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Article

Trends and Opportunities in Enzyme Biosensors Coupled to Metal-Organic Frameworks (MOFs): An Advanced Bibliometric Analysis

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Abstract: The unique properties of metal-organic frameworks (MOFs) such as their large surface area and high porosity have attracted considerable attention in recent decades. The MOFs are a promising class of materials for developing highly efficient biosensors due to these same properties. This bibliometric analysis focused on the use of MOFs as enzyme-coupled materials in biosensor construction and aimed to provide a comprehensive overview of the research field by analyzing a collected database. The analysis included identifying the countries that have published the most, the most prominent applications, and trends for future directions in the field. The study used three databases with different numbers of documents, differentiated by research areas, with refinements made to the search as needed. The results suggest that MOF-derived biosensors are a growing field, with the Republic of China emerging as a significant contributor to research in this area. The study also used computational processing of trend analysis and geocoding to reveal these findings.

Keywords: metal-organic frameworks; biosensor design; coupled enzymes; bibliometric analysis

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1. Introduction

In recent decades, metal-organic frameworks (MOFs) have become a highly researched topic due to their unique structural properties and versatility in applications [1]. MOFs are composed of metal coordination cores bound by organic ligands (linkers) to form a network of three-dimensional (3D) extended structures with significant porosity. The materials' high porosity, large surface area, and diverse chemical structure and functionality make them attractive for catalytic activity, with promising applications in biotechnology and bioremediation [2–7]. MOFs are highly specific, making them an ideal class of materials for the construction of highly efficient biosensors and chemosensors for various analytes [8].

Biosensors have recently received considerable attention as a potential solution to the limitations of current detection methods due to their rapid activity, sensitivity, specificity, and low manufacturing cost [9]. In the medical field, biosensors are considered to be excellent tools for the detection of various biomarkers [2]. Biosensors are categorized based on the type of transduction technology used in their fabrication, which can be electrochemical, optical, or piezoelectric [10]. MOF-derived materials have also found numerous applications in nonbiological fields including gas adsorption, separation, catalysis, and energy storage [11,12].

The three-dimensional structure of MOFs, coupled with their interactions with enzymes, can improve the loading/immobilization ratio of these biomolecules, leading to improved efficiency in a number of catalytic applications. The large surface area per mass of MOFs, compared to other commonly used supports, makes them an exceptionally promising option for immobilizing enzymes.

There are several techniques for synthesizing a MOF@Enzyme system including in situ entrapment during synthesis, surface functionalization, and diffusion into pores [13]. Some of these methods can increase the likelihood of the stable immobilization (docking) of the enzymes [14–21]. Enzymes are highly specific catalysts that may have different solubilities when used in conditions other than their natural environment [22–33]. Therefore, immobilizing them on solid supports such as MOFs can transform these homogeneous catalysts into reusable heterogeneous catalysts [13,14,34–42]. MOFs have been widely used as promising materials for enzyme immobilization due to their large hierarchical surface area and significant porosity, providing a high surface area for enzyme loading [43]. Overall, enzymes can be added to MOFs by two different strategies: the de novo approach in which structures are built around the enzyme molecules, and binding to pre-synthesized MOFs, which involves surface immobilization, covalent binding, and pore encapsulation. Enzyme–MOF biocatalytic supports are expected to have a wide range of useful applications, one of which is biosensing [44].

Bibliometric analysis is a rigorous and well-established methodology for examining and analyzing scientific data on a large scale [45]. This approach helps researchers understand the changing characteristics of a particular field while also revealing information about emerging areas of research. Although bibliometric analysis is widely used in scientific research, its use in business research is relatively new and often does not reach its full potential due to limited datasets [46]. Advanced bibliometric reviews can be challenging to conduct because they often rely on a limited set of data, resulting in an incomplete understanding of the area under study [46,47]. In addition, reviews conducted within a given period may not comprehensively capture all scientific advances [48]. In this review, a bibliometric search was conducted using specific parameters on the Web of Science—Core Collection website. The databases used in this work were selected using an information-adding methodology, in which new search terms were added to each database to estimate the volume of publications in the field. The bibliometric search shows the number of publications related to MOFs, enzymes, and biosensors by year in the collected databases, highlighting the large number of articles published between 2012 and 2022. Although the difference in the number of publications is noticeable, a numerical trend was observed in the three databases studied, demonstrating the interest of researchers in this field, especially in 2020 and 2021. The relationship between the two largest databases showed a division of knowledge between enzymes for biosensor development and MOFs for their multiple applications. The smaller database served to correlate the other databases, allowing for a more in-depth study of biosensor development using the enzyme-MOF set. The third database was smaller than the others, indicating that the specific research area covered by this paper had little literary repertoire. To gain a comprehensive view of the topic, a systematic analysis of the database represented by the color red was used, as it contained articles from the smallest database, allowing for an in-depth understanding of the topic. Overall, bibliometric analysis is a valuable tool for exploring scientific data on a large scale and can provide insights into the evolving characteristics of a particular field.

This paper provides an in-depth bibliometric analysis of recent advances and prospects in the design of biosensors and MOF@Enzyme materials. The primary objective is to demonstrate the evolution of research in this field over the last decade, Figure 1. The collected data will be thoroughly analyzed to identify emerging patterns, overarching themes, new subfields of study, significant keywords, and collaborative networks. The data were carefully selected based on relevance and addressed the following research questions (RQs):

- RQ1: How has the scientific literature related to MOF been developed?
- RQ2: What is the relevance of biosensors created from MOFs coupled to enzymes related to other topics?
- RQ3: In which field of applications did the MOFs generate more interest from the researchers of the collected database?
- RQ4: What are the overall results on search trends (keywords and search areas) related to MOFs in emerging research fields?

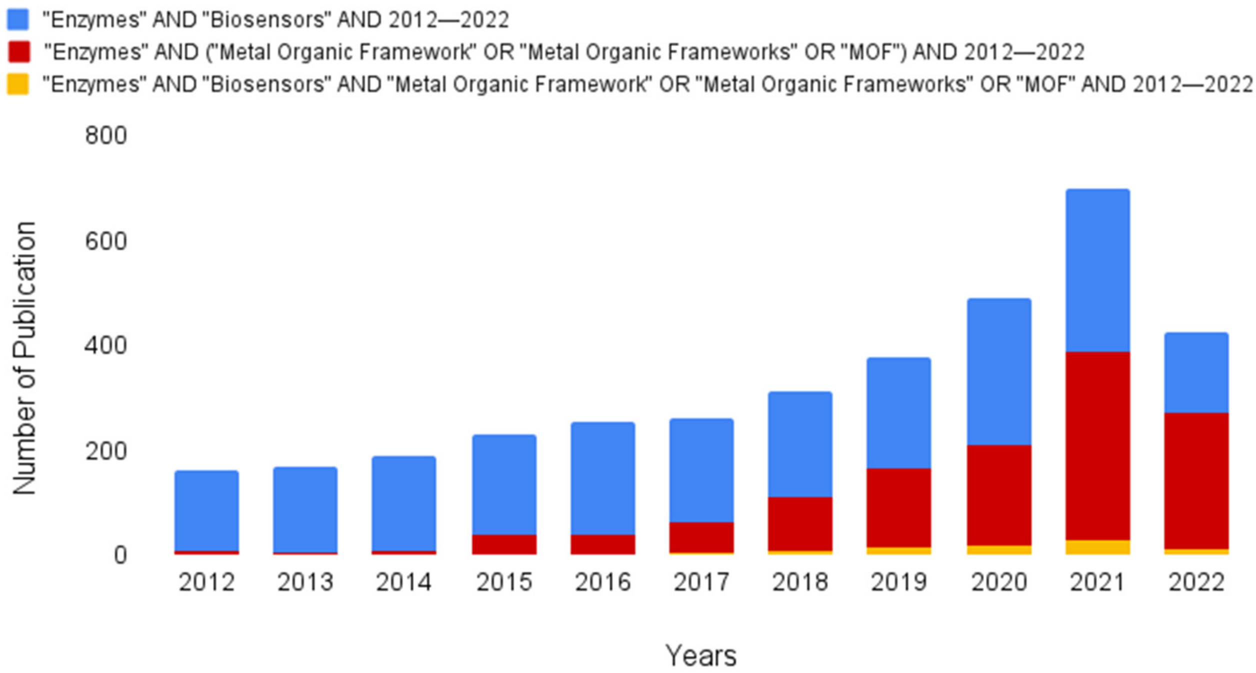

Figure 1. Annual publications in metal-organic framework research related to enzymes and biosensors.

2. Methodology

2.1. Data Source

The analytical procedures required access to a database, which was accessed through the Web of Science—Core Collection website. By using the search tools available on the website and modulating the search criteria, data related to advanced bibliometric analysis was collected for the field of biosensors and MOF@Enzyme material design. The CAPES PERIODICOS platform provided access to the website used to download the database files. The research procedure was illustrated in Figure 2, and the article was delimited by the period from 2012 to 2022. The site performed searches by using logical operators (AND, OR, NOT) to identify articles with terms entered in the search bars present in the title, keywords, author, etc. The first dataset collected had its main terms as "Enzymes" and "Biosensors", and a total of 2264 papers were obtained related to these topics. The second dataset used the same protocol, but the term "Biosensors" was replaced by "("Metal Organic Framework" OR "Metal-Organic Frameworks" OR "MOF")", which obtained a total of 1220 articles. The third dataset followed the same method as the previous two searches, where all terms were used, and 87 related articles were found. The second database was used instead of the third one because all articles in the third dataset were part of the second one. The dataset with 1220 articles associated with "Enzymes" and "Metal-Organic Frameworks" was further refined when the term "Biosensors" was added. The other articles complemented and helped build a more precise and direct analysis of the area of study, revealing characteristics of the scientific research trend and the authors' interest in developing this field of research.

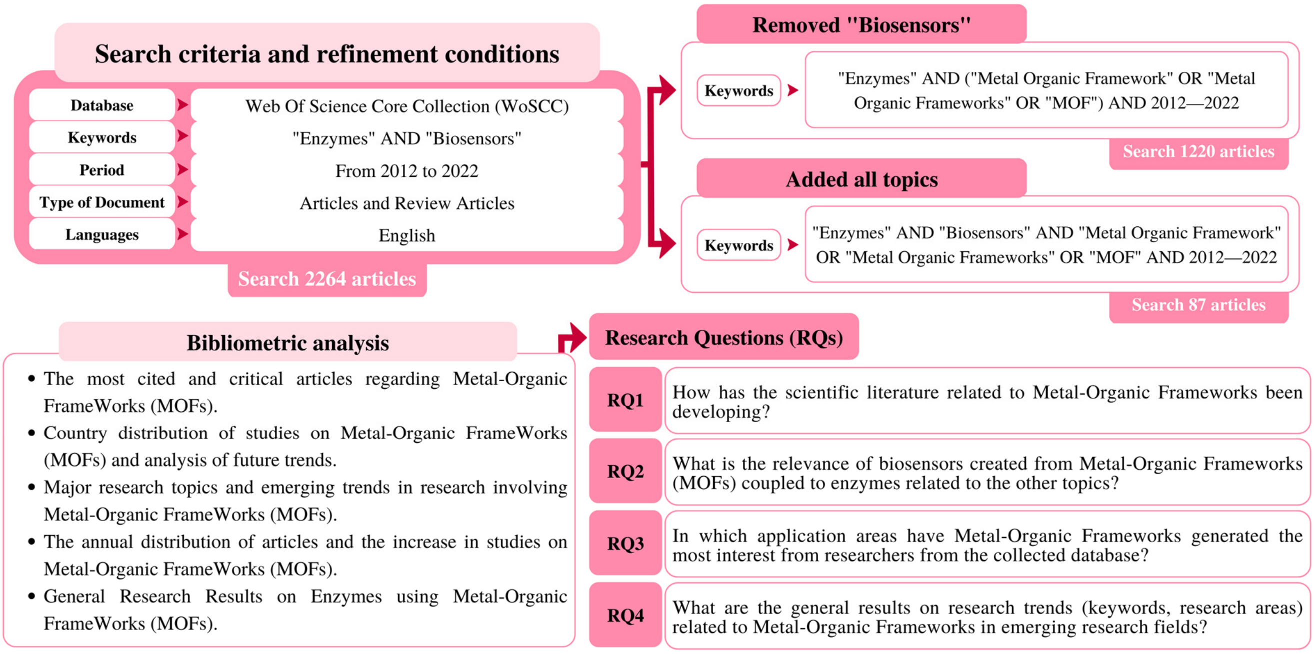

Figure 2. Structural representation of the search and analysis criteria.

The search strategy used in this study (Figure 2) was selected based on the article "*Sustainability and challenges in hydrogen production: An advanced bibliometric analysis*", published in 2022 [49]. The authors emphasized that this approach facilitates the creation of a precise and consistent database in line with the research objectives while improving the visualization and analysis of the results in the research field. It is crucial to objectively understand the characteristics identified for analysis, as only through an extensive collection of academic papers can numerous significant specifics be identified in the research. The types of analysis used were designed to explore all of the different aspects covered by the database processing, which will be explained in more detail in the following sections.

2.2. Data Analysis

Three different software were used to perform the bibliometric analysis: VOSviewer (version 1.6.17, Leiden, South Holland, The Netherlands), CiteSpace (v.5.8.R3, Philadelphia, PA, USA), and ArcGIS (version 10.5, Redlands, CA, USA).

The VOSviewer software was developed by the Center for the Study of Science and Technology (CWTS) at Leiden University in the Netherlands. The CiteSpace software was developed by Dr. Chaomei Chen at Drexel University in the United States. CiteSpace is part of a suite of products developed by the Environmental Systems Research Institute (Esri) in Redlands, California, USA. ArcGIS 10.5 software was used to analyze the geographic distribution of publications, and VOSviewer [50] was used for data visualization. In addition, CiteSpace was used to identify and predict potential future research subfields in a given field using keywords and clusters [51].

3. Results and Discussion

3.1. Bibliometric Analysis

3.1.1. Publication Result: Overall Results

A considerable number of research articles related to enzymes and biosensors (2264 documents) between 2012 and 2022 were found through the Web of Science online platform for scientific literature. A second database was created from this search, resulting in 1220 articles. Among these articles, the most relevant, according to the website, was "Catalytic Applications of Enzymes Encapsulated in Metal-Organic Frameworks," published in February 2019 [52], which reviewed the techniques of enzyme immobilization in MOF cages and pores for catalytic applications and discussed the future of this strategy. The third database, which had "Enzymes", "Biosensors", and "("Metal-Organic Framework" OR "Metal-Organic Frameworks" OR "MOF")" as topics, contained 87 articles, and the most prominent research was published by Zhu, entitled "Metal-Organic Framework/Enzyme Coated Optical Fibers as Waveguide-based Biosensors", published in June 2019 [53]. This paper explored the use of MOFs as promising vectors for enzyme encapsulation due to their porous structures. Researchers have developed MOF-based bio-nanomaterials with novel properties using various strategies including post-infiltration, one-pot synthesis, or bioconjugation. These strategies include the self-assembly of enzyme-containing MOFs, which is mainly driven by hydrophobic, electrostatic, and hydrogen bonding interactions. Inspired by nature, various MOF-based biosensor designs have emerged that are related to the coupling of enzymes to MOFs [54].

An important analysis to be carried out is the study of the distribution of scientific journals since it reveals the methodological developments of each study and its research scope. The downloaded database contained 393 scientific journals associated with the published articles, indicating a large number of journals dedicated to research in this area, despite the reasonable number of articles. On average, each journal had about 3.1 published articles. This observation suggests that the field of study is promising and attractive to researchers from different affiliations.

Table 1 shows the top ten scientific journals ranked by their citation rates for papers on metal-organic frameworks that cite enzymes. These ten journals accounted for 18.30% of the total number of publications in the database, which was approximately 224 documents. This information indicates that there was a dispersion of publications in this field of study, which means that there was no concentration of scientific production by a particular group. Moreover, among these outstanding journals, four were from England, which highlights the scientific importance of this country, which had 6776 citations, even though it does not appear in Table 2, which presents the most productive countries. "Chemical Society Reviews" occupied the first position in this ranking, with the highest number of citations and an impact factor about 28% higher than the combined value of its next three competitors. This journal is very important in this field of research because its average number of citations per publication was relatively high, at 254.571 citations per document, which demonstrates the quality of the articles produced and makes it a reference for researchers. Europe dominated this ranking at the continental level, with eight of the ten journals present, underlining the scientific strength of this region.

Table 1. The top ten scientific journals published in the research area.

Rank	Journal	C	IF	NP	NC	AC	P
1	Chemical Society Reviews	ENG	60.615	14	3564	254.571	1.14%
2	Angewandte Chemie-International Edition	GER	16.823	30	3231	107.700	2.45%
3	Journal of the American Chemical Society	USA	16.383	33	3209	97.242	2.70%
4	ACS Applied Materials & Interfaces	USA	10.383	54	1787	33.092	4.42%
5	Advanced Materials	GER	32.086	12	1519	126.583	0.98%

Table 1. *Cont.*

Rank	Journal	C	IF	NP	NC	AC	P
6	Coordination Chemistry Reviews	NL	24.833	22	1476	67.090	1.80%
7	Nature Communications	ENG	17.694	11	1436	130.545	0.90%
8	Chemical Communications	ENG	6.065	18	969	53.833	1.45%
9	RSC Advances	ENG	4.036	14	807	57.642	1.14%
10	Analytical Chemistry	USA	8.008	16	755	47.187	1.31%

C = country; IF = impact factor in 2021; NP = number of publications; NC = number of citations; AC = average citation; P = percentage with the total number of papers. GER = Germany; USA = United States of America; NL = the Netherlands; ENG = England.

Table 2. The ten most productive countries in the field of MOFs and enzymes.

Rank	Country	NP	NC	AC	TLS	P
1	People's Republic of China	831	25,877	31.139	4205	51.87%
2	USA	159	12,665	79.654	2833	9.92%
3	India	57	1304	22.877	573	3.55%
4	Australia	53	3206	60.490	1483	3.30%
5	South Korea	50	1440	28.800	321	3.12%
6	Iran	31	650	20.967	280	1.93%
7	Germany	29	1143	39.413	242	1.81%
8	Spain	25	635	25.400	247	1.56%
9	Brazil	23	507	22.043	188	1.43%
10	Taiwan	21	1891	90.047	708	1.31%

NP = number of publications; NC = number of citations; AC = average citation (NC/NP); TLS = total link strength; P = percentage; USA = United States of America.

3.1.2. The Distribution by Country and Institution

This study aimed to analyze the countries with the highest number of publications related to the second database, which was the main focus of this work. Table 2 shows the top 10 countries in terms of scientific production, as reported by the authors in their publications. It should be noted that some articles may have had contributions from authors belonging to several countries, so the percentages in the table represent the total number of occurrences of countries in the 1220 articles analyzed. The countries listed in this table accounted for about 80% of the total number of occurrences of countries in scientific publications. The analysis in Table 2 showed a concentration of publications in a group of countries, particularly China and the United States. Chinese researchers contributed to more than half of the scientific productions with the highest number of citations (25,877 citations), but when looking at the average number of citations per publication, the United States outperformed China with more than twice as many citations. This suggests that while China is a prolific producer in terms of quantity, the United States has stronger scientific support because its authors are more frequently used as references.

The distribution of scientific publications highlights the active participation of the countries in the research process. The high number of published articles reflects the significant interest in this research area and the growing need to find more sustainable and efficient solutions for various processes using MOFs. This analysis is crucial to identify global trends, highlight scientific and technological aspects, and encourage the development of innovations or improvements in the existing processes. Therefore, it is essential to address the lack of scientific results that meet the constantly evolving needs of society.

From the analyzed data on the countries, it is essential to understand, in an illustrative way, the distribution of the number of publications, as shown in Figure 3. This reveals some interesting aspects about the field such as the fact that countries with large economies are more prominent in the illustration (the United States and China), in addition, numerous countries did not even have publications in the collected database. Compared to the data from the third database, the figures maintained a similar pattern to the second database, where the two leading countries maintained similar percentages of publications (48% and

10%). This shows an equivalent level of the trend. Furthermore, an interesting feature can be observed in the visualization of Figure 4, which will contribute to the analysis made in the previous figure, which is the relationship between China and the United States. Between these two countries, there was a significantly thick line, which means that there is a scientific interest in using authors from one country for the other. This information can be deduced from the form used in the construction of the figure, which takes into account the number of citations (i.e., this relationship between countries means that Chinese authors have referenced American authors and vice versa).

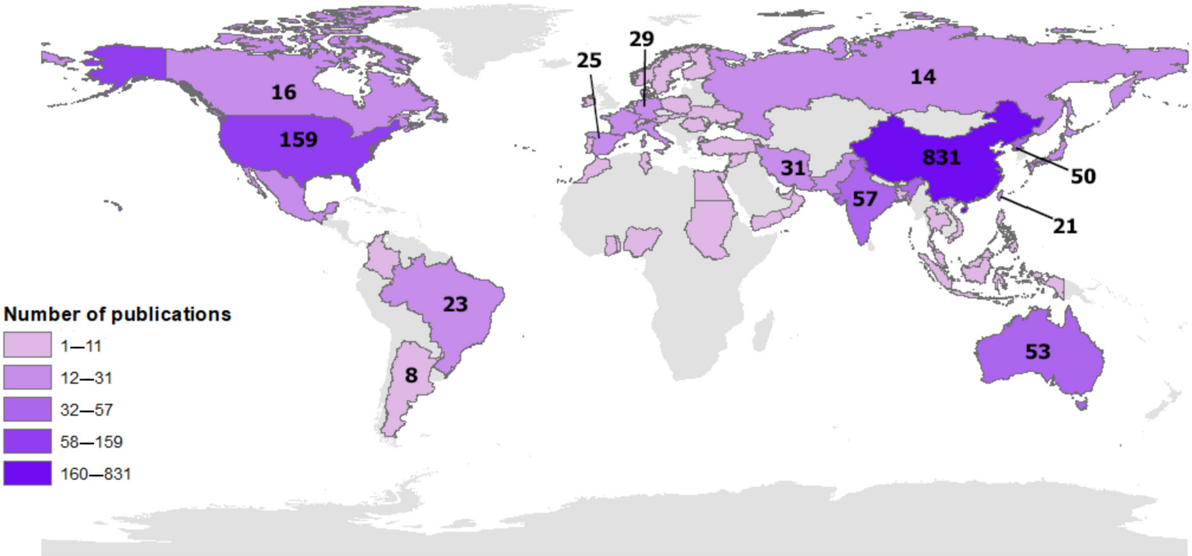

Figure 3. Representation of the number of articles published by country in the analyzed period.

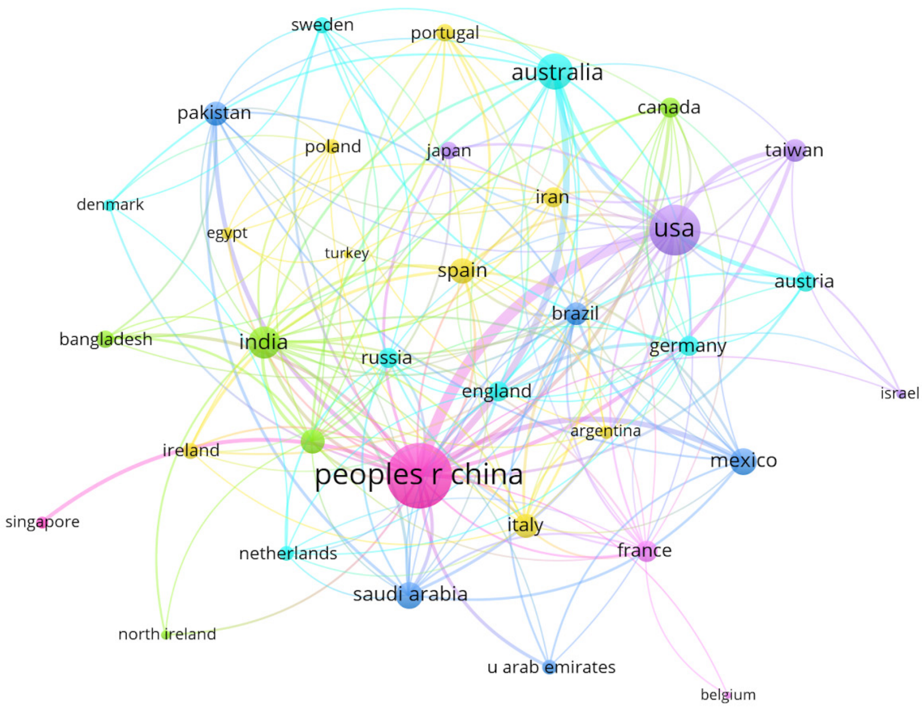

Figure 4. Network visualization map related to the collaboration between countries with at least five published papers. The thickness of the lines connecting the two countries strongly indicates the accumulation of co-authorship, and the colors divided into clusters demonstrate the countries with high collaboration in each cluster.

To gain a better understanding of the distribution of the articles analyzed, it is crucial to examine the organizations associated with them. It was possible to identify 118 institutions with five or more publications in the database, the most prominent of which was the Chinese Academy of Sciences, which received 5389 citations and produced 68 documents. An important detail from this analysis is that the 10 most productive organizations were Chinese, which is reflected in the number of articles published by the country (accounting for more than 50% of the documents), and they also collectively gathered a large number of citations (17,132 citations). In addition, Figure 5 shows the co-authorship relationships in the publications, reinforcing an important aspect: institutions benefit from each other by collaborating in the construction of other articles and taking credit through citations.

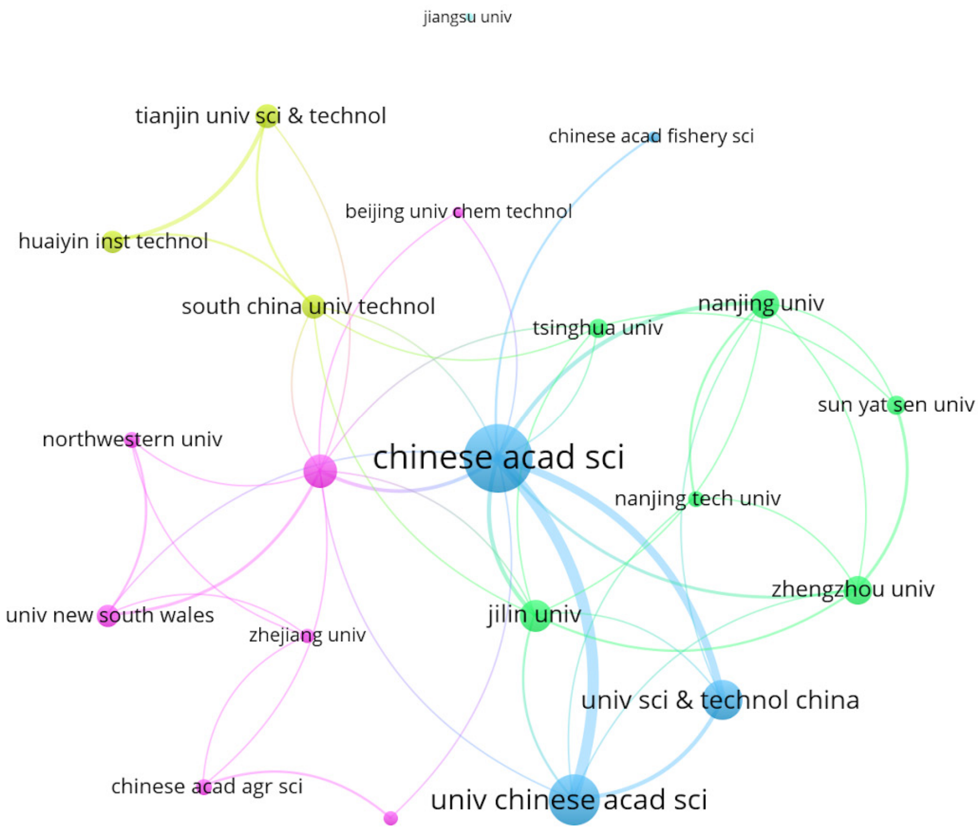

Figure 5. Network visualization map depicting the collaboration among organizations with at least 15 occurrences. The thickness of the lines connecting the two institutions indicates a high accumulation of co-authorship, and the colors, which are divided into clusters, demonstrate the groups of institutions with significant collaboration.

Another way to examine the basic characteristics of the research area is to look more closely at the geographic distribution. For this purpose, the geocoding map exploration of the organizations in the database was used. Figure 6 shows the geocoded addresses of these organizations and the concentration of points in different countries. The map illustrates that organizations in China are mainly concentrated around the capital Beijing, and similarly, those in the United States are located near Washington D.C. In addition, despite a significant concentration of organizations, Europe only has two countries (Germany and Spain) among the top 10 most productive countries, indicating a disproportion between the number of organizations and the production rate. Figure 6 also highlights the consistent presence of Asian countries among the top producers, particularly India, which has the highest number of organizations. However, it has only about one fifteenth of the number of publications of China, revealing the remarkable efficiency of Chinese institutions in producing articles on a larger scale.

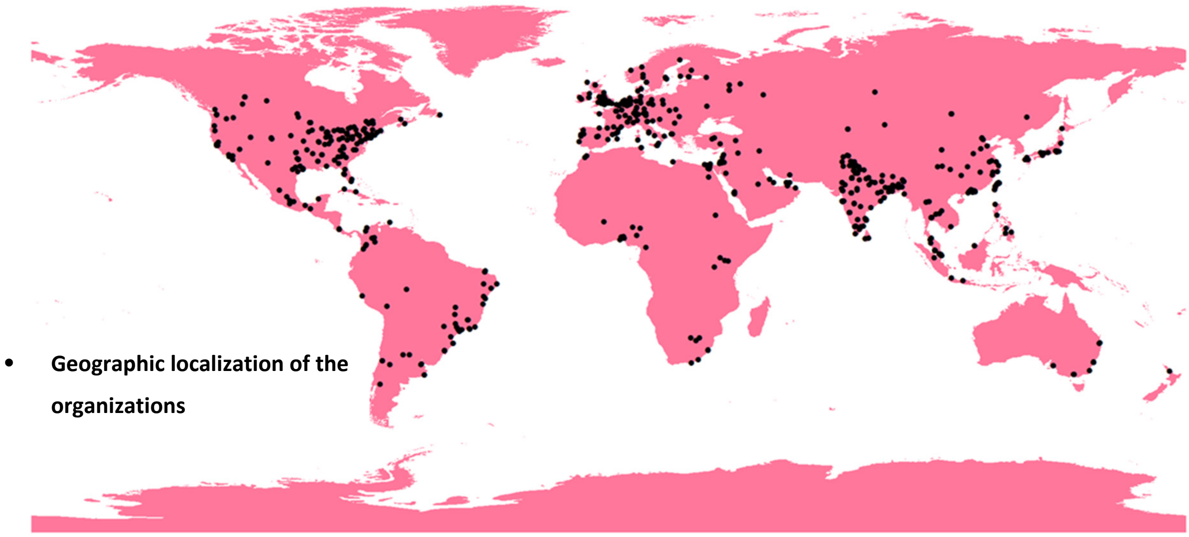

Figure 6. Geocoding of organizations cited in the 1220 articles analyzed.

In this analysis, the authors who published articles in the field of study were considered as an evaluation criterion. The collected database contained a total of 5760 different authors, indicating great interest in the research area studied. However, after modifying the criteria to create the map in VOSviewer (which shows the authors according to their participation in publications), it was found that 4724 authors participated in the production of only one publication, which represents approximately 82% of the authors. To understand the authors most involved in the field and the relationships of collaboration between them, a visualization map of the collaboration between authors with at least 10 scientific publications bearing their names was created (Figure 7). There are two possible classifications to define the importance of the authors: by the number of publications or by the number of citations. Since the scientific quality of the authors must be taken into account, the number of citations is a more efficient aspect to consider. This is because the number of times an author has been cited indicates the interest of other researchers in searching for the content developed by the author in question. The quantity of articles in which an author is involved does not necessarily reflect their scientific support or the quality of the information they have developed. Accordingly, the authors Wei and Zhou led the ranking of authors with the highest number of citations (3627 and 3412 citations, respectively) in the database. An interesting feature of these two authors, as shown in Figure 7, is that there were no links connecting them among the most influential authors, indicating individual work or work with specific research groups. Wei participated in the development of the most cited article entitled "Nanomaterials with enzyme-like characteristics (nanozymes): next-generation artificial enzymes (II)" [55], which received 1651 citations, accounting for about 46% of the author's total citations. In addition, Figure 7 shows a significant research characteristic: the dispersion of small groups of researchers, which reveals a non-concentrated research interest.

3.1.3. The Most Cited Articles

This analysis included a significant section devoted to bibliographic and bibliometric evaluation, focusing in particular on the most cited articles in the database. By examining the most influential documents, it is possible to understand the authors' coverage of specific content and its direct relevance to the topic of the study. Due to the large amount of data, some articles may be directly related to the topic, while others may only cover a specific aspect of the content. Table 3 shows the top 10 most cited articles, accumulating a total of 7879 citations, with Wu's article [55] occupying the first position and accounting for approximately 21% of all citations. This article discusses various types of nano-enzymes, the corresponding nanomaterials, and their catalytic mechanisms. It also summarizes various strategies for modulating the selectivity and activity of nano-enzymes and explores their diverse applications including biomedical analysis and imaging for theranostics and environmental protection. The second most cited article, "Zirconium-Metalloporphyrin PCN-222: Mesoporous Metal-Organic Frameworks with Ultrahigh Stability as Biomimetic Catalysts" [56], received 1187 citations and discusses the use of Fe-TCPP as a heme-like ligand and highly stable Zr6 clusters as nodes for the assembly of stable Zr-MOFs. The various applications of the study, especially enzyme coupling in biosensors, make it applicable in various fields. Figure 8 shows the future trends of the scientific literature related to the research area and identifies clusters of related works. For example, a keyword cluster on biosensors revealed "glucose detection," which refers to the process of glucose detection where MOFs can be used. Some examples of these applications include enzyme-free glucose detection in an alkaline medium [57], a highly selective colorimetric method with the peroxidase-like activity of Cu-MOF@Pt [58,59], a ratiometric fluorescence sensor [60,61], and high-density charged Ni-MOF nanoflow arrays [62].

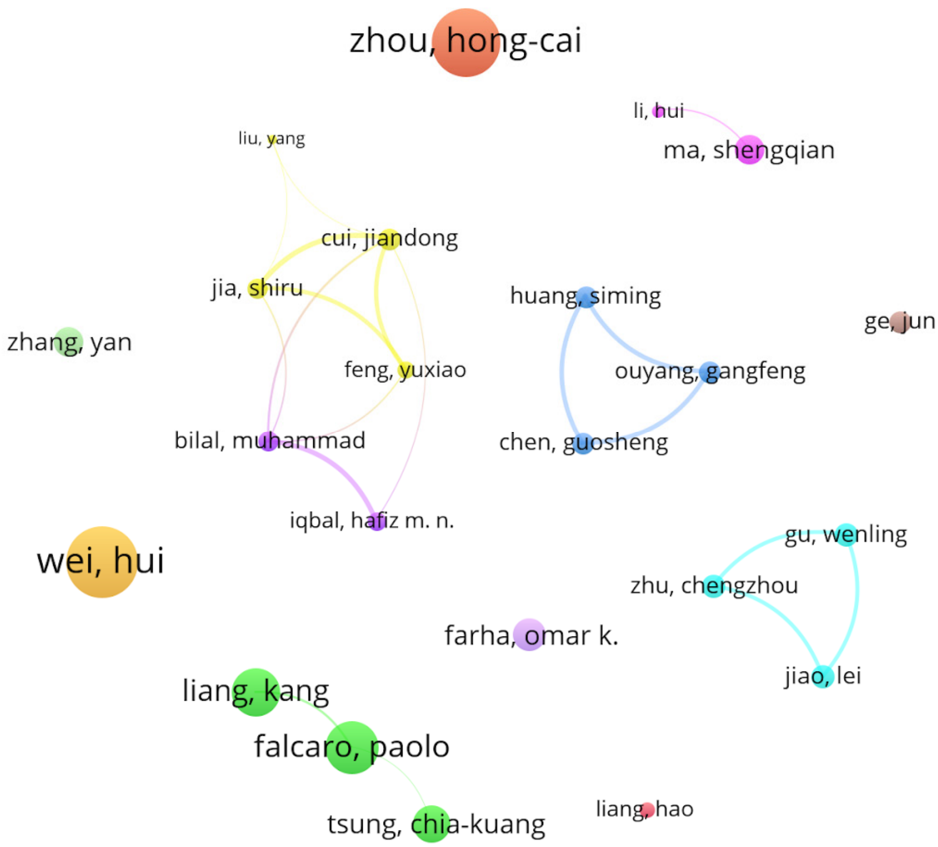

Figure 7. Network visualization map referring to the collaboration between authors with at least 10 publications; the number of citations defines the length of each item. The thickness of the lines that connect each author to another indicates the accumulation of co-authorship, and the clusters divided in different colors illustrate groups of authors with a high level of collaboration.

Table 3. The most cited papers in the field of metal-organic frameworks and enzymes.

Rank	Papers	Authors	Year Published	Citation
1	Nanomaterials with Enzyme-Like Characteristics (Nanozymes): Next-Generation Artificial Enzymes (II) [55]	Wu, Jiangjiexing; Wang, Xiaoyu; Wang, Quan; Lou, Zhangping; Li, Sirong; Zhu, Yunyao; Qin, Li; Wei, Hui	2019	1651

Table 3. *Cont.*

Rank	Papers	Authors	Year Published	Citation
2	Zirconium-Metalloporphyrin PCN-222: Mesoporous Metal-Organic Frameworks with Ultrahigh Stability as Biomimetic Catalysts [56]	Feng, Dawei; Gu, Zhi-Yuan; Li, Jian-Rong; Jiang, Hai-Long; Wei, Zhangwen; Zhou, Hong-Cai	2012	1187
3	Nanozymes: Classification, Catalytic Mechanisms, Activity Regulation, and Applications [63]	Huang, Yanyan; Ren, Jinsong; Qu, Xiaogang	2019	992
4	Cooperative Insertion of CO_2 in Diamine-Appended Metal-Organic Frameworks [64]	McDonald, Thomas M.; Mason, Jarad A.; Kong, Xueqian; Bloch, Eric D.; Gygi, David; Dani, Alessandro; Crocella, Valentina; Giordanino, Filippo; Odoh, Samuel O.; Drisdell, Walter S.; Vlaisavljevich, Bess; Dzubak, Allison L.; Poloni, Roberta; Schnell, Sondre K.; Planas, Nora; Lee, Kyuho; Pascal, Tod; Wan, Liwen F.; Prendergast, David; Neaton, Jeffrey B.; Smit, Berend; Kortright, Jeffrey B.; Gagliardi, Laura; Bordiga, Silvia; Reimer, Jeffrey A.; Long, Jeffrey R.	2015	778
5	Biomimetic Mineralization of Metal-Organic Frameworks as Protective Coatings for Biomacromolecules [65]	Liang, Kang; Ricco, Raffaele; Doherty, Cara M.; Styles, Mark J.; Bell, Stephen; Kirby, Nigel; Mudie, Stephen; Haylock, David; Hill, Anita J.; Doonan, Christian J.; Falcaro, Paolo	2015	754
6	Enzyme–MOF (Metal-Organic Framework) Composites [66]	Lian, Xizhen; Fang, Yu; Joseph, Elizabeth; Wang, Qi; Li, Jialuo; Banerjee, Sayan; Lollar, Christina; Wang, Xuan; Zhou, Hong-Cai	2017	703
7	Imparting Functionality to Biocatalysts via Embedding Enzymes into Nanoporous Materials by a de Novo Approach: Size-Selective Sheltering of Catalase in Metal-Organic Framework Microcrystals [67]	Shieh, Fa-Kuen; Wang, Shao-Chun; Yen, Chia-I; Wu, Chang-Cheng; Dutta, Saikat; Chou, Lien-Yan; Morabito, Joseph V.; Hu, Pan; Hsu, Ming-Hua; Wu, Kevin C. -W.; Tsung, Chia-Kuang	2015	550
8	Nanozyme Decorated Metal-Organic Frameworks for Enhanced Photodynamic Therapy [68]	Zhang, Yan; Wang, Faming; Liu, Chaoqun; Wang, Zhenzhen; Kang, LiHua; Huang, Yanyan; Dong, Kai; Ren, Jinsong; Qu, Xiaogang	2018	446
9	Stable Metal-Organic Frameworks Containing Single-Molecule Traps for Enzyme Encapsulation [69]	Feng, Dawei; Liu, Tian-Fu; Su, Jie; Bosch, Mathieu; Wei, Zhangwen; Wan, Wei; Yuan, Daqiang; Chen, Ying-Pin; Wang, Xuan; Wang, Kecheng; Lian, Xizhen; Gu, Zhi-Yuan; Park, Jihye; Zou, Xiaodong; Zhou, Hong-Cai	2015	410
10	Nanozymes in Bionanotechnology: from Sensing to Therapeutics and Beyond [70]	Wang, Xiaoyu; Hu, Yihui; Wei, Hui	2016	408

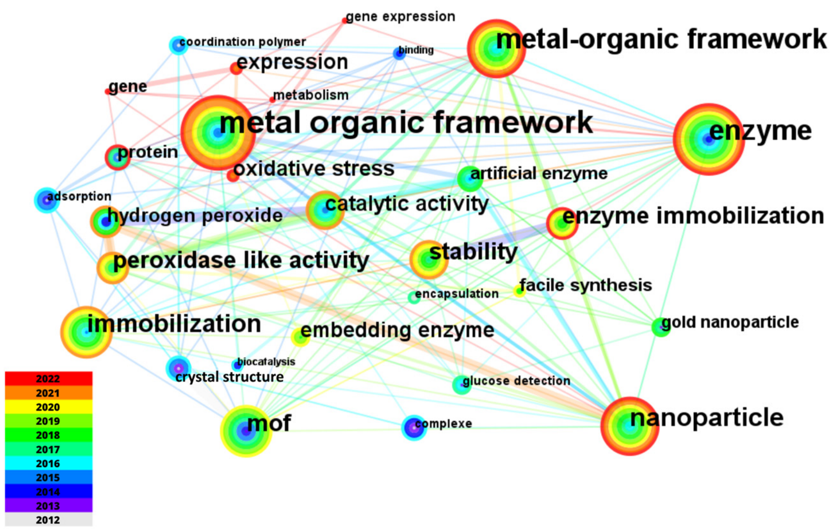

Figure 8. Keyword visualization network for the period 2012 to 2022.

3.1.4. The Research Areas

Different research methodologies applied to papers on MOFs reveal specific information on the processes, methods, and other aspects, highlighting the wide variability of research areas. The database documents identified 48 research areas, and 11 were considered the most relevant. Figure 9 shows the organization of the research areas in a radar chart, subdividing the relationships between quantity and countries with greater prominence. The chart shows that most countries tended toward research with a greater affinity for specific chemistry, with the United States, India, and Australia concentrating more than 40% of their production in this area. China had 34% of its publications in this research area and South Korea had 18%. An important feature of this graph is that China, the United States, and Australia had very similar research fields, and their quantitative representations had a similar format. In addition to "Chemistry", these countries were associated with "Materials Science" and "Science, Engineering, and Others". India and South Korea had a less concentrated distribution of their publications in other research fields. Furthermore, an article may be classified as research in two or more different fields of knowledge, and the proportion of documents in the research fields may proportionally exceed the number of documents in the database.

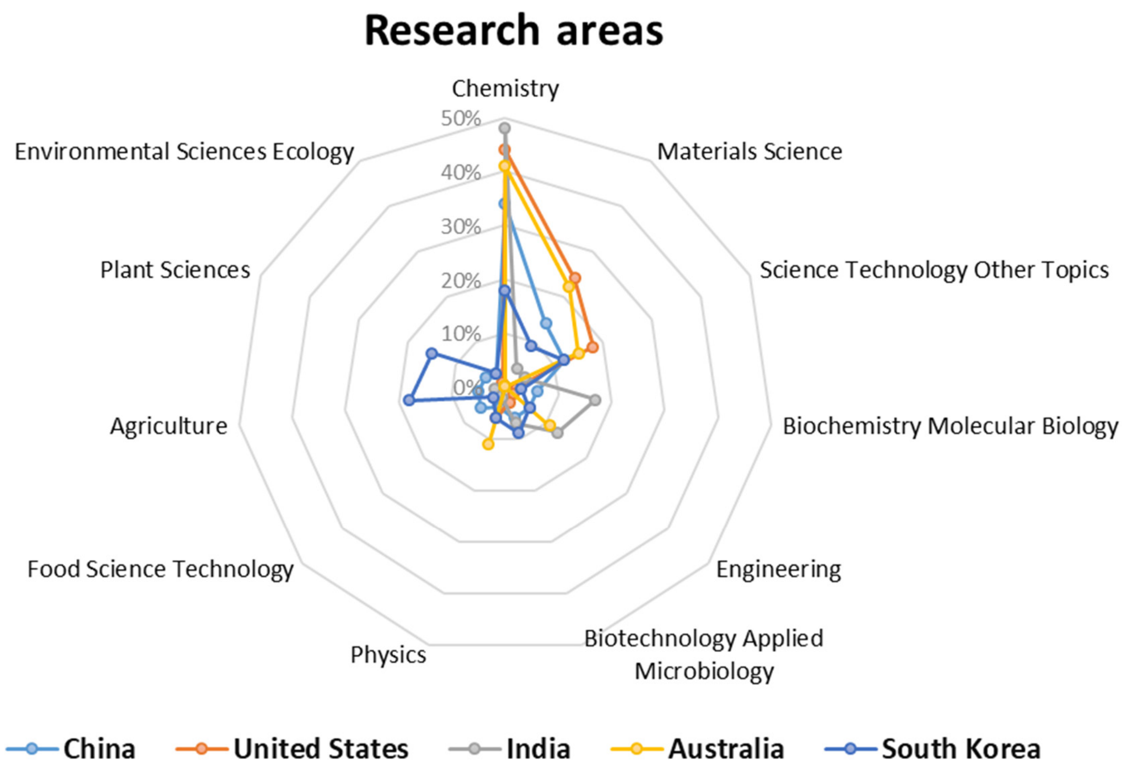

Figure 9. Distribution of research areas by country related to metal-organic frameworks and enzymes.

By analyzing the keywords present in the database using the data processing tools CiteSpace (Figure 8) we can gain insights into the general characteristics of the topic addressed in the articles. The database contained 2969 author keywords, and the classification of the terms with the highest frequency revealed some trends such as the processes in which MOFs are more involved and the relevance of biosensors in this environment. The keyword "metal-organic frameworks" was the most cited term (430) and is highlighted in Table 4 as a general term of research. However, many terms in this table are specific correlations of the topic addressed and do not provide much information about a particular research topic such as "nanoparticles", "enzymes", and "immobilization". Although these terms are essential for the detection of substances using various study methods, some terms are crucial to highlight such as "peroxidase-like activity", which appears in scientific papers dealing with structures that have peroxidase-like activity [71–78].

Table 4. The top 24 keywords in the field of metal-organic frameworks and enzymes.

Rank	Keyword	Frequency	TLS	Rank	Keyword	Frequency	TLS
1	Metal-Organic Frameworks	430	1066	13	Catalytic-activity	77	297
2	Nanoparticles	185	553	14	Hydrogen-peroxide	77	252
3	Enzymes	178	431	15	Encapsulation	74	289
4	Immobilization	172	585	16	Facile synthesis	73	285
5	Metal-Organic Framework	155	392	17	Biocatalysis	68	260
6	Enzyme immobilization	129	417	18	Oxidative stress	66	48
7	Peroxidase-like activity	110	412	19	Colorimetric detection	65	270
8	Stability	104	377	20	Expression	63	38
9	MOF	103	337	21	Biomimetic mineralization	56	220
10	Enzyme	87	282	22	Glucose	55	194
11	Embedding enzymes	79	244	23	Catalysis	54	163
12	Gold nanoparticles	78	245	24	Nanozymes	54	191

TLS: total link strength.

The topics that appear in Table 4 are consistently addressed in the articles and serve as targets for some of the methods discussed. For example, "colorimetric detection", "biomimetic mineralization", and "one-pot synthesis" are recurring themes. This highlights the versatility of MOFs in various applications, as shown in Figure 10, and underscores their potential for use in the development of biosensors.

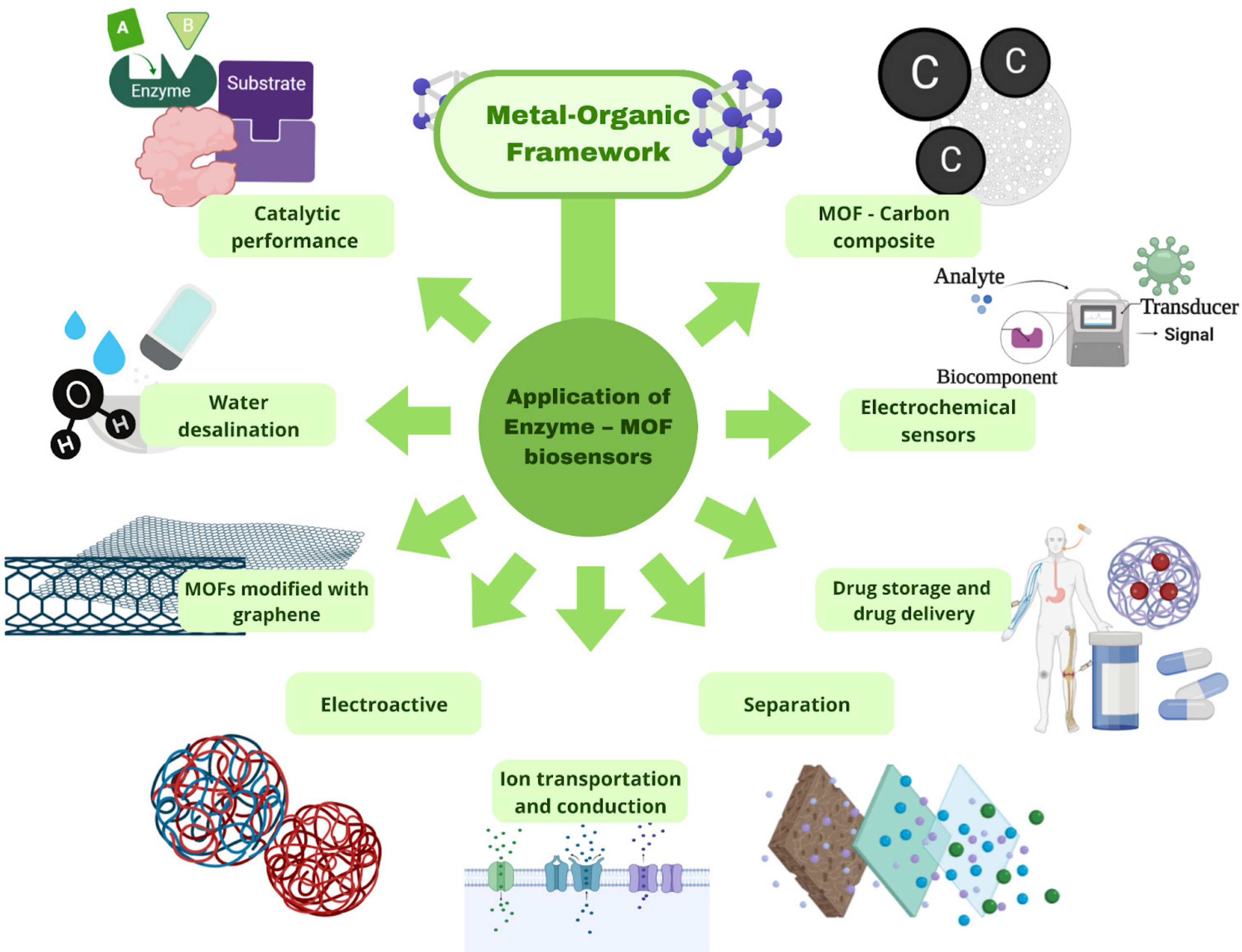

Figure 10. Applications of a metal-organic framework.

3.2. Biosensors Design

3.2.1. MOF-Based Chemosensors and Biosensors

The field of research related to chemosensory processes has gained significant attention due to the specific signaling and recognition actions involved [79]. In recent years, chemosensors and biosensors have been developed to detect food contaminants using various techniques such as fluorescence (FL) [80], electrochemical (EC) [81], photoelectrochemical (PEC) [82], and solid phase extraction (SPE) [83]. Zirconium-based MOFs (Zr-MOFs) are considered as a promising family of MOF materials for practical applications due to their structural variability, optimal stability, and attractive properties. Luminescent Zr-MOFs with appropriate metal nodes, ligands, and encapsulated guest molecules exhibit unique fluorescence responses, making them efficient and sensitive for the detection of various harmful pollutants and hazardous materials, which is crucial for human health and environmental protection [84]. In addition, MOFs have a large surface area, which makes them ideal for electrochemical applications by providing favorable conditions for the preconcentration of analytes on electrode surfaces. Therefore, MOFs and their derivatives have been used as electrochemical sensors, energy storage devices, and electrode materials for electrocatalysis [85]. Extensive research has been conducted on the photoelectrochemical detection (PEC) technique, which has resulted in the development of several biosensors for applications in DNA bioanalysis, enzyme detection, immunoassays, and cell-related monitoring due to its high potential in the field of bioanalysis. Lab-on-paper biosensors are considered to be one of the most promising analytical platforms [86]. In addition, MOFs have been used in solid phase extraction [87,88], dispersive solid phase extraction [89,90], and magnetic solid phase extraction [91,92].

As above-mentioned, MOFs have the potential to detect various biomarkers in health care. They are considered as strong candidates for the development of electrochemical sensors due to their ability to provide a favorable environment for the anchoring of biorecognition molecules [93]. An example is gout, a well-known inflammatory arthritis with increasing prevalence worldwide. Uric acid is an effective biomarker for the diagnosis of gout, as the disease typically manifests as excessive swelling and severe pain in a single joint caused by a high concentration of uric acid crystals, leading to joint inflammation [94].

3.2.2. MOFs for Catalytic Performance

MOFs have a wide range of potential applications in catalysis due to their large specific surface area, well-defined porosity, tunable function, and varied structural topology [95]. Specifically in multiphase catalysis, MOFs have shown promising results in promoting oxidation reactions of alkanes, alcohols, olefins, and other organic substances as well as CO due to their large specific surface area, regular pore structure, and highly dispersed metal active sites [96]. In addition, MOFs can be used to fabricate single-atom electrocatalysts and photocatalysts due to their porous structure, which enables high mass transfer performance. The adsorption of carbon dioxide and other molecules and species active in the reaction process enables easier interaction with catalytic sites. In addition, the metal nodes and organic ligands of some MOFs possess inherent electrochemical and photochemical activity, making them ideal platforms for the construction of single-atom electrocatalysts and photocatalysts [97].

MOFs possess unique properties that make them effective in the process of the spatial separation of catalytic sites, resulting in improved activity [98–100]. These structures are structurally adaptable with atomic precision, similar to homogeneous catalysts, but are also readily recyclable from the reaction system. MOFs exhibit many unique properties that are superior to traditional inorganic or organic materials by combining the advantages of homogeneous and heterogeneous catalysts. In particular, they integrate metal nodes and organic ligands into periodic structures, providing an ideal model for an accurate understanding of the structure–property relationship [101].

3.2.3. Nonenzymatic Electrochemical Detection

Metal-organic frameworks hold great promise as immobilization supports for enzymes and other biomolecules due to their high stability, controllability, and selectivity. However, the use of enzyme–MOF complexes often results in reduced enzyme activity and substrate affinity due to the restricted structure of the enzyme and limited substrate mass transfer, limiting their potential for use in biocatalysis and biosensing [102,103]. However, as above-mentioned, MOFs have shown significant potential in electrochemical sensors, particularly in non-enzymatic electrochemical methods that are inexpensive, highly sensitive, selective, and easy to use [104,105]. MOFs typically consist of metal ions (M^{n+}) or clusters coordinated with organic ligands [106], and M^{n+} enhanced MOFs have shown promising results for the catalytic oxidation/reduction of various molecules [107].

Nonenzymatic detection using metal-organic frameworks has shown promising results for various applications. For instance, MOFs can be utilized for glucose detection [108–115], glyphosate detection [116], organophosphate detection [117], ultrasensitive detection of miR-721 [118], hydrogen peroxide detection [119], and the detection of H_2O_2 released from living cells [120], as reported in the scientific literature.

Electrochemical sensors provide a fast, accurate, straightforward way to detect diseases in the medical industry compared to traditional laboratory techniques. The search for non-noble metal nanomaterials with high conductivity and large surface areas for enzyme-free sensor detection is an ongoing research area [121]. Therefore, MOF materials, with their ability to customize structures and functions, hold great potential for energy storage and electrochemical sensing applications. This demonstrates that MOFs have promising prospects for use in the field of electrochemical sensing [122].

3.2.4. Enzyme–MOF Composites

Enzyme–MOF composites have demonstrated high stability and optimal catalytic performance. In the last decade, considerable efforts have been made to develop enzyme–MOF composites for new applications. The dimensionality of the MOFs has a significant impact on the catalytic performance of enzyme–MOF composites [123]. Recent studies have explored the potential of enzyme–MOF composites in terms of their promising properties and characteristics including thermal/chemical stability, recyclability, Michaelis–Menten kinetics, and storage stability [44,124]. Various enzymes such as laccase, lipase, and cytochrome c have been successfully immobilized on MOFs with the promise of improving enzyme properties. The immobilization process of enzymes on MOFs typically involves covalent bonding, physical adsorption, or in situ encapsulation [125].

MOFs show great potential for the preservation of enzymes under harsh conditions [126,127]. However, there are two major limitations in immobilizing enzymes on MOFs: the need to match the molecular size of the enzyme with the pore size of the MOF and the need for a suitable pH range for the enzyme@MOF composite to remain stable. Fortunately, several strategies have been developed to overcome these challenges. For example, Zn^{2+}, imidazolate, and enzyme co-precipitation compounds have been used to overcome the size limitation of enzyme molecules and maintain stability under alkaline conditions. In the development of biosensors, several approaches have been explored, such as the combination of enzyme–MOF composites on polydopamine/polyethyleneimine flat patterns to enhance enzyme stability and sensitivity [128].

In this format, MOFs will develop a stabilizing microenvironment to provide protection to enzymes from denaturation and promote enzyme performance by performing the control of pore/surface properties (hydrophilicity, for example), which greatly enhances their application in various fields [129]. Most MOF compounds have naturally small electrical conductivity, limiting their application as electrical sensors [130]. Because of this factor, their applications in electrochemical sensing platforms have required developments both in conductivity and their composites and in strategies for interfacing these materials with electrode surfaces [131].

One can also cite pertinent examples such as a composite using nanometer MOF called NEQC-340, which is used for the efficient immobilization of urease (NEQC-340@Urease) at physiological pH and temperature to enhance the performance of enzymes in blood cleansing and water biotreatment [132]. Furthermore, the immobilization of various enzymes such as glucose oxidase [133], lacase [134], lipase [135], L-asparaginase [136], and strong root peroxidase [137]. Enzyme immobilization based on MOFs, in general, shows several advantages such as mild immobilization conditions, high loading capacity, low enzyme leaching, and short time for enzyme immobilization, which contributes to the application of biosensors [138].

3.2.5. Point-of-Care Sensors

In recent decades, there has been a rising trend to develop access to health care using point-of-care (POC) technologies [139]. POC devices are diagnostic tools that provide quick results in the presence of the patient, even when used by untrained individuals. Some requirements are defined for POC diagnostic devices: easy to use, sensitive, accessible, specific, fast and robust, equipment-free, and delivered to users, following the criteria guaranteed by the World Health Organization (WHO) [140]. One of the main impasses of the medical application of point-of-care biosensors is to enable appropriate and simple-to-use diagnostic tests that decrease the wait for therapeutic response when compared to a central laboratory for the monitoring and diagnosis of serious diseases [141].

Due to their various attractive characteristics, MOFs have become a promising material for the development of new sensing methods [142], so they are excellent candidates for various applications within the POC field such as nanomaterial-based biosensors for COVID-19 diagnostics [143], electrochemical sensors integrated into smartphones [144], optical biosensors for detection of antibiotics in aqueous media [145], and fluorescence detection of glucose in urine [146]. The use of MOFs for sensors has shown great results in several studies such as in the article "Lanthanide metal-organic framework as a paper strip sensor for visual detection of sulfonamide with smartphone-based point-of-care platform" published in 2022 by Yan [147] and the article "A novel metal-organic frameworks composite-based label-free point-of-care quartz crystal microbalance aptasensing platform for tetracycline detection" published in 2022 by Yang [148], which effectively show the potential of these frameworks in this field of research.

4. Trendy Research Topics

4.1. Quantitative Analysis of Frequent Keywords

An advanced bibliometric analysis examines the keywords used in scholarly articles within a given database. This research can reveal current trends and directions of research and provide insights into the relationships between different productions and fields of work. Table 4 shows the 24 keywords with the highest frequency within the database and the total number of links to other topics. The top keyword, "metal-organic frameworks," appeared 430 times, which is not surprising given that it was the central theme under study. It is worth noting that not all articles necessarily contain this term at least once, as some variations of the term are also included in the table. Positions 5 and 9 reflect this discrepancy, with 155 and 103 occurrences, respectively. It is also important to note that the terms can appear in fields other than keywords such as titles and abstracts, which could explain the differences between the values in the table and the total number of articles analyzed.

Based on the total number of author keywords (2969) and excluding the primary term and its variations, the top five keywords with the highest frequency were as follows: nanoparticles (185 with 553 links), enzymes (178 with 431 links), immobilization (172 with 585 links), enzyme immobilization (129 with 417 links), and peroxidase-like activity (110 with 412 links). By examining Table 4, it is evident that there was a trend in studies related to the topic that focuses on improving the coupling of enzymes to metal-organic frameworks (MOFs) for various processes such as hydrogen peroxide detection, biocatalysis, colorimetric detection, biomimetic mineralization, and glucose detection. The goal of these studies is to improve the stability, catalytic activity, and ease of synthesis of enzyme–MOF composites.

Figure 11 shows a more interactive representation of the data presented in Table 4. This figure shows distinct clusters of keywords separated by VOSViewer software. The purple cluster, which was the largest, contained keywords closely related to the enzyme MOF process. The blue cluster contained terms related to nanoparticle detection techniques such as glucose detection. Finally, the red cluster, which was the smallest, referred to studies directly related to enzymes, with MOFs less actively involved and present in some process examples. The size of each node in the figure corresponds to the number of occurrences of the keyword, while the size of the lines connecting the nodes represents the strength of the relationship between the terms.

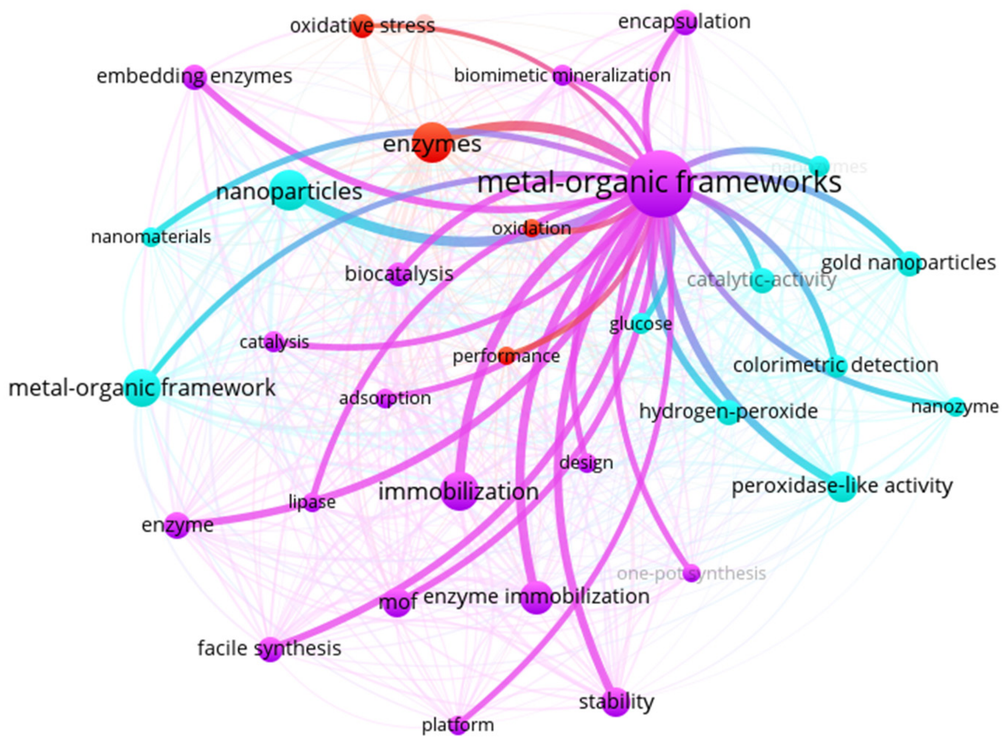

Figure 11. Visualization map of the co-occurrence network of all keywords in the research related to metal-organic frameworks.

4.2. Research Areas

In this study, the Citespace program was used for data processing to analyze emerging trends in the field and the research conducted during the decade of analysis [149] ass it allowed us to examine the evolution of knowledge in a particular research area. By examining finite groups or clusters, important information about the field and the individual characteristics of each term in the database can be revealed [150]. Table 5 presents a list of the top five representative terms for each cluster, highlighting the major research themes and the importance of each keyword concerning them. In addition, Figure 12 illustrates a timeline visualization of the trending keywords using a cluster analogy. The nodes and the overlapping color layers within them indicate the search strength of each term over a given year. For example, the term "dismutase" was predominantly yellow, indicating its strong presence in recent studies. This term refers to superoxide dismutases, which are antioxidant enzymes that protect organisms from reactive oxygen species [151]. Conversely, the term "coordination polymer" appeared mostly in purple, indicating its older fixation. This keyword is associated with the class of MOFs, which are coordination polymers structured from energetic organic compounds and inorganic salts [152].

Table 5. The top ten scientific journals published in the research field.

CID	Label	NS	Mean	Top Five Terms	Representative Papers
#0	metal-organic framework	32	2014	metal-organic framework; ascorbic acid; tandem catalysis; sensitive detection; oxidase-like activity	[153,154]
#1	exo selectivities	19	2012	exo selectivities; enantioselective diels-alder reaction; flexible chiral supramolecular catalyst; anthryl side-group; single-crystal structural dynamics	[155,156]
#2	metal-organic framework	18	2012	metal-organic framework; myst protein acetyltransferase activity; active site lysine autoacetylation; cofactor surrogate; labeling lysine acetyltransferase substrate	[157,158]
#3	signaling pathway	17	2014	signaling pathway; metal-organic framework; antioxidant capacity; large yellow croaker; lipid metabolism	[159,160]
#4	metal-organic framework	17	2012	metal-organic framework; intrinsic peroxidase-like catalytic activity; pH-responsive drug delivery; coordination polymer; prepared using metal-organic framework template	[161,162]
#5	multicopper complex	16	2012	multicopper complex; mild oxidative functionalization; coordination polymer; alkane; cooperative insertion	[64,163]

CID = cluster ID, NS = node size.

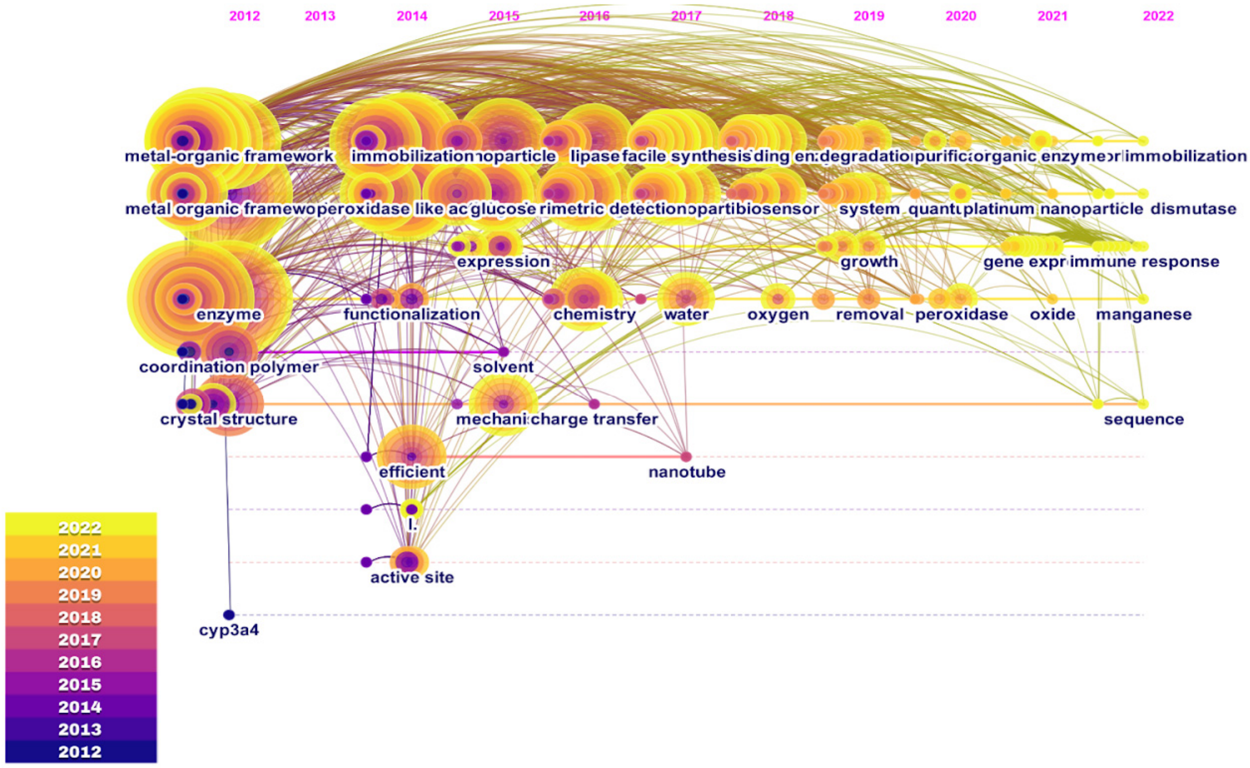

Figure 12. Visualization of the timeline view of hot keywords.

Figure 13 corresponds to the method used in Figure 12, where highlighted keywords and their research intensity in a certain time frame are shown. For example, the term "adsorption" had its peak occurrence in research from 2012 to 2016, while "magnetic nanoparticles" had a longer lifespan with good frequency in research from 2012 to 2019. This indicates that, compared with the former term, the latter term has attracted more interest from researchers to develop research related to it directly or indirectly. "Artificial enzyme" is a keyword that showed great relevance with a strength of 13.64 (the highest among the highlights) but had a shorter lifespan of only four years. This shows that this research topic had a lot of interest during this period, but was replaced by more attractive searches. The term related to glucose detection, which was cited a lot earlier in this paper, had the shortest lifespan of only two years due to the abundance of studies and results in this area. As a result, interest in scientific research has waned, leading to a migration to more attractive topics with fewer studies developed. An example of this is the lower part of the figure, where the term "water" is inserted into the use of MOFs to filter and purify water for human consumption.

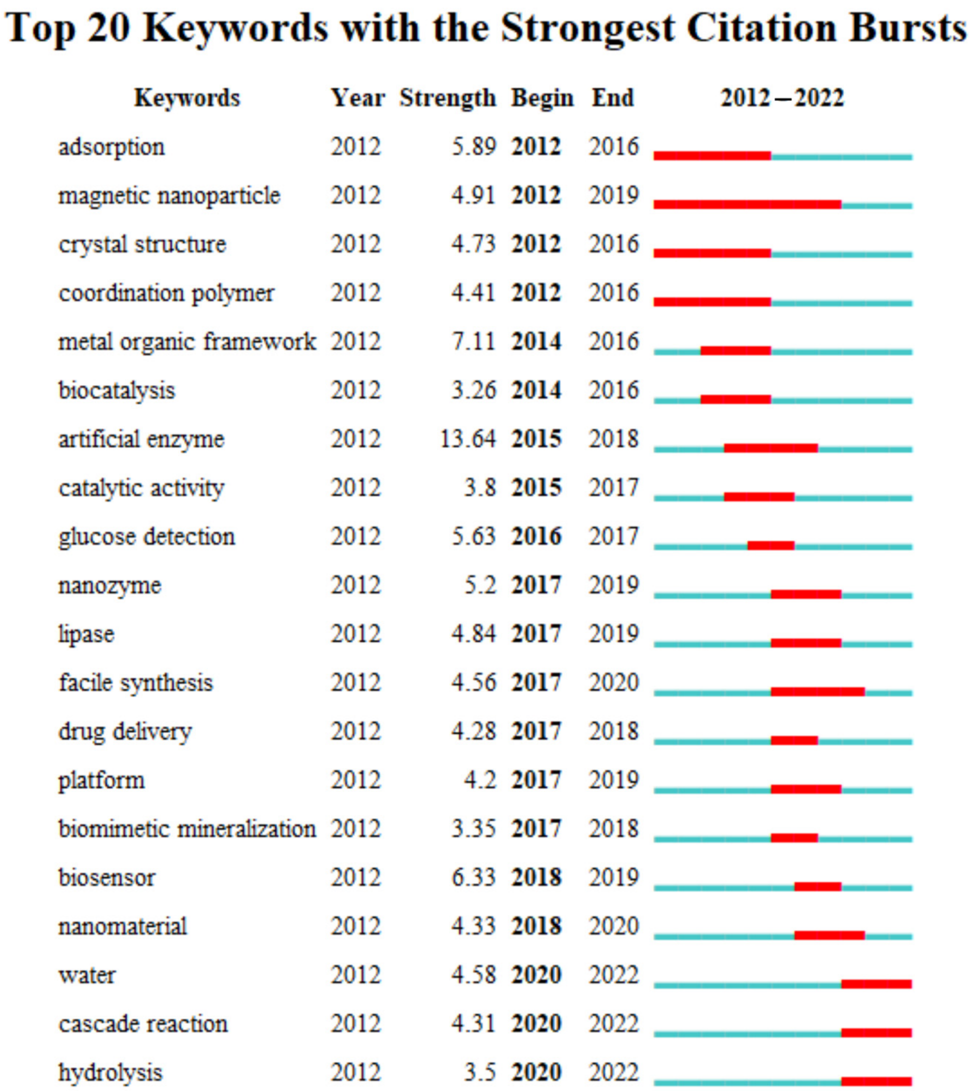

Figure 13. The top 20 keywords with the strongest citation bursts.

4.2.1. Research Fields

To analyze the clusters generated by the Citespace software, the terms that represented each group of research keywords was examined to understand the organization and importance of the study area. Each term reflected a topic of scientific importance for this group, which may be directly or indirectly related. The year with which the term was associated is shown in the "Mean" column of Table 5, which is linked to the most significant occurrence article. Cluster #0 contained the term "metal-organic framework", which is associated with the group of terms representing the research area related to the use of MOFs for immobilization methods in discoveries. This can be confirmed by its representative articles. For example, Liu [153] described the development of an enzyme-NBD@MOF bioreactor with optimal proteolytic performance using a simple and rapid multipoint immobilization technique without chemical modification of the solid support.

The second article [154] aimed to explore promising gold nanomaterials in engineered enzymes such as nuclease mimicry, peroxidase, silicatein, esterase, glucose oxidase, catalase, and superoxide dismutase.

It can be observed that the term "metal-organic framework" was present in three different clusters (Cluster #0, Cluster #2, and Cluster #4), reflecting the different research areas in which MOFs are being studied. In Cluster #1, the representative term was "exo selectivities", which is related to the study of the dynamics of group interaction with the selectivity of structural additions and reactions, an area in which MOFs have been of great interest. Hatano's article [155] discussed the anomalous endo/exo selective Diels–Alder reaction and reviewed the development of catalysts including recent chiral catalysts that are highly active and supramolecularly flexible. Singh's paper [156] described a recently synthesized two-dimensional coordination polymer using a flexible ligand based on 5-[(anthracen-9-ylmethyl)-amino]-isophthalic acid carboxylate and Gd(III) ions by the solvothermal technique.

4.2.2. Emerging Trends

MOFs have shown great potential in health research, with applications ranging from disease detection [164–166] to combating harmful microorganisms [167,168] and specific biomedical applications [169,170]. This is reflected in Clusters #2 and #3 in Table 5, which had "metal-organic framework" as their primary term. In Cluster #2, the first representative paper was by Yuan [157], who demonstrated that the acetyltransferase activity of the MYST protein requires self-acetylation of lysine at the active site, providing a method for controlling important cellular activities. The second paper by Yang [158] focused on the design and application of chemical probes to facilitate the labeling and substrate detection of the three major human KAT enzymes. These papers highlight the potential of MOFs in the health field and demonstrate the diverse applications of this material.

Cluster #3 was represented by the keyword "signaling pathway" and encompassed a diverse set of integrated terms. In addition to the emerging themes above-mentioned, this group also included research on energy harvesting using MOFs. This was evident from the representative papers included in this cluster. Xiao [159] discussed the metal-organic structure Fe_2 (dobdc) ($dobdc^{4-}$ = 2,5-dioxido-1,4-benzenedicarboxylate) and its magnesium-diluted counterpart, $Fe_{0.1}Mg_{0.2}$ (dobdc), which can activate the C–H bonds of ethane and convert it to ethanol and acetaldehyde using nitrous oxide as a terminal oxidant. Kuang's paper [160] described the development of a DNAzyme-based sensor that combined the identification and catalysis of DNAzyme with the optical properties of certain nanomaterials for the determination and quantification of lead ions (Pb^{2+}).

The fourth cluster was dominated by the keyword "metal-organic framework." The research area of this cluster was exemplified by the papers selected to represent it. Zhou [161] discussed recent advancements in immobilizing enzymes on mesoporous materials, highlighting their potential use as biocatalysts in the chemical and pharmaceutical industries. In contrast, AI [162] explored the peroxidase-like activity of an iron-based metal-organic framework, MIL-53(Fe), and its ability to perform the essential colorimetric detection of hydrogen peroxide and ascorbic acid.

Finally, Cluster #5 focused on multicopper oxidase enzymes and was represented by the keyword "multicopper complex". The multicopper-oxidase superfamily consists of oxidoreductase enzymes that use copper as a cofactor to reduce O_2 to H_2O [171]. Kirillov's [163] representative paper summarized recent advances in the oxidative activity of alkanes catalyzed by multicopper systems due to copper's well-assured biological function, which is present in the active sites of several oxidation enzymes including multicopper particulate methane monooxygenase (pMMO). Mcdonald's [64] paper demonstrated that diamine-attached MOFs can act as 'phase change' adsorbents, with CO_2 exhibiting unusual step-shaped adsorption isotherms that varied greatly with temperature.

4.2.3. Two Key Insights

The bibliometric review methodology offers several possibilities for analyzing a specific field of research. However, to carry out such an investigation using large databases and computer processing, a well-defined strategy is essential. It is important to keep in mind that not all articles directly address the subject, and there may be papers that only mention it in passing. To generate a cohesive and scientifically rich dataset, a well-advanced analysis methodology is required. Citespace is an essential tool in this regard, as it allows for the identification of scientific articles and displays trends and development dynamics by analyzing co-citation networks. Developed by Chaomei Chen, Citespace utilizes cluster analysis as the underlying algorithm and generates an independent co-citation analysis from multiple literature research perspectives, confirming the trends identified in previous analyses [172].

The focus of this paper was on biosensors, which is a promising area of research. However, due to the recent nature of this research, there are relatively few publications related to the enzyme–MOF combination for biosensor development (Figure 13). Therefore, a comparative analysis with other applications was conducted to understand their relevance, dynamics, and scientific trends. This analysis revealed that there are several applications where the combination of enzymes and metal-organic frameworks is promising. One such application is the development of biosensors for glucose detection, which has resulted in a large number of articles in the database [173–185]. MOF-based sensors have recently gained significant interest among researchers due to the inherent structural and functional compositional advantages of MOFs, optimal biodegradability, high biocompatibility, and excellent thermal stability, which make them ideal for sensing and imaging purposes [186].

The second perspective concerns the multitude of studies that explore the applications of metal-organic frameworks beyond their combination with enzymes for sensor development. For example, there is a considerable amount of research focusing on the use of MOFs for the removal of pollutants from water [187–194]. In addition, in the field of biodiesel production, MOFs are used as catalysts, and accurate characterization using various analytical techniques is necessary to predict catalytic activity for better quality biodiesel production [195]. These examples illustrate the flexibility and relevance of MOFs in different research areas.

5. Conclusions

This article has presented several features of metal-organic framework applications with data processing that have helped to visualize the research field. The primary focus of this study was on enzyme-coupled MOFs for biosensor development and the research trends and opportunities associated with them. The research methodology was designed to provide a comprehensive view of other applications of MOFs to understand how the scientific literature on biosensors is developing compared to other processes. It was observed that biosensors have shown promising potential due to the recent increase in the developed research. MOFs have been increasingly applied in various fields such as human health, sustainable energy, and the environment. In particular, in the field of biomedicine, MOFs have been explored for the development of biosensors to detect specific compounds.

Based on the information presented, several emerging areas in the literature were identified, which provide insight into the current direction of scientific research. These findings illustrate how the field has evolved over the past decade and provide insight into potential areas of future interest for researchers worldwide. Therefore, the following conclusions can be drawn from this review:

- Through the analysis conducted, it was found that biosensors were a highly researched topic during the period analyzed, indicating a growing interest in this emerging field of scientific literature. The promising applications of MOFs coupled with various materials, especially enzymes, suggest the potential for future developments.
- The non-enzymatic use of MOFs is more prominent due to its long history of use in various fields of research. This combination has been explored more extensively than

the enzyme-MOF combination, which is a relatively recent development. As a result, areas that have received more research attention in the past have not included the enzyme–MOF combination, resulting in a lack of studies in this area of science.

- The analysis of publishing countries revealed that China (831 articles), followed by the United States (159 articles) and India (57 articles), had the most significant contributions in this research area. This is a common trend in several research fields as these countries have a significant engagement in building scientific knowledge. Furthermore, this information indicates the relative importance of this research area to China compared to the United States, as evident from the quantitative data of the documents produced.
- Based on the analysis of the topics addressed in each article and the post-processing of the Citespace data, it can be concluded that the field of medicine is the most prominent research area in the application of MOFs. This is mainly due to the large number of articles, identified by relevance levels, that have focused on the detection and removal of harmful compounds that affect human health. Energy applications of MOFs are also considered important, but to a lesser extent compared to medicine.
- An important aspect to note in the methodology is the comparison of the number of articles found in the two largest databases. A search using the keywords "Enzymes" and "Biosensors" returned 2264 articles. However, by adding the keywords "Metal-Organic Framework", "Metal-Organic Frameworks", or "MOF", the number of articles increased to 1220. Therefore, searches related to enzymes and MOFs represented about 53% of the total database related to enzymes and biosensors. However, when all of these keywords were combined, the number decreased to 87, indicating that there were significantly more studies on other applications of MOFs coupled with enzymes.

Therefore, this review provided insights into the research trends and directions in this field and highlighted the critical aspects to be considered when analyzing relevant studies. The prospects of this research field are significantly related to the health care sector and in addressing urgent human needs that require diverse outcomes such as pharmaceutical solutions and environmental care beyond conventional aspects such as water purification. This unique property of MOFs offers numerous opportunities for scientific advancement including undiscovered methods and unexplored research avenues. Most of the reviewed articles highlighted the potential of MOFs in various applications, indicating the great potential for future research in this field.

The structure of this study was designed to provide a more accurate understanding of the scientific field surrounding MOFs by using advanced bibliometric analysis methods that require extensive data processing. Performing such an analysis manually would be time-consuming and impractical for hundreds or thousands of documents, potentially leading to important papers being overlooked. However, this study overcame these limitations by generating graphical and descriptive results that provide richer scientific information than traditional manual research. This methodology is particularly useful for gaining a more comprehensive understanding of the subject matter, which is only possible through computational processing.

Finally, the understanding of this research area is crucial for the advancement of scientific literature that connects various fields including chemical engineering, chemistry, biomedicine, and biosensors. Research on metal-organic frameworks has experienced a significant increase in interest and growth, indicating its potential in the development of sustainable solutions, a topic that is rapidly gaining importance in society and is likely to become a pressing concern in the literature. The results of this thesis contribute to a better understanding of MOFs and provide an opportunity to observe critical aspects for further studies. Therefore, this topic is crucial as a source of knowledge for current and future needs and holds a position of great importance in the scientific community.

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