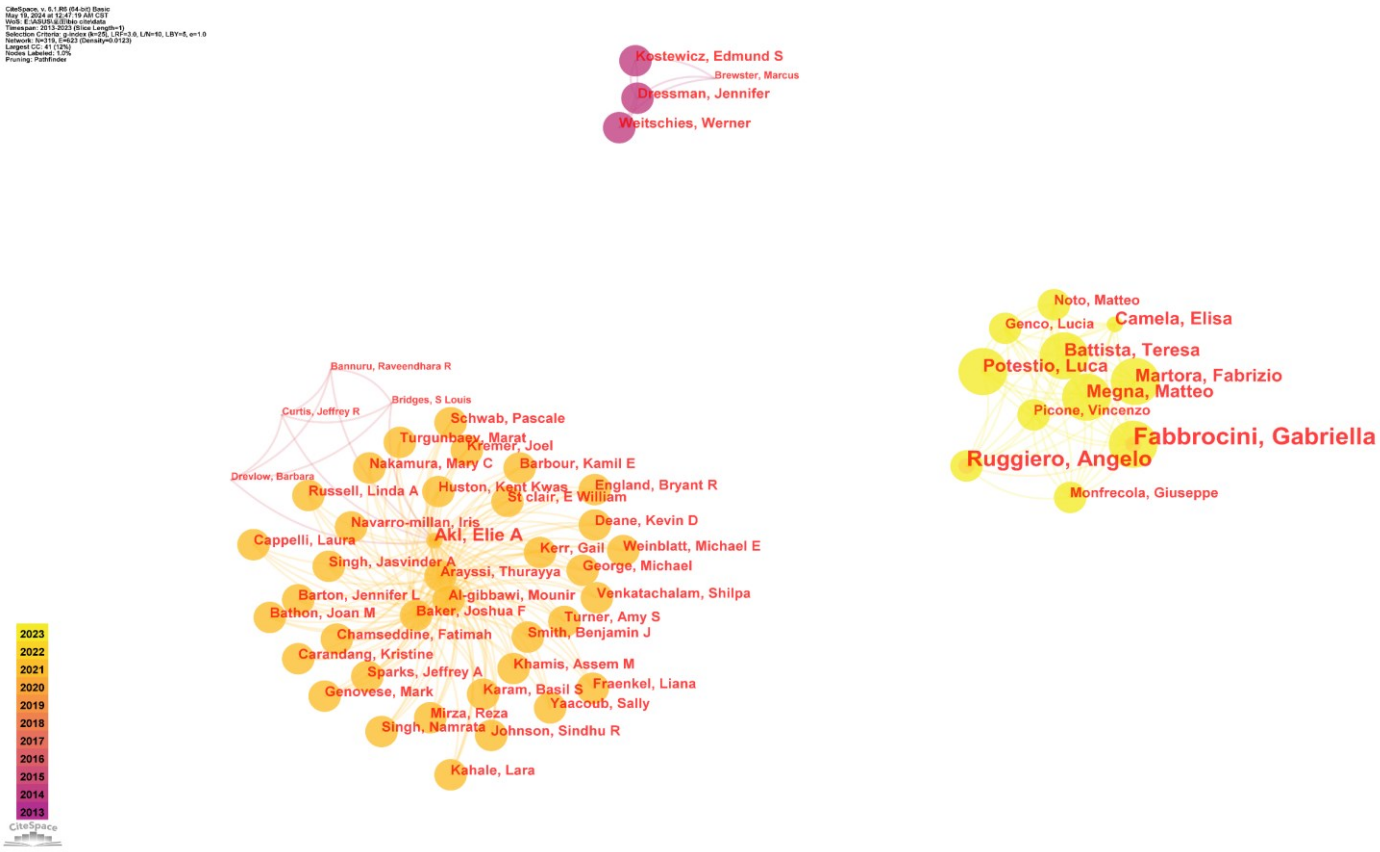


Figure 6. Network visualization of authors collaborations analysis of 193 highly cited papers.

3.6. Analysis of keywords

A total of 313 keywords were identified among the 193 highly cited papers. The top 10 keywords are drug delivery (14, 0.35), double blind (11, 0.15), in vitro (11, 0.16), monoclonal antibody (9, 0.06), in vivo (8, 0.21), antitumor necrosis factor (6, 0.10), adalimumab (6, 0.17), design (5, 0.03), controlled release (5, 0.08), and efficacy (5, 0.05) (**Table 6**).

Table 6. Top 10 co-occurring keywords in the 193 highly cited papers on biological products.

Rank	Keyword	Count	Centrality
1	drug delivery	14	0.35
2	double blind	11	0.15
3	in vitro	11	0.16
4	monoclonal antibody	9	0.06
5	in vivo	8	0.21
6	antitumor necrosis factor	6	0.10
7	adalimumab	6	0.17
8	design	5	0.03
9	controlled release	5	0.08
10	efficacy	5	0.05

Figure 7 shows the keywords linked to a functional index of biological products. These keywords are further subdivided into 11 clusters (**Figure 8a,b**), which are listed as follows: cluster 0 (3d printing), cluster 1 (antitumor necrosis factor), cluster 2 (treatment), cluster 3 (small molecule), cluster 4 (biomaterials), cluster 6 (wilsons disease), cluster 7 (quorum sensing), cluster 8 (biologic agent), cluster 9 (nanomedicines), cluster 10 (solubilization), and cluster 11(red blood cells).

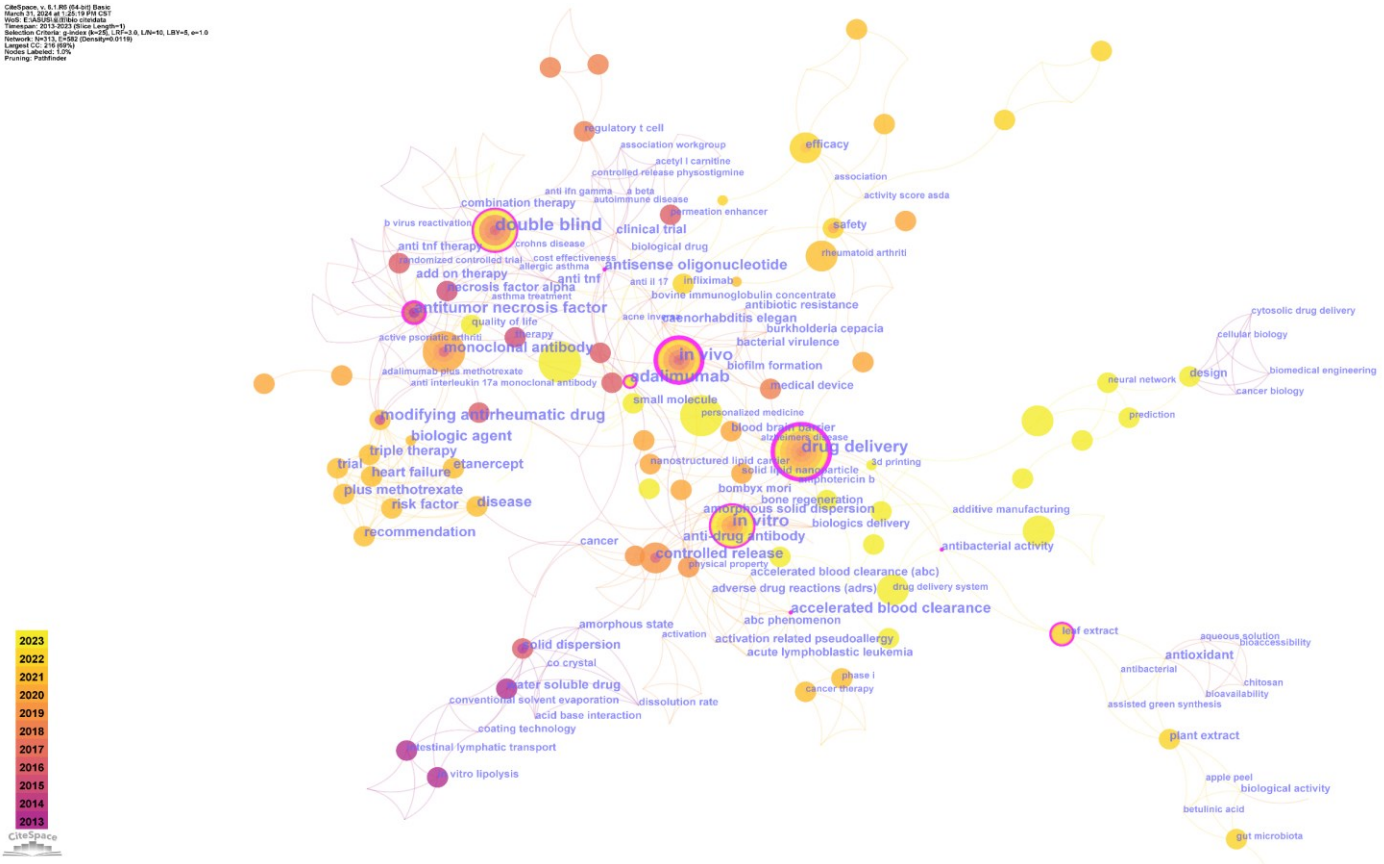


Figure 7. Network visualization of the co-occurring keywords that contributed to the 193 highly cited papers.

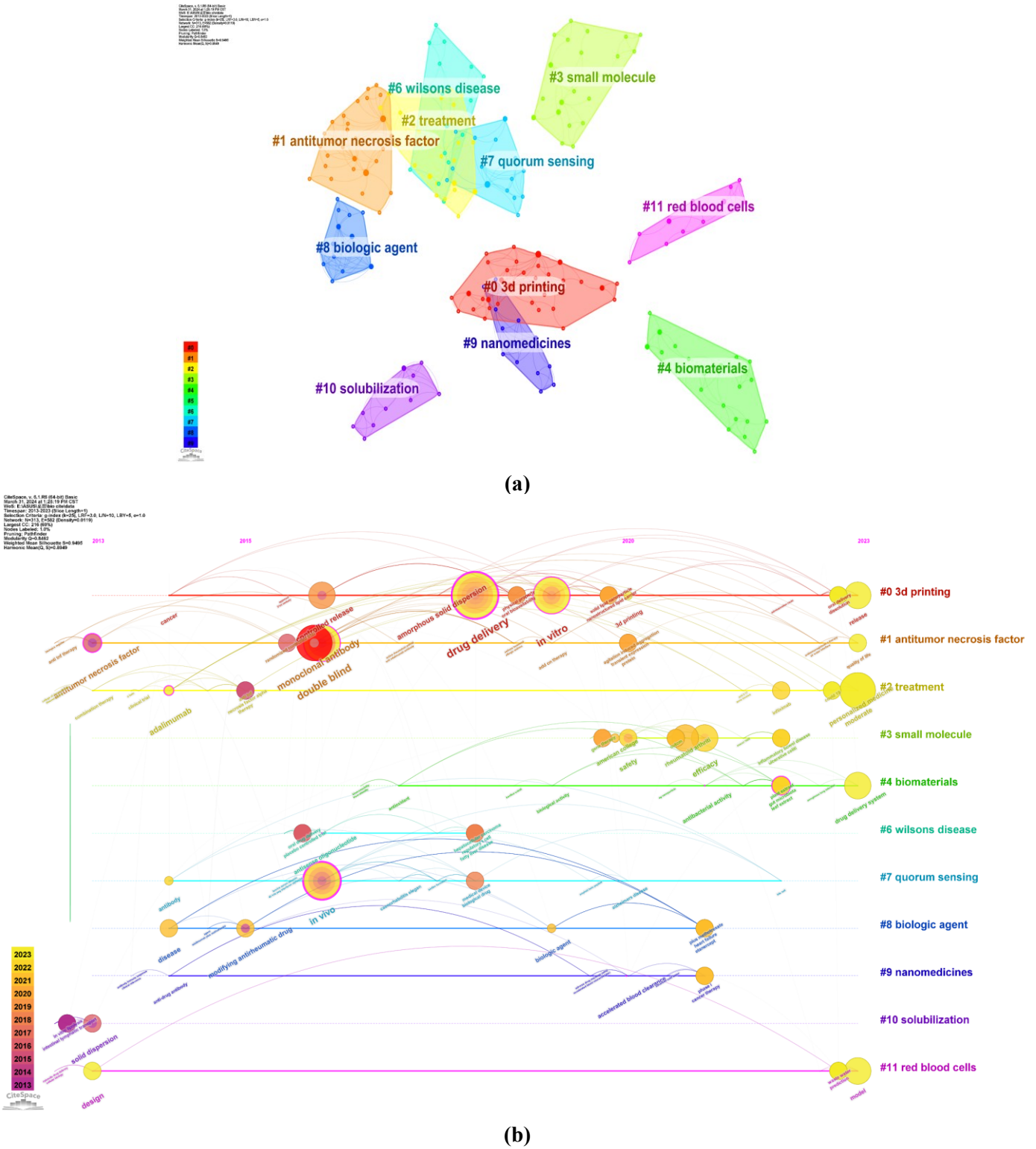


Figure 8. (a) Network visualization of the keywords clustering analysis that contributed to the 193 highly cited papers; **(b)** keyword clustering analysis of the 193 highly cited papers changes by year.

We created a visual map to illustrate the trend of keyword modifications over the years (**Figure 9**). The keywords with the highest burst strength were monoclonal antibody (3.16, from 2019), followed by efficacy (2.41, from 2021), double blind (2.36, from 2018). In the recent three years, the high burst of keywords that emerged were

American college (from 2020), accelerated blood clearance (from 2020), efficacy (from 2021), and antibacterial activity (from 2021).

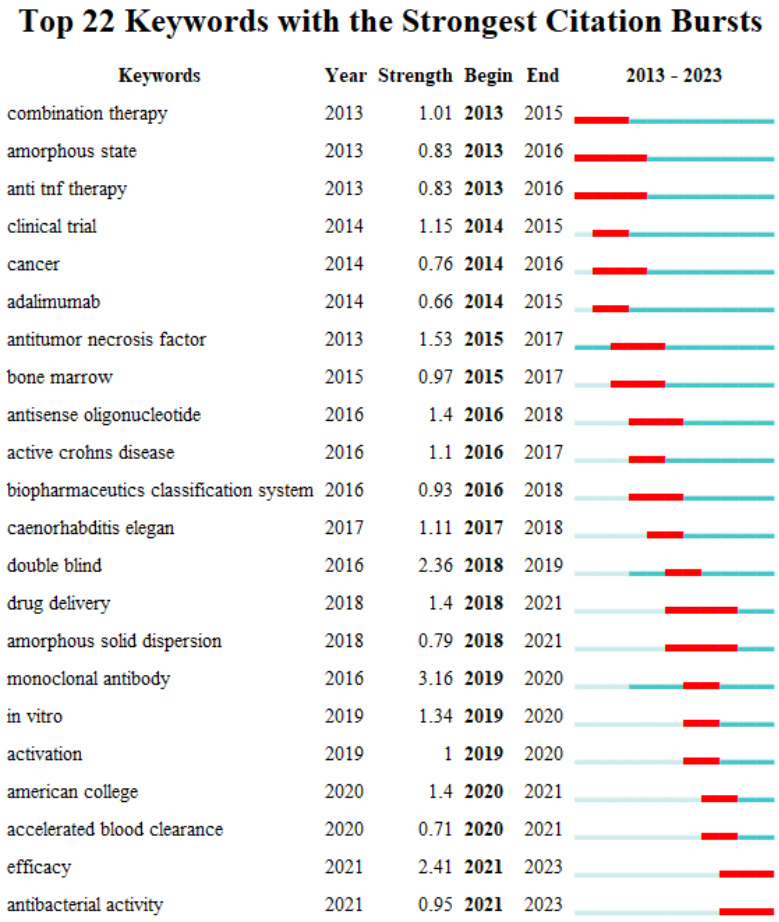


Figure 9. Network visualization of the keywords with the strongest citation bursts of the 193 highly cited papers.

4. Discussion

Most of the 193 highly cited papers are related to the treatment of clinical diseases and the efficacy of drugs. Involving most of the diseases is rheumatoid arthritis. Biological products are widely used in clinics, which are first-line drugs in osteosarcoma [10] and rheumatoid arthritis [11], and are also used as adjuvant drugs in chemotherapy in renal cancer [12], squamous cell carcinoma, [13] and other diseases. In addition, the immunogenicity of the drug has important implications for the efficacy of the treatment [14].

4.1. General information

According to the results from our analysis, all the highly cited papers about biological products were published after 2013, with more studies published between 2020 and 2023. The increase in the number of landmark publications during this period likely reflects the emergence of the development of new therapies for diseases [15–17], and concern for environmental protection [18,19]. In 2017, Kenneth F Baker and John D Isaacs reviewed the latest approaches to the treatment of IMIDs, such Psoriasis,

RA, SLE, IBD [15]. In 2018, EULAR proposed new treatment guidelines for large vessel vasculitis. For selected patients with GCA (refractory or relapsed disease, development or increased risk of GC-related adverse reactions or complications], adjunctive therapy with tolizumab should be used. For all patients with TAK, Tocilizumab or a TNF inhibitor may be considered in cases of disease relapse or refractory disease after conventional DMARD therapy [17]. Also in 2018, Jaya Mary Jacob et al. reviewed the use of biological products such as plants and microorganisms to eliminate heavy metal pollution [18]. In 2020, the review [19] suggests that the use of natural biological products with antifouling activity as antifouling agents is an important research direction. Of note, several landmark articles published in 2022, such as "Liposome-based delivery of biological drugs" [20], "European Groundshot-addressing Europe's cancer research challenges: a Lancet Oncology Commission" [20], did not generate sufficiently high citation counts and are likely underestimated. This likely reflects the recency of publication, that is, less time for citation, as compared to papers that were published earlier and that have a longer latency period. The most frequently cited article, "Trends in GPCR drug discovery: new agents, targets and indications" [21], mainly talks about the status of the use of GPCR drugs. Followed by "2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis" [22], in which Singh et al. proposed new guidelines for Rheumatoid Arthritis in 2015. Of the remaining three articles with more than 1000 citations, S. Mitragotri et. summarized the articles of drug delivery systems [23], Aletaha et al. review that early treatment with methotrexate plus glucocorticoids followed by other DMARDs such as TNF, IL-6 or Janus kinase inhibitors improves prognosis and prevents RA-related disability [11], and Isakoff et al. introduced the current treatment status of osteosarcoma and the prospect for the future [10].

Nature Reviews Rheumatology is the journal with the largest number of published articles ($N = 7$), with the second most citations ($N = 2779$), and with an IF of 33.7, so it may be the most important journal on biological products. The top 10 journals in the 193 highly cited papers on biological products include Nature Reviews Rheumatology, Nature Reviews Drug Discovery, and Jama-journal of the American Medical Association, which means that articles in the field of biological products are of high quality.

Our study showed that the majority of top-cited publications on biological products originate from North America and Western Europe. Results demonstrate that the USA has contributed significantly to the advancement of biological products research. The University of California San Diego is the institution with the most partnerships, collaborating with Harvard Medical School, Mayo Clinic and Monash University to develop guidelines, application deadlines, and precautions for biological products for immune disease [16,24,25]. In collaboration with the University of British Columbia and the University of Calgary, it found that vedolizumab and tumor necrosis factor antagonist have different therapeutic effects on different types of inflammatory bowel disease [26].

We identified 11 independent authors who have contributed to three or more articles on 193 highly cited papers. Seven of the authors co-authored the same four articles on psoriasis [27–30] and Megna, M. is the first author of three of these articles, which were published from 2022 to 2023. The finding indicates that Megna, M has

been a central figure in the field of psoriasis therapy research in recent years, and her main research direction may be antibody treatment for psoriasis.

4.2. Hot research topic

2021 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis [24] suggests that biological DMARDs are one of the currently recommended treatments. The European League Against Rheumatism (EULAR) recommends that any biological (b) DMARDs (TNFi, IL-6Ri, Co-stimulation-I, anti-B-cell (CD20)) must be added if conventional synthetic DMARDs for rheumatoid arthritis do not improve at 3 months or do not achieve target at 6 months and if there are poor prognostic factors [4]. Biological products available for the treatment of rheumatoid arthritis include anti-tumor necrosis factor, IL-1 receptor antagonists, and monoclonal antibodies to the IL-6 receptor [11].

The paper [31] states that nano preparations can be used for the treatment of diseases. Nanocarriers such as solid lipid nanoparticles, crystalline nanoparticles, gold, silver, cadmium sulfide, and titanium dioxide polymer nanoparticles can improve drug solubility and bioavailability and control drug release. However, the safety/toxicity of nanomedicines remains to be investigated, whereas lipid nanoparticles are generally considered to be non-toxic, biocompatible, and easy-to-produce formulations [32]. Therefore, lipid nanoparticles need more research in the future to prove their therapeutic value in practical applications.

Anti-tumor necrosis factor (anti-TNF) therapies are the most widely used biological products for the treatment of immune-mediated diseases [33]. Anti-tumor necrosis factor (TNF) therapies such as infliximab and adalimumab are used in the treatment of various inflammatory diseases, especially inflammatory bowel disease [34]. However, the impact of immunogenicity of monoclonal antibody drugs on efficacy and safety is an important issue and is an important, although not the only, consideration in treatment decisions [35].

Studies [11] have suggested that anti-tumor necrosis factor (TNF) in combination with methotrexate allows 75% of patients with rheumatoid arthritis to reach their treatment goals. Substantial interindividual variation exists for serum drug levels for infliximab and other TNF inhibitors. Higher serum drug levels are associated with greater efficacy [36–38]. Therapeutic drug monitoring (TDM) has been proposed as a method to maximize the efficacy, safety, and cost-effectiveness of TNF inhibitor therapy in 2019 [39–41].

Hauser, Alexander S [21] mentioned that biological products are becoming increasingly important in GPCR drug discovery, especially in areas of complex pharmacological processes and a lack of small molecule targets. And reviewed possible mechanisms, by activating or inhibiting their ligand binding and signaling pathways to treat a wide range of diseases, including cancer, inflammatory diseases, neurological and metabolic diseases, etc. in class A GPCRs; by acting in a manner like their natural ligand structure achieving biological effects by enhancing or inhibiting ligand binding in class B, C, and F GPCRs.

4.3. Research front

In the recent three years, the high burst of keywords that emerged was American college, accelerated blood clearance, efficacy, and antibacterial activity, which indicated researchers have been paying attention to efficacy [42,43], accelerated blood clearance, [44] and antibacterial activity [45,46].

The increasing resistance of pathogens to antibiotics has led to serious health problems in recent years. Scientific progress in nanotechnologies and materials science is allowing the production of new substances with intrinsic antimicrobial activity. MOFs are porous crystalline compounds based on metal ions or clusters linked in a regular manner by organic linkers, which currently have potential for biomedical applications such as delivery of biopharmaceuticals, antimicrobial protection, biosensing, biocatalysis, biobanking, and manipulation of cells and viruses [45].

The most common immune system-related adverse events with IL-17 inhibitor therapy are mucosal infections and opportunistic infections (risk difference RD = 0.09, $P = 0.02$) [47]. The immunogenicity of the drug triggers the production of anti-drug antibodies (ADA), which accelerates the clearance of the drug from the blood leading to reduced efficacy and severe hypersensitivity reactions [48].

Additionally, Research Strategies to Develop Environmentally Friendly Marine Antifouling Coatings [19] shows that the extraction of natural biological products with antifouling activity from marine organisms as antifouling agents is an important research direction. In addition, Artificial Intelligence and Machine Learning (AI-ML) offer great potential for optimal design, monitoring, and control of biological products production [49].

5. Limitations

This study is subject to several limitations primarily due to the reliance on the Web of Science database, which may not encompass all older publications, potentially affecting the comprehensiveness of the analysis. Additionally, a Subject Keywords search method was employed rather than a Title Keywords search strategy, which, while aimed at enhancing the accuracy of the analysis, may have resulted in a lack of precision in the search outcomes. Furthermore, the observed high percentage of reviews among the highly cited papers in the field of biological products could be influenced by the search strategy employed and the screening criteria of the WOSCC, which prioritizes highly cited works. These factors should be considered when interpreting the findings of this study.

6. Conclusions

Biological products play an essential role as adjunctive therapies for immune-mediated inflammatory diseases, and several key findings emerged from the analysis. Notably, significant studies on biological products have been predominantly published in Nature Reviews Drug Discovery, underscoring its prominence in this field. Moving forward, research on drug efficacy is identified as a critical area for future investigation. Additionally, there are pressing needs to explore strategies for lowering the nanotoxicity of biological products, reducing adverse events associated with

immunogenicity, and monitoring therapeutic drug efficacy (TDM). Furthermore, the development of new substances with intrinsic antimicrobial activity presents a promising direction for advancing therapeutic options in the treatment of these diseases.

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