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# Mapping the landscape of metal-organic frameworks in orthopedics: a review

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## Abstract

This study presents the first bibliometric analysis of metal-organic frameworks (MOF) in orthopedics, highlighting key research trends and investigative focuses. An exhaustive review of 219 records from the Web of Science core collection database provided insights into the development and potential uses of MOF in orthopedic interventions and bone tissue engineering. Known for their unique architecture, large surface areas, and adjustable porosity, MOF have shown promise in a variety of biomedical applications, including drug delivery, bone restoration, and as components in orthopedic implants. This investigation identifies prominent MOF series and summarizes their main functions in orthopedic settings. In vivo studies have confirmed the versatility and effectiveness of MOF in promoting bone regeneration, combating infections, targeting bone tumors, and reducing osteoporosis. However, challenges persist in translating MOF research into clinical orthopedic applications, particularly in ensuring biocompatibility and stability in the human body and uniformity of MOF composites. Future directions include expanding MOF applications through global collaboration and interdisciplinary efforts to accelerate their integration into clinical orthopedics. This research emphasizes the substantial potential of MOF to transform orthopedic treatments, advocating for further investigation and collaboration to fully exploit their clinical capabilities.

**Keywords:** Bibliometric analysis, Metal-organic frameworks, Orthopedics

## 1.Introduction

Orthopedic research, which focuses on musculoskeletal health and therapeutic interventions for bone-related disorders, is instrumental in improving the quality of life.[1–3] Yet, there's an urgent demand for more innovative solutions to treat extensive bone defects, joint inflammation, bone infections, and tumor damage.[4–6] Traditional materials employed in these interventions face numerous limitations,[7,8] thereby leading to a growing interest in advanced materials to address challenges in bone regeneration, osseointegration, and bone disease treatment. In this context, the evolution of materials science and biomedical engineering has brought to light novel synthetic biomaterials such as bioactive glass, bioceramics, bone morphogenetic protein (BMP), polycaprolactone, metal-organic frameworks (MOF).[9–12] MOF, in particular, have gained substantial attention in biomedical research due to their unique structure, large surface area, adjustable porosity, biodegradability, and customizability,[13–15] positioning them as a promising candidate material for promoting orthopedic treatment and bone tissue engineering.

MOF, distinguished by their organic ligands coordinated with metal ions or clusters, present a diverse array of structures with unique properties. These characteristics make MOF particularly promising in the field of orthopedics.[16,17] Previous research has underscored the multifaceted applications of MOF in this area, ranging from faciliating bone regeneration to acting as a drug delivery vehicle and improving the effectiveness of orthopedic implants.[18–20] Despite these advancements, the exploration of MOF in orthopedics remains relatively unexplored, with a lack of comprehensive understanding of the current research landscape. Bibliometric methods, pivotal in assessing scientific progress and academic impact, offering insights into research quality, trends, and influence, thereby supporting decision-making in scientific policy and resource allocation. While previous studies have explored into MOF applications in biomedicine[21] and photo-/electrochemistry,[22] there is a notable gap in bibliometric analysis concerning their orthopedic applications.

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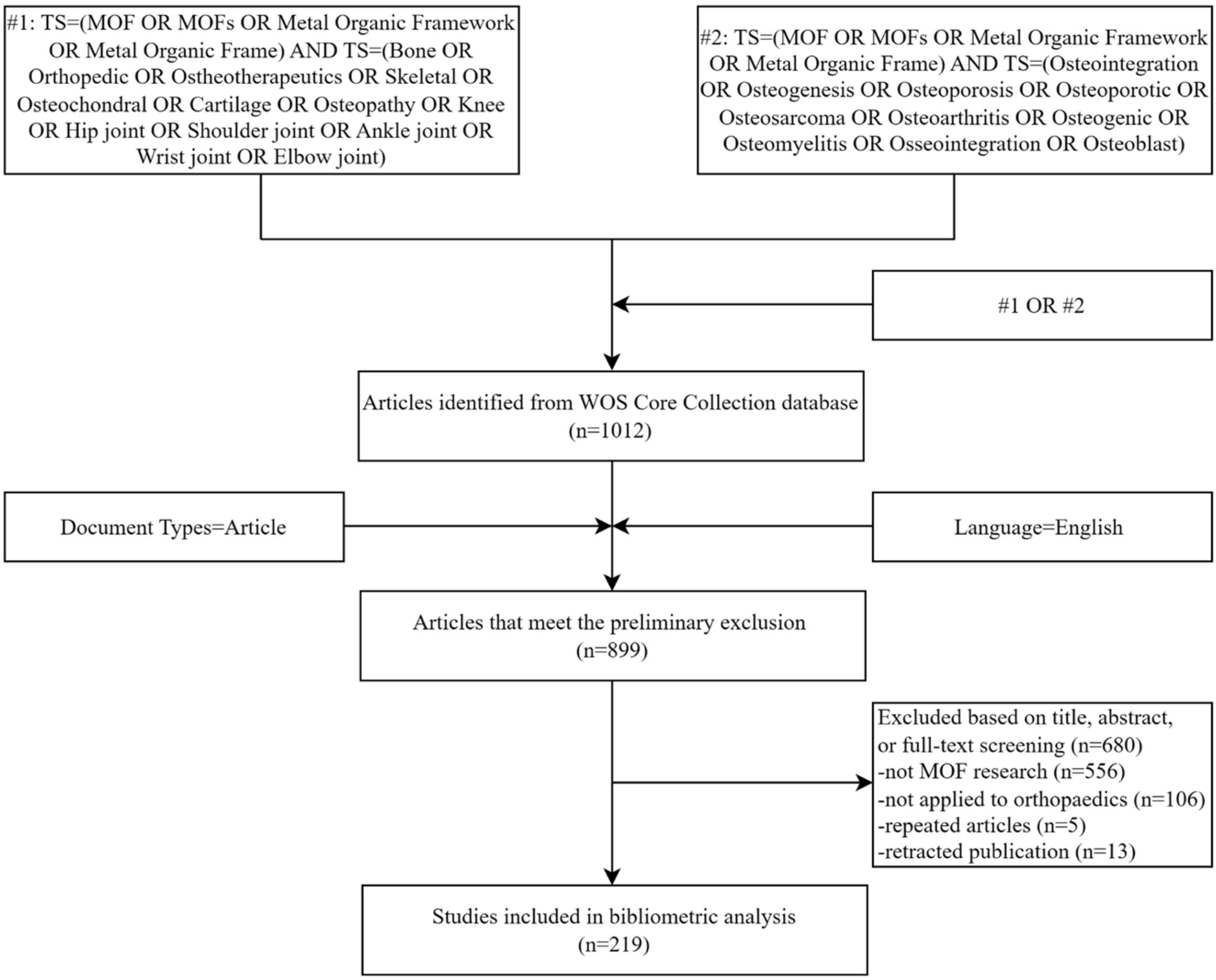


**Figure 1.** Flowchart for publication retrieval, exclusion, and inclusion.

This article endeavors to shed light on the prevailing trends, pivotal publications, influential journals, and primary research directions in the orthopedic utilization of MOF materials. Through comprehensive analysis of an extensive array of publications, this study aims to delineate the current state of research and identify emerging frontiers, thereby directing subsequent research endeavors and optimizing the potential of MOF in orthopedics. Moreover, this investigation is anticipated to serve as a reference for MOF applications across diverse disciplines, promoting interdisciplinary integration and furthering advancements in fields such as materials science and biomedicine. The exploration of MOF within the field of orthopedics is expected to pave the way for future personalized and precision medicine, underscoring the crucial role of pioneering materials science in healthcare evolution.

## 2. Data and methods

### 2.1 Data sources and search strategies

An exhaustive online bibliographic search was performed using the Web of Science Core Collection (WOSCC) database. The search strategy employed was as follows: TS= (MOF OR MOFs OR Metal-Organic Framework OR Metal-Organic Frame) AND TS= (Bone OR Orthopedic OR Ostheotherapeutics OR Skeletal OR Osteointegration OR Osteogenesis OR Osteoporosis OR Osteoporotic OR Osteosarcoma OR Osteoarthritis OR Osteogenic OR Osteomyelitis OR Osseointegration OR Osteoblast OR Osteochondral OR Cartilage OR Osteopathy OR Knee OR Hip joint OR Shoulder joint OR Ankle joint OR Wrist joint OR Elbow joint). The data retrieval process was unconstrained by time, and to minimize bias resulting from frequent database updates, all searches and data exports were completed on March 25, 2025.

### 2.2 Article screening

A total of 1012 results were retrieved from the WOSCC database. All records were screened and evaluated by 2 independent authors. If there was a disagreement between the 2 authors, a third author participated in the discussion and reached a consensus. Firstly, the screening results were initially refined by limiting the language of the publication to English and the type of publication to article. Second, the records were further screened by reading the title or abstract or full text to exclude unsuitable articles. The specific screening process was shown in Figure 1. Finally, 219 records were included in our study.

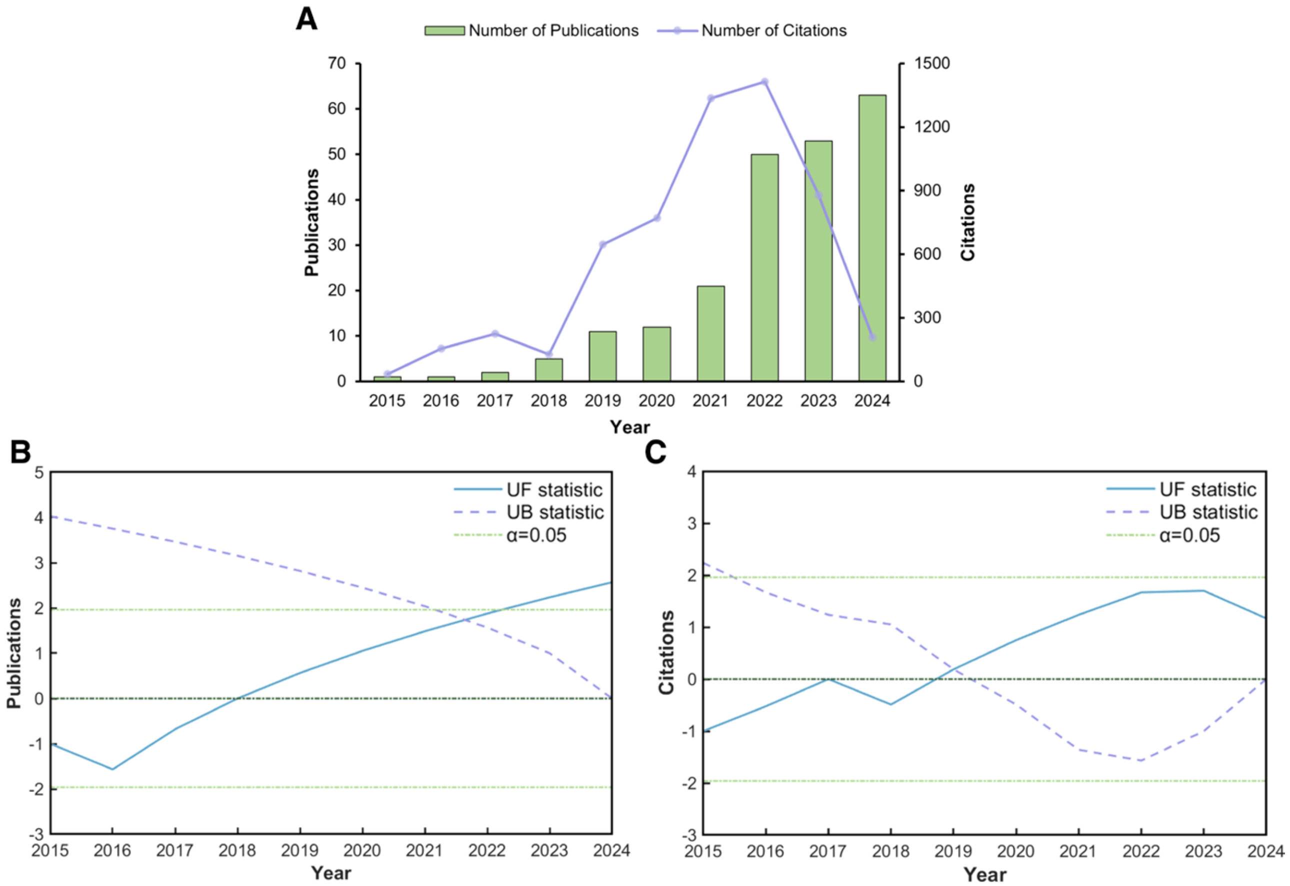


**Figure 2.** (A) Trends in annual publications and citations. The Mann-Kendall trend test is applied to analyze the trends in (B) publications and (C) citations. The UF curve represents the directional trend, while the UB curve signifies the inverse series of the UF curve. A positive UF value indicates an increasing trend, whereas a negative UF value signifies a decreasing trend. The significance level, set at 0.05, corresponds to a value of ±1.96. A UF value exceeding 1.96 indicates a significant increasing trend, while a UF value < −1.96 indicates a significant decreasing trend. The point of intersection within the confidence interval (±1.96) denotes the mutation point.

### 2.3 Data collection and extraction

The eligible publications were meticulously annotated and exported from the WOSCC database. The data extracted from these publications encompassed article information (title and keyword), author information (author name, institution, country, corresponding author, or reprint author), publication information (journal, year of publication, and impact factor), citation information (total number of citations and cited references).

### 2.4 Statistics analysis

To illustrate the trends in article publications and citations, we employed histograms and line graphs. The temporal changes of these trends was analyzed using the Mann-Kendall mutation test in MATLAB software. Keyword clustering cooccurrence networks and time coverage maps were used to determine the main research focal points. The geographical distribution of research activity and publication status across various countries was depicted using a world map. Furthermore, an in-depth analysis of literature collaborative networks was performed to understand the relationships between different research entities. For data analysis and visualization, we used several tools: VOS viewer[23] 1.6.18 (Leiden University Centre for Science and Technology Research), the Bibliometrix R package version 4.0 (https://www.bibliometrix.org), Charts and Maps (https://amcharts.com), Diamond (Crystal Impact GbR, University of Bonn, Germany), and Microsoft Excel (Microsoft Corporation, Redmond, WA).

## 3. Results

### 3.1 Visualization of annual publications and citations

We analyzed the number of articles and total citations per year, including articles published between 2015 and 2024 in this study. The total number of articles increased annually, with the number of citations reaching a peak in 2022 before gradually declining, resulting in a relatively low citation count in 2024 (Figure 2A). The Mann-Kendall abrupt change test revealed a change point in the publication of articles after 2021, indicated by the intersection of the UF and UB curves. Meanwhile, the UF curve showed an upward trend in article publications after 2018 and a significant upward trend after 2022 (Figure 2B). Additionally, the citation change point occurred in 2019, followed by a sustained upward trend in citations (Figure 2C).

### 3.2 Analysis of high productive journals and highly cited articles

Among the top 11 journals by publication volume, there were a total of 83 articles, accounting for 37.9% of the total

**Table 1**

**The top 11 most productive journals.**

| Journal | Publications | Total citations | Average citation | Impact factor |
|---|---|---|---|---|
| ACS Applied Materials & Interfaces | 16 | 624 | 39.00 | 8.5 |
| Chemical Engineering Journal | 13 | 494 | 38.00 | 13.4 |
| Advanced Healthcare Materials | 7 | 219 | 31.29 | 10 |
| Journal of Materials Chemistry B | 7 | 336 | 48.00 | 6.1 |
| Small | 7 | 162 | 23.14 | 13 |
| Journal of Nanobiotechnology | 7 | 215 | 30.71 | 10.6 |
| Journal of Colloid and Interface Science | 6 | 94 | 15.67 | 9.4 |
| Biomaterials | 5 | 437 | 87.40 | 12.8 |
| Bioactive Materials | 5 | 350 | 70.00 | 18 |
| ACS Nano | 5 | 379 | 75.80 | 15.8 |
| Advanced Science | 5 | 140 | 28.00 | 14.3 |

publications (Table 1). *ACS Applied Materials & Interfaces* had the highest number of publications, followed by *Chemical Engineering Journal*, and *ACS Applied Materials & Interfaces* had the highest number of citations. The top 3 journals with the highest impact factors were *Bioactive Materials*, *ACS Nano*, and *Advanced Science*. The MOF materials studied in articles with the highest annual citation counts were illustrated in Figure 3A. Among these studies, 4 research items demonstrated the role of enhancing bone regeneration, 1 study showed its potential in treatments for osteomyelitis, 2 study highlighted its role in promoting osteogenic, 1 study applied it in treating bone tissue diseases, 1 study shows its ability to treat osteoarthritis, and 1 study focused on its application in treating bone joint tuberculosis. The top 10 most cited articles were listed in Table 2, all originating from institutions in China, with 2 articles from Chongqing University, 2 from Sichuan University, and others from Hubei University, Jilin University, China Medical University, Shanghai Jiao Tong University, Guangdong Medical University, and Zhejiang University.

### 3.3 Analysis of keywords

A total of 66 keywords appeared 4 times or more in frequency. The network cooccurrence and time overlay visualization of these keywords could be seen in Figure 3B, C. These keywords were divided into 3 clusters (Figure 3B). The red cluster was primarily associated with the applications of MOF materials as drug delivery systems and drug carriers. The blue cluster mainly encompasses properties of MOF as bioactive materials, such as osteogenic activity, biocompatibility, surface modification, and so on. The green cluster focused on the application of MOF in the field of orthopedics and their functional roles, including osteogenesis, bone regeneration, bone repair and angiogenesis. The average appearance year of keywords was color-coded in Figure 3C, indicating the evolution of these keywords over time, where purple signifies earlier appearances overall, while yellow indicated later appearances. Keywords like "sonodynamic therapy," "bone tissue engineering," "bone regeneration," and "bone repair" appeared relatively later.

### 3.4 Analysis of country/region, institution, and author characteristics of publications

China was the primary contributor, with a publication count as high as 184 articles, firmly maintaining the top position. The second positions were held by Iran, with publication counts of only 12 articles (Table 3). The geographical distribution of 21 countries/regions engaged in related research worldwide was depicted in Figure 4A. Concerning international cooperation, China, Australia, the United States, Iran, and the United Kingdom were the 5 countries participating in more collaborative efforts. China had the most collaboration partners (including the United States, the United Kingdom, Germany, India, Australia, Singapore, and Portugal). Five countries (Denmark, Canada, Saudi Arabia, Egypt, and Turkiye) did not participate in international collaboration (Figure 4B). The collaborative network among institutions, as shown in Figure 4C (publications ≥ 4), comprises 33 institutions, where the Chinese Academy of Sciences had the most extensive collaborative network (total link strength = 26), followed by the Huazhong University of Science and Technology (total link strength = 20). Shandong University, Guangxi Medical University, Shandong University, and Dalian University of Technology (China) did not engage in interinstitutional collaboration. The top 11 most prolific institutions all hailed from China (Table 4), with Sichuan University leading in publication volume (29 articles, 13.24%), followed by Chinese Academy of Sciences (20 articles, 9.13%). A total of 33 authors with 4 or more publications formed a collaborative network, divided into 9 collaboration clusters as shown in Figure 4D. The largest collaboration cluster, marked in red, predominantly comprises individuals from Sichuan University, primarily including Q.B. Wan, X. Zhang, J.Y. Chen, J. Wang, X.B. Pei, and others. The second-largest collaboration cluster, represented in blue, primarily comprised X.M. Liu from Hebei University of Technology, Y.F. Zheng and S.L. Wu from Peking University, along with individuals from Tianjin University, including Z.D. Cui, S.L. Zhu, and Z.Y. Li. The top 10 most prolific authors were all from China (Table 5), with the first 6 originating from Sichuan University and belonging to the same collaboration cluster within the author collaboration network.

## 4. Discussion

The ongoing progression of science and technology has consistently revealed the extensive potential of MOF materials, garnering increasing interest and research within the scientific community. The application of MOF materials in the biomedical sector, particularly in orthopedics, has recently witnessed a remarkable surge. This article is the inaugural bibliometric analysis of MOF applications in orthopedics, providing insights into the current trends and focal areas of research in this domain. Our analysis in the results section offers an in-depth examination of the developmental trajectory of MOF materials in orthopedic applications.

The analysis reveals a year-over-year increase in the number of orthopedic research papers related to MOF, highlighting the growing interest among researchers in this field. Moreover, after reaching a peak in 2022, the number of citation has declined, which is likely associated with the time accumulation of literature. However, recent high-quality literature has not received adequate time accumulation.

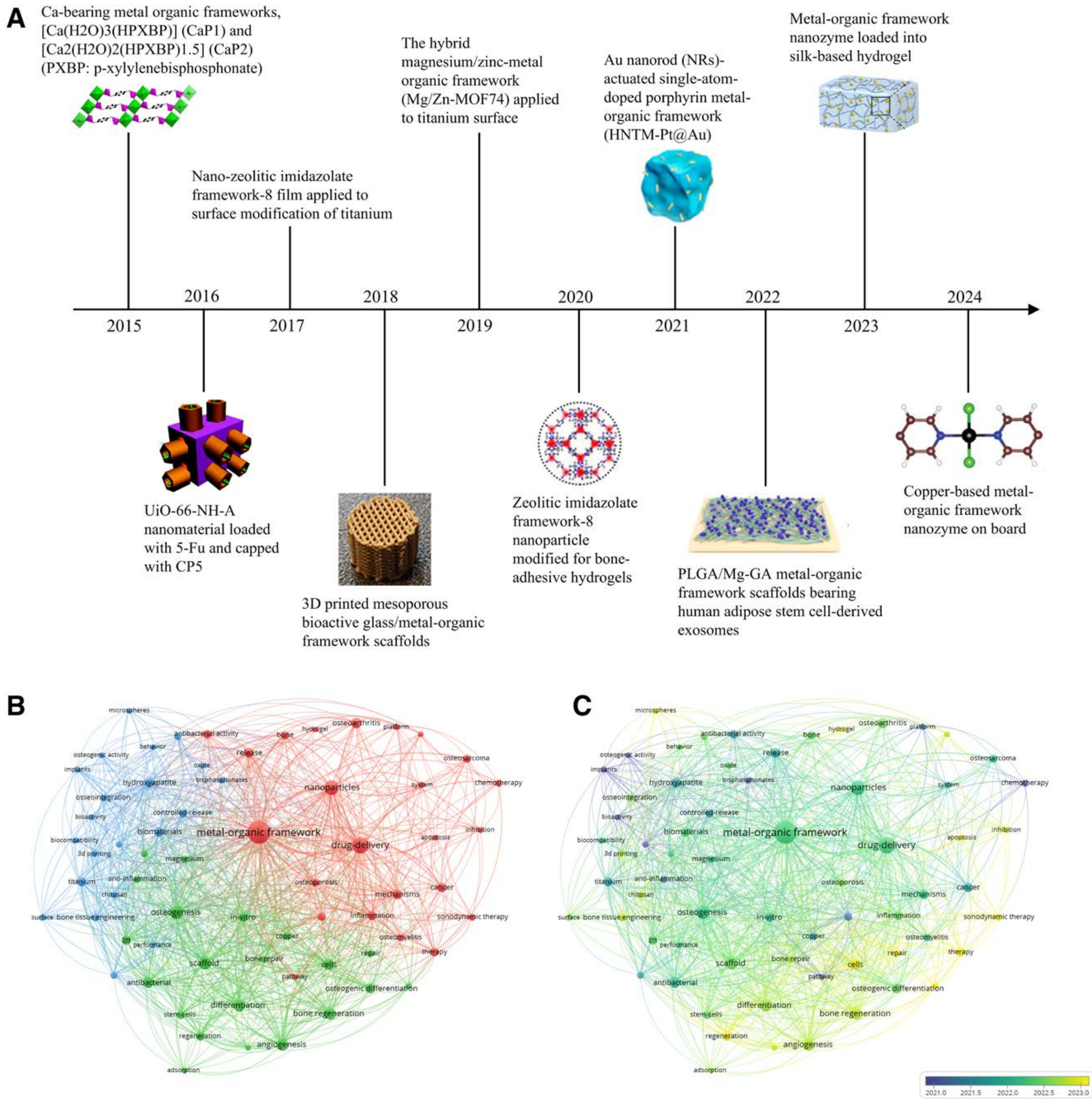


**Figure 3.** (A) The timeline presents the annually most cited studies on MOF materials in orthopedics. Keyword cooccurrence analysis: (B) Web-based clustering of keywords. (C) Distribution of meantime occurrence of keywords. Information was adapted and modified from A.[19,24–32]

Our study also encompasses a thorough analysis of influential journals and articles in this research arena. Notably, *ACS Applied Materials & Interfaces* has emerged as a leading journal in publishing MOF material research, highlighting its critical role in the field. Other journals like *Bioactive Materials*, *ACS Nano*, and *Advanced Science*, known for their high impact factors, also play a significant role in MOF research. We have identified several highly cited papers focusing on areas such as bone tissue regeneration and treatments for osteomyelitis and osteoarthritis. These articles, through their extensive citation, demonstrate their pivotal contribution to the field and guide future research trajectories in understanding and harnessing MOF materials in orthopedic applications. This study also provides guidance for researchers to select representative types from a wide range of MOF series.

## 4.1 Classification of common series of MOF materials

### 4.1.1 Zeolitic imidazolate frameworks series

Zeolitic imidazolate frameworks (ZIF), a subclass of MOF, are synthesized from metal ions and imidazolidone groups. Their structure, akin to zeolite, primarily comprises imidazolidone rather than oxygen, endowing ZIF with a highly ordered pore structure and surface area, exceptional thermal stability and solubility, and mild synthesis conditions. These features contribute to ZIF outstanding gas adsorption capabilities and multifunctionality, making them suitable for various applications such as gas adsorption, storage, drug delivery, and biological imaging. ZIF-8, a prominent MOF variant, exhibits excellent biocompatibility, pH-responsive drug release, high drug loading capacity, and stability under physiological neutral conditions, while

**Table 2**

**The top 10 most cited references.**

| Title | Institution | Journal | Year | Citations |
|---|---|---|---|---|
| Fabrication of magnesium/zinc-metal-organic framework on titanium implants to inhibit bacterial infection and promote bone regeneration | Chongqing University, China | Biomaterials | 2019 | 228 |
| Single-atom catalysis for efficient sonodynamic therapy of methicillin-resistant Staphylococcus aureus-infected osteomyelitis | Hubei University, China | Acs Nano | 2021 | 188 |
| ZIF-8-modified multifunctional bone-adhesive hydrogels promoting angiogenesis and osteogenesis for bone regeneration | Sichuan University, China | ACS Applied Materials & Interfaces | 2020 | 182 |
| Ca2+, pH and thermo triple-responsive mechanized Zr-based MOFs for on-command drug release in bone diseases | Jilin University, China | Journal of Materials Chemistry B | 2016 | 154 |
| Surface modification of titanium implants by ZIF-8@Levo/LBL coating for inhibition of bacterial-associated infection and enhancement of in vivo osseointegration | Chongqing University, China | Chemical Engineering Journal | 2020 | 150 |
| Exosome-functionalized magnesium-organic framework-based scaffolds with osteogenic, angiogenic and antiinflammatory properties for accelerated bone regeneration | China Medical University, China | Bioactive Materials | 2022 | 145 |
| Cartilage-targeting peptide-modified dual-drug delivery nanoplatform with NIR laser response for osteoarthritis therapy | Shanghai Jiao Tong University, China | Bioactive Materials | 2021 | 130 |
| Osteogenic activity and antibacterial effect of porous titanium modified with metal-organic framework films | Sichuan University, China | Journal of Biomedical Materials Research Part A | 2017 | 119 |
| Current status and prospects of metal-organic frameworks for bone therapy and bone repair | Guangdong Medical University, China | Journal of Materials Chemistry B | 2022 | 114 |
| Controlled release of naringin in metal-organic framework-loaded mineralized collagen coating to simultaneously enhance osseointegration and antibacterial activity | Zhejiang University, China | ACS Applied Materials & Interfaces | 2017 | 106 |

**Table 3**

**The top 10 most productive countries.**

| Country | Articles | Total citations | Average citations | Percentage |
|---|---|---|---|---|
| China | 184 | 5235 | 28.45 | 84.02 |
| Iran | 12 | 187 | 15.58 | 5.48 |
| Australia | 7 | 291 | 41.57 | 3.20 |
| United States | 7 | 129 | 18.43 | 3.20 |
| Singapore | 5 | 102 | 20.40 | 2.28 |
| India | 5 | 157 | 31.40 | 2.28 |
| United Kingdom | 4 | 88 | 22.00 | 1.83 |
| Portugal | 3 | 44 | 14.67 | 1.37 |
| Poland | 3 | 34 | 11.33 | 1.37 |
| Turkiye | 3 | 174 | 58.00 | 1.37 |

gradually decomposing in acidic microenvironments. As one of the most extensively researched and promising types of MOF, ZIF-8 has extensive applications in the biomedical field and is a series with the most research literature.

#### *4.1.2 Porphyrin series*

The Porphyrin Series MOF consist of crystal-structured materials, derived from porphyrin organic ligands and metal ions or clusters. Porphyrins, a class of N-heterocyclic compounds prevalent in nature, possess notable photophysical and photochemical properties, as well as biosafety. These attributes make them ideal organic ligands in MOF. The structural flexibility of porphyrins allows for diverse coordination modes, thereby facilitating their utilization as multifunctional carriers. This versatility significantly enhances the loading and precise release of diverse functional materials, such as drugs, thereby increasing efficacy and minimizing side effects. The Porphyrin Series MOF have shown promising applications in biomedical, optoelectronic, energy storage, and environmental management fields. Notably, PCN-222, a standout in this series, demonstrates exceptional capabilities in gas adsorption, drug delivery, biological imaging, and photocatalysis, garnering significant attention and research interest.

#### *4.1.3 Universitetet i Oslo series*

The Universitetet i Oslo (UiO) series, a collection of MOF, consists of crystal-structured compounds featuring metal ions (predominantly transition metals) and organic ligands. These MOF are distinguished by their highly adjustable pore structures and surface characteristics, alongside exceptional gas adsorption capabilities, chemical stability, and biocompatibility. UiO-66, a zirconium-based MOF, is a notable example, renowned for its orderly pore structure, efficient gas adsorption, and versatile applications in gas separation, energy storage, catalysis, and drug delivery.

#### *4.1.4 Isoreticular MOF series*

Introduced in the 1990s by Professor Yaghi et al.,[33] the isoreticular MOF (IRMOF) series comprises a family of structurally analogous MOF, designated as IRMOF-n, where “n” signifies varying structures. Despite their structural similarities, these MOF offer modifiable pore structures and surface properties through alterations in ligand length and bridging group types. Owing to their varied configurations, high porosity, and exceptional gas adsorption capacities, IRMOF have garnered significant interest in materials science. Their potential applications include across gas storage, catalysis, drug delivery, separation technologies, sensors, and energy storage. Notably, MOF-5 has been particularly recognized for its unique structure and outstanding properties, making it particularly useful in hydrogen storage and gas separation.

#### *4.1.5 Materials of Institute Lavoisier series*

Named in honor of the French chemist Lavoisier, the materials of Institute Lavoisier (MIL) series comprises a diverse range of MOF renowned for their tunable pore structures, extensive surface areas, biocompatibility, and chemical stability. Such characteristics render MIL series MOF highly valuable for research and applications, particularly in gas storage, separation, catalysis, drug delivery, and environmental protection. Notably, MIL-100 has attracted considerable attention due to its outstanding pore structure, high surface area, $CO_2$ adsorption capacity, and

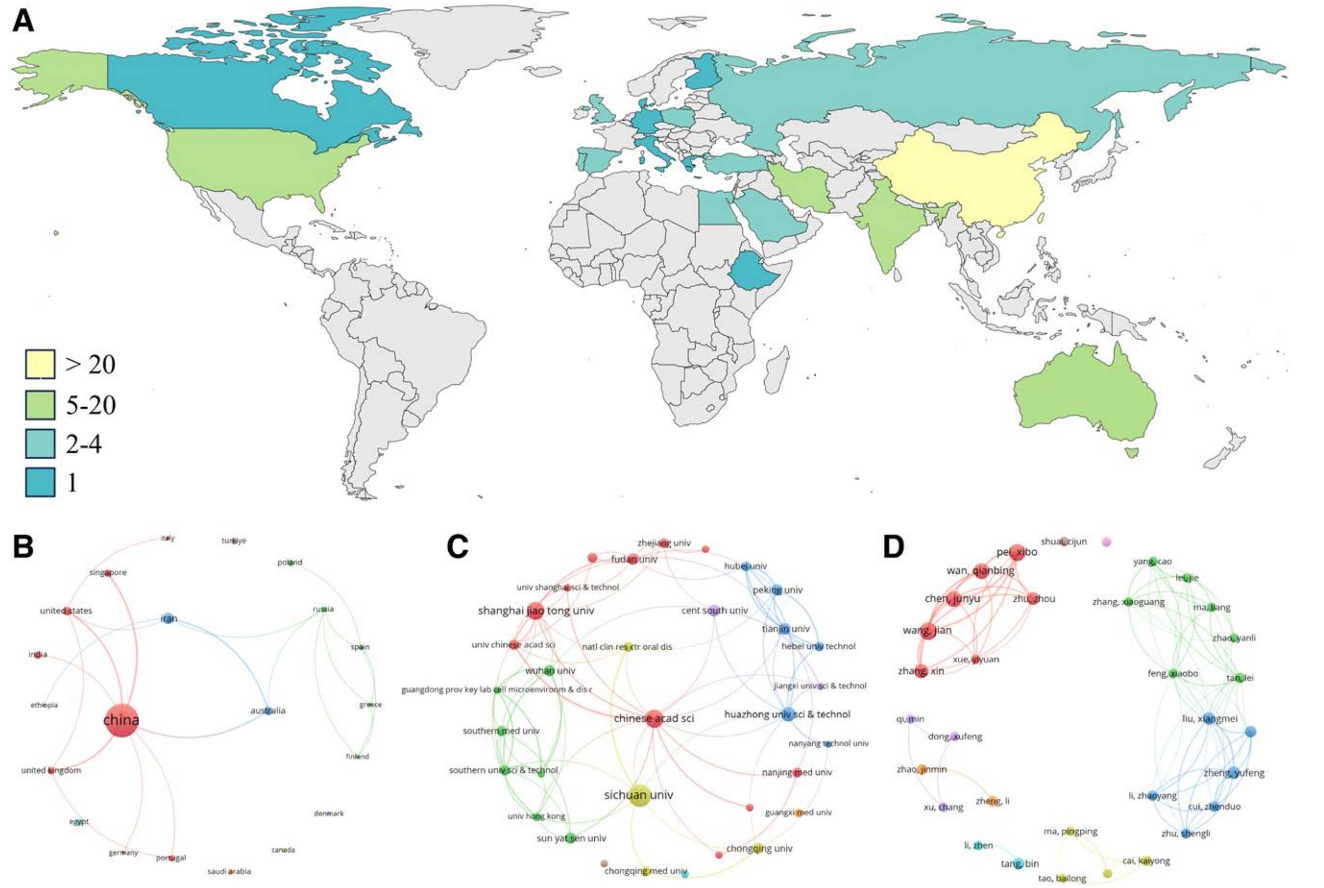


**Figure 4.** (A) Distribution of publishing countries on the world map. (B) Clustering of country collaboration network visualizations. (C) Interinstitutional collaboration network visualizations (articles ≥ 4). (D) Author collaboration network visualization analysis (articles ≥ 4).

catalytic efficiency, showcasing its potential in fields such as gas adsorption, catalysis, and biomedicine.

#### *4.1.6 Other series*

This section includes specific, lesser-known series such as the Northwestern University (NU) series. Developed by a team at NU, USA, the NU series MOF exhibit highly controllable pore structures, remarkable gas adsorption capabilities, and catalytic efficiency, finding applications in gas adsorption, separation, and catalysis. Another notable series is the HKUST-1 series, named after the Hong Kong University of Science and Technology. HKUST-1, a copper-based MOF incorporating copper ions and benzoic acid, demonstrates efficacy in catalytic reactions. This type of MOF is distinguished by its excellent gas adsorption performance, highly porous structure, and large surface area. These characteristics suggest potential for applications in gas adsorption, catalysis, and biomedical applications.

### *4.2 Practicality and usability of MOF materials in orthopedic clinical applications*

#### *4.2.1 Current key challenges and needs in orthopedics*

Orthopedic medicine currently faces several critical challenges and demands. A primary area of concern involves the treatment of complex fractures and repair of extensive bone defects, such as those encountered in postsurgical reconstructions and severe trauma cases.[34] Additionally, there is a pronounced need for the development of biomaterials characterized by biocompatibility and degradability to mitigate the risks of rejection and secondary surgeries.[35,36] Moreover, there is a growing anticipation for functional materials that support bone cell proliferation, enhance bone tissue formation, accelerate healing, and prevent infection.[37,38]

In the realm of drug delivery and bioactive substance integration, there is an escalating requirement for precise drug delivery systems that optimize therapeutic effectiveness while reducing side effects.[39] Bioactive substances in orthopedics necessitate stable carriers and suitable release mechanisms to ensure long-term efficacy. Furthermore, there is a pressing need for advancements in clinical therapy. This encompasses personalized and customized treatment strategies, considering individual patient needs and conditions, and integrating advanced technologies like 3D printing and nanotechnology. Such innovations aim to develop more effective, sustainable therapies, thereby driving progress in orthopedics.

#### *4.2.2 Advantages of MOF material properties*

MOF offer a plethora of benefits due to their diverse series and structures, making them highly advantageous in various applications, particularly in addressing orthopedic challenges.[40] These materials herald new prospects for tackling different facets of orthopedic issues, potentially revolutionizing the field. The highly adaptable and multifunctional nature of MOF introduces novel approaches to orthopedic treatments. Their flexible structure can be customized to meet specific requirements,[41]

**Table 4**

**The top 11 most productive institutions.**

| Institution | Country | Articles | Total citations | Average citations | Percentage |
|---|---|---|---|---|---|
| Sichuan University | China | 29 | 1026 | 35.38 | 13.24 |
| Chinese Academy of Sciences | China | 20 | 416 | 20.80 | 9.13 |
| Shanghai Jiao Tong University | China | 19 | 688 | 36.21 | 8.68 |
| Huazhong University of Science and Technology | China | 13 | 452 | 34.77 | 5.94 |
| Tianjin University | China | 9 | 353 | 39.22 | 4.11 |
| Central South University | China | 9 | 145 | 16.11 | 4.11 |
| Peking University | China | 8 | 393 | 49.13 | 3.65 |
| Wuhan University | China | 8 | 208 | 26.00 | 3.65 |
| Fudan University | China | 8 | 247 | 30.88 | 3.65 |
| Chongqing University | China | 8 | 622 | 77.75 | 3.65 |
| Sun Yat-sen University | China | 8 | 159 | 19.88 | 3.65 |

**Table 5**

**The top 10 most productive authors.**

| Author | Country | Institution | Articles | Total citations | Percentage |
|---|---|---|---|---|---|
| Jian, Wang | China | Sichuan University | 13 | 714 | 5.94 |
| Xibo, Pei | China | Sichuan University | 12 | 725 | 5.48 |
| Junyu, Chen | China | Sichuan University | 11 | 687 | 5.02 |
| Qianbing, Wan | China | Sichuan University | 11 | 687 | 5.02 |
| Xin, Zhang | China | Sichuan University | 9 | 675 | 4.11 |
| Zhou, Zhu | China | Sichuan University | 7 | 412 | 3.20 |
| Xiangmei, Liu | China | Hebei University of Technology | 7 | 465 | 3.20 |
| Yufeng, Zheng | China | Peking University | 7 | 393 | 3.20 |
| Shuilin, Wu | China | Peking University | 6 | 379 | 2.74 |
| Bin, Tang | China | Southern University of Science and Technology | 6 | 165 | 2.74 |

fulfilling multiple roles such as promoting bone tissue regeneration,[42] and preventing infections.[24,43–45] This adaptability is essential for meeting the intricate demands of orthopedic treatments.

Moreover, MOF are characterized by their extensive surface area and intricate pore structure,[13,46] enhancing their capacity to carry higher drug loads and support bone cell adhesion and proliferation.[47–49] This feature addresses the requirement for materials with larger surface areas in therapeutic applications. Some MOF exhibit excellent biocompatibility and degradability,[50,51] maintaining stability under physiological conditions and efficiently decomposing posttreatment, thereby minimizing the risks of foreign body rejection and secondary surgeries. These materials also provide controlled drug delivery and release capabilities, facilitating precise and sustained drug administration by modulating their pore structure and chemical properties.[39] This avoids the "burst effect" – an immediate, concentrated drug release – making them ideal for delivering radiotherapy and chemotherapy agents in bone tumor treatments.

Since MOF are synthesized through the coordination of organic ligands with metal ions, they can incorporate a variety of metal ions with specific physiological functions into their structures. For instance, MOF incorporating $Mg^{2+}$, $Zn^{2+}$, $Cu^{2+}$, $Zr^{2+}$, and $Co^{2+}$ ions have demonstrated significant osteogenic effects through the controlled release of these ions.[40,52–54] Additionally, these MOF exhibit antibacterial and antiinflammatory properties. These characteristics position MOF as a promising approach for the treatment of orthopedic diseases. In addition, the nanoscale dimensions and customizability of MOF cater to the demand for small, precisely engineered materials in orthopedics, enabling targeted applications in tissue engineering and potentially enhancing therapeutic efficacy while reducing side effects.[14]

#### *4.2.3 The in vivo application of MOF in orthopedic diseases treatment*

Recent studies have highlighted the significant potential of MOF in orthopedics, particularly within the realms of bone tissue engineering and repair. In vivo investigations are essential for confirming MOF efficacy and functionality, setting the stage for potential clinical applications.

***4.2.3.1 Bone defect models*** Significant research has demonstrated the effectiveness of MOF, such as ZIF-8, in enhancing osteogenesis and angiogenesis in rodent models with critical-sized bone deficits (Table 6). The research conducted by Li et al.[58] demonstrates the role of MOF in promoting bone regeneration through a bone defect model (Figure 5A). Another study[69] showcases the superior chondroprotective and antisynovial hyperplasia effects of MOF at the level of joint tissues (Figure 5B), Both contribute to bone tissue regeneration by promoting osteoblast differentiation. Building upon this, Shen et al.[70] research further illustrated MOF role in combating osteoporosis by inhibiting osteoclast differentiation (Figure 5C). Moreover, MOF composites have been formulated to modulate drug release for angiogenesis induction, and magnesium-based MOF scaffolds have been demonstrated to optimize the bone healing environment.[60–63] MOF hydrogel nanocomposites releasing cobalt ions have proven effective in vascular and bone tissue regeneration.[67] These findings highlight MOF potential as multifaceted, bioactive scaffolds in bone tissue engineering, capable of orchestrating the release of biologically active molecules.

***4.2.3.2 Arthritis models*** In the realm of musculoskeletal disorder research, MOF have emerged as innovative therapeutic tools, particularly for rheumatoid arthritis and osteoarthritis. Notable developments include dual-targeted MOF-based nano-platforms for delivering complement inhibitors[69] and pH-responsive MOF for precise drug release.[71] Further progress has been made in areas such as cartilage-targeting, peptide-modified MOF,[18] ultrasound-activated single-atom catalysts for treating deep tissue infections,[25] and antioxidant as well as antiinflammatory functionalized MOF for regenerating cartilage and subchondral bone.[72,73] The integration of MOF-based nanozymes into silk hydrogels has been promising in advancing osteogenesis and chondrogenesis,[26] marking a significant leap in bone-cartilage tissue engineering.

***4.2.3.3 Models of internal implant-associated infections*** Recent progress in antibacterial coatings for titanium implants using MOF is noteworthy, particularly in preventing postsurgical infections and improving osteointegration. Bailong Tao and his team have pioneered the development

**Table 6**

**Literature related to bone defect modeling.**

| Authors | Research findings and conclusions | References |
|---|---|---|
| Xue et al. | MOF triggered the recruitment of bone marrow mesenchymal stem cells by providing pH-responsive release of $Zn^{2+}$ ions and provided the underlying microenvironment for osteoblasts, ultimately enabling simultaneous bone and vascular repair | [55] |
| Toprak et al. | Encapsulating BMP-6 within the ZIF-8 has shown significant efficacy in bone regeneration, attributable to the sustained and controlled release of BMP-6 | [56] |
| Feng et al. | Encapsulation of MicroRNA using ZIF-8 notably enhances its stability against degradation, improves cellular absorption, and facilitates endosomal escape. This process significantly contributes to the promotion of osteogenesis and angiogenesis | [57] |
| Li et al. | Zeolitic imidazolate framework-8, infused with deferoxamine (DFO), effectively modulates the release of DFO and $Zn^{2+}$, significantly enhancing angiogenesis and osteogenesis | [58] |
| Kang et al. | Exosome-functionalized magnesium organic frameworks synergize the advantages of magnesium ions, gallic acid, and exosomes from human adipose stem cells, enhancing osteogenesis and angiogenesis while exhibiting antiinflammatory effects, simultaneously improving the biocompatibility and functionality of the scaffold in bone regeneration | [19] |
| Lao et al. | Metformin-loaded ZIF-8 nanoparticles, a type of MOF, were integrated with methacrylated gelatin hydrogels to form a composite. The composite's effectiveness lies in the combined action of metformin and zinc ions released from the MOF, which synergistically disrupts the ROS-inflammation cycle, thereby facilitating bone regeneration in diabetic conditions | [59] |
| Al-Baadani et al. | Alendronate-loaded ZIF-8 nanoparticles were successfully incorporated into electrospun nanofibers, forming a novel MOF composite. This innovative MOF-based material demonstrates significant potential in promoting bone regeneration and inhibiting osteoclast formation, offering a viable solution for treating osteoporotic bone defects | [60] |
| Xu et al. | The integration of exosomes with MOF-modified scaffolds facilitates a dual synergistic release of bioactive copper ions and exosomes, significantly enhancing bone regeneration and angiogenesis | [61] |
| Xu et al. | MOF composites, consisting of MIL-88 loaded with dimethyloxallyl glycine (DMOG) and combined with poly (lactic acid-co-glycolic acid) (PLGA), promote bone regeneration and vascularization in damaged areas. This effect is achieved through the synergistic release of DMOG and ferric ions | [62] |
| Zheng et al. | The magnesium-based metal-organic framework (Mg-MOF) scaffold significantly enhanced the bone repair microenvironment, markedly improving bone regeneration. This was achieved through the regulation of macrophage polarization, angiogenesis, and osteogenesis | [63] |
| Zhu et al. | These variants of Mg-MOF74 promote osteogenesis and angiogenesis, processes critical for bone formation and the development of new blood vessels, respectively. The nano-sized Mg-MOF74, in particular, is distinguished by its superior biological interactions and the continuous release of magnesium ions, making it especially suitable for biomedical applications | [64] |
| Gao et al. | Nano-structured ZIF-8 (nano ZIF-8) has shown considerable promise in facilitating the differentiation of rat bone mesenchymal stem cells (rBMSCs) into osteoblasts, thus promoting osteogenesis in both in vitro and in vivo settings. Furthermore, nano ZIF-8 endocytosis predominantly influences the canonical mitogen-activated protein kinase (MAPK) pathway, which plays a crucial role in the osteogenic differentiation of rBMSCs | [65] |
| Zhang et al. | Encapsulation of DMOG within nano-structured ZIF-8 nanoparticles significantly promotes osteogenesis and angiogenesis. The efficacy of this approach is linked to ZIF-8 nanoparticles' proficient drug delivery and prolonged release properties | [66] |
| Sun et al. | An innovative hydrogel composed of a MOF designed for bone repair applications. The MOF-based composite material facilitates the controlled release of cobalt ions, effectively simulating hypoxia to enhance angiogenesis and osteogenesis | [67] |
| Liu et al. | The ZIF-8 modified hydrogel, meticulously engineered for bone regeneration. This hydrogel significantly enhances bone adhesion and mechanical stability while actively fostering angiogenesis and osteogenesis. Furthermore, its biocompatibility, combined with antibacterial attributes, effectively reduces the risk of infections after surgery. | [31] |
| Dong et al. | The MOF hydrogels, characterized by their pH-responsive nature, are engineered to selectively release biomolecules in reaction to pH fluctuations. This targeted release mechanism is crucial in effectively regulating inflammatory responses, as well as fostering angiogenesis and osteogenesis | [68] |

of a multifunctional hybrid coating incorporating ZIF-67 nanoparticles on titanium substrates.[74] This innovative coating has exhibited potent antibacterial properties against both Escherichia coli (Gram-negative bacteria) and *Staphylococcus aureus* (Gram-positive bacteria) in infected femoral animal models (Figure 6A). Furthermore, in addressing deeper levels of biofilm infections, Zhang et al.[75] have developed ultrasound-activated, copper-doped porphyrin MOF-based nanodots that effectively mitigate implant biofilm infections (Figure 6B). Other innovations include Mg/Zn-MOF coatings,[24] simvastatin-loaded MOF with polydopamine nanolayers,[76] Co-MOF coatings with osteogenic growth peptides,[47,74,77] and pH-responsive ZIF-8 frameworks containing antibiotics.[78] These advancements play a pivotal role in the creation of orthopedic implants that exhibit superior biocompatibility and resistance to infection.

***4.2.3.4 Tumor models*** In the management of bone tumors, early studies leveraging 3D printing technology have shown that MOF scaffolds can effectively dissolve bone tumors in animal models. Due to their tunable structure, high loading capacity, biocompatibility, ease of modification, and functionalization, researchers increasingly utilize MOF as platforms for targeted drug delivery. Ma et al.[79] developed a nanoplatform featuring an Au nanoparticle core with a dual shell comprising MOF and mesoporous silica, which demonstrated exceptional antitumor efficacy and significantly reduced bone resorption (Figure 7A). Further advancements by Tao Li and team explored novel approaches in combating the antiradiation and immunosuppressive microenvironments associated with metastatic osteosarcoma,[80] culminating in the creation of a Ta-Zr codoped nano-MOF (TZM). This innovation marked a pioneering step in enhancing the efficacy of radiotherapy and radiodynamic therapy, eliciting strong antitumor immune responses and establishing TZM as a potential multifaceted radiosensitizer (Figure 7B). Moreover, the integration of MOF in sonodynamic therapy and as platforms for multimodal cancer treatment highlights their critical role in the development

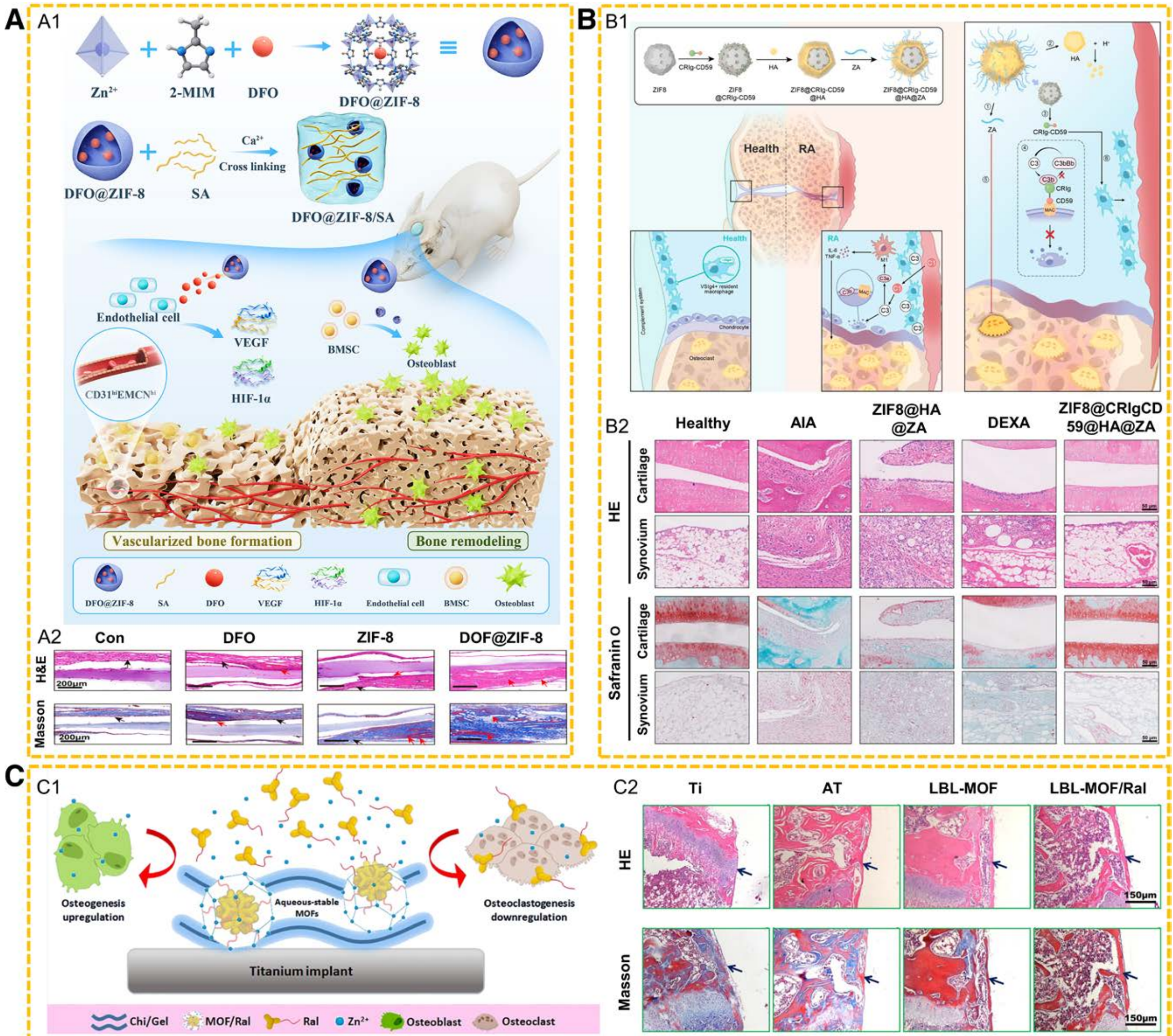


**Figure 5.** (A1) Synthesis of DFO@ZIF-8 nanocomposites and their promotion of bone regeneration. (A2) H&E and Masson's trichrome staining and detailed images of bone tissue after 4 weeks of implantation in different groups of rat skull defect models (red arrows indicate newly mineralized bone, black arrows indicate soft tissue). DFO, deferoxamine. (B1) The synthesis process and therapeutic mechanism of a dual-targeted nanoplatform based on a metal-organic framework for the treatment of rheumatoid arthritis. (B2) Cartilage and synovium after different groups of joint tissue samples treated with hematoxylin and eosin (H&E) and safranin O fast green staining. (C1) Schematic diagram of Zn-based MOF/raloxifen coating to promoting early bone osseointegration. (C2) Representative H&E and Masson staining images of different peri-implant bone tissues (The arrows represent new bone tissues. While the blue and red colors in the Masson image represent bone tissue with low and high maturity, respectively). Information was adapted and modified from (A)[58] (B)[69] and (C).[70]

of personalized, minimally invasive, and precision-targeted therapeutic approaches.[81,82]

In summary, MOF exhibit significant potential in the treatment of orthopedic diseases. However, the effectiveness of MOF varies across different conditions, with distinct advantages and limitations in each case. (1) In fracture repair, MOFs' primary advantage lies in their ability to control the release of metal ions such as magnesium, calcium, and zinc, which promote osteoblast proliferation and differentiation, thereby accelerating bone tissue regeneration and effectively shortening the healing time. Additionally, MOF can be used for localized antiinflammatory and bone regeneration drug delivery, enhancing therapeutic efficacy due to their adjustable drug release properties. However, degradation of MOF may produce immunostimulatory byproducts that could trigger local inflammatory responses.[83] (2) MOF have demonstrated promise in treating osteoporosis by promoting bone matrix mineralization, increasing bone mineral density, and addressing bone loss through the delivery of antiresorptive drugs. Some MOF also possess antiinflammatory and antioxidant properties, which may help mitigate bone degeneration. Nevertheless, their long-term stability and biodegradability in vivo require optimization to ensure safety and efficacy in managing osteoporosis over extended periods.[40] (3) In bone tumor therapy, MOF offer distinct advantages by enabling targeted drug delivery, enhancing the concentration of antitumor agents at the tumor site while minimizing damage to healthy bone tissue. Furthermore, MOF can be combined with antimicrobial therapies to reduce the risk of postoperative infections. However, biologically active degradation byproducts may provoke local immune responses or adverse physiological effects, emphasizing the need for stringent safety standards in

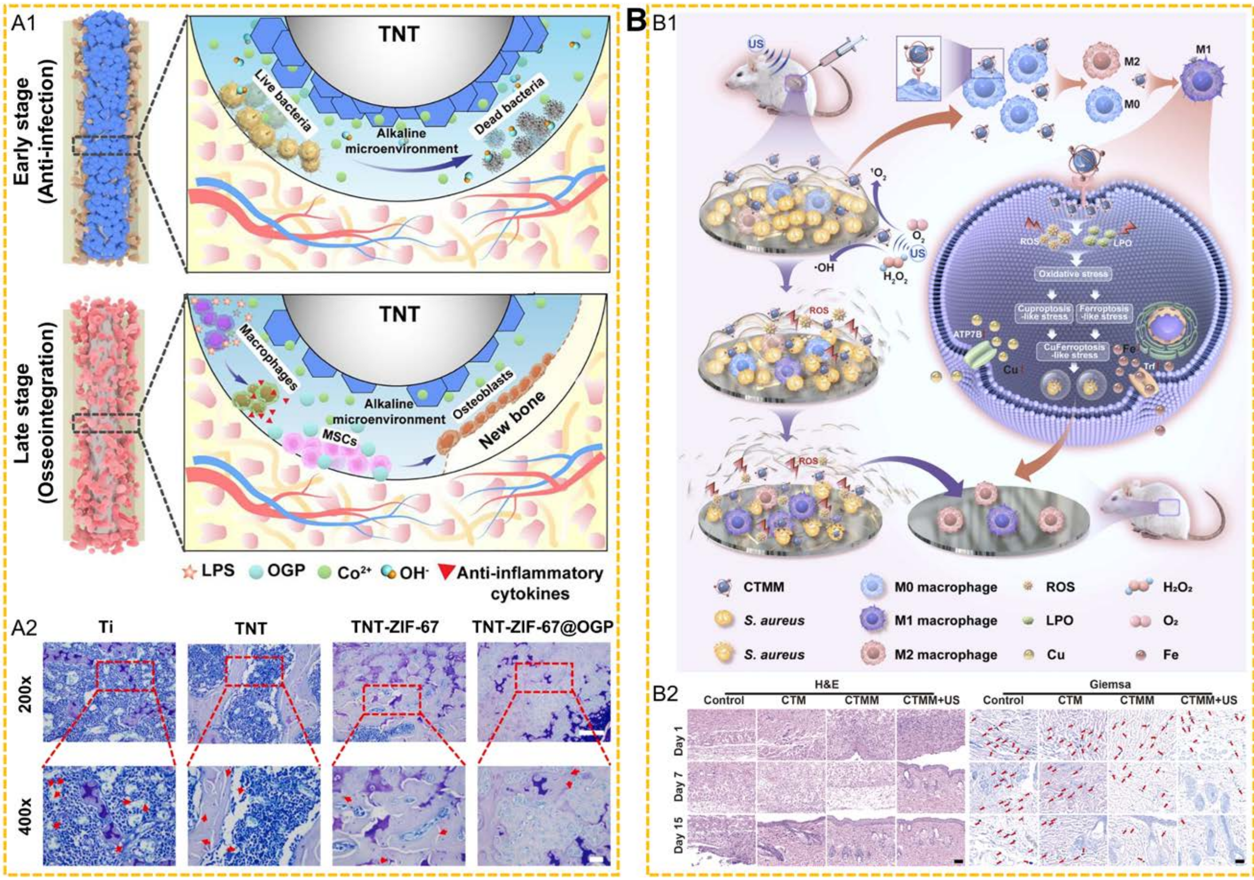


**Figure 6.** (A1) TNT-ZIF-67@OGP substrate binding antimicrobial and bone immunomodulatory activity promotes bone regeneration. (A2) Observation of residual Staphylococcus aureus on Giemsa staining images of different implants. (B1) Schematic illustration of ultrasound-driven CTMM eliminating intracellular bacterial infection. (B2) H&E and Giemsa staining images of subcutaneous tissues from different groups at days 1, 7, and 15. Scale bars, 50 μm. CTMM, CuTCPP@MOF nanodots@mannose; OGP, osteogenic growth peptide; TCPP, Tetrakis (4-carboxyphenyl) porphyrin; TNT, titanium dioxide nanotube; ZIF-67, zeolitic imidazolate frameworks-67. Information was adapted and modified from (A)[74] and (B).[75]

clinical applications.[84] (4) Research on MOF in osteoarthritis treatment has largely focused on their antiinflammatory and slow-release drug capabilities. By releasing metal ions such as copper and zinc, MOF can directly inhibit inflammatory responses while also serving as carriers for antiinflammatory drugs or biologics to enhance therapeutic efficacy. However, certain metal ions may be toxic to joint tissues, particularly when used for prolonged periods or at high doses.[85,86] Moreover, the therapeutic potential of MOF remains limited in cases of severely degenerated joint tissues. (5) The primary application of MOF in osteomyelitis treatment is their antimicrobial properties and targeted delivery capabilities. MOF can facilitate the loading and controlled release of antibiotics, increasing drug concentration at the infection site, enhancing antimicrobial effectiveness, and reducing the side effects associated with systemic antibiotic use. However, due to the need for prolonged implantation, the biocompatibility of MOF degradation products must be thoroughly evaluated to minimize potential immune reactions or toxic side effects.[87,88]

Future research should focus on the following areas to optimize the application of MOF in orthopedic diseases: (a) Optimizing the synthesis process of MOF: Developing more efficient and controllable synthesis methods to improve biodegradability and ensure that degradation products do not exhibit toxic side effects on bone tissue or other organs. (b) Enhancing the long-term stability and controlled drug release of MOF: Improving the chemical stability of MOF in vivo through material modification or surface functionalization, enabling precise and controlled drug release to improve therapeutic outcomes. (c) Reducing the synthesis cost of MOF: Current synthesis methods are complex and costly, limiting their feasibility for large-scale clinical application. Future research should focus on developing simpler, more efficient, and cost-effective synthesis techniques to facilitate their application in orthopedic clinics. (d) Developing multifunctional MOF: Introducing additional functionalities, such as antitumor, antibacterial, and antioxidant properties, to enable MOF to address multiple aspects of orthopedic disease treatment, including bone tissue regeneration, inflammation control, and infection prevention.

### *4.2.4 Challenges in applying MOF materials in orthopedic clinics*

Despite the vaired functional roles of MOF in orthopedics, identified through in vitro and in vivo animal studies, their application in orthopedic clinics faces significant challenges. Initially, while MOF have demonstrated biocompatibility and stability in simulated human physiological environments and animal studies, the complex, dynamic, and variable physiological environment of the human body, with its fluctuating pH levels, presents a stark contrast to animal models.[89,90] This raises concerns

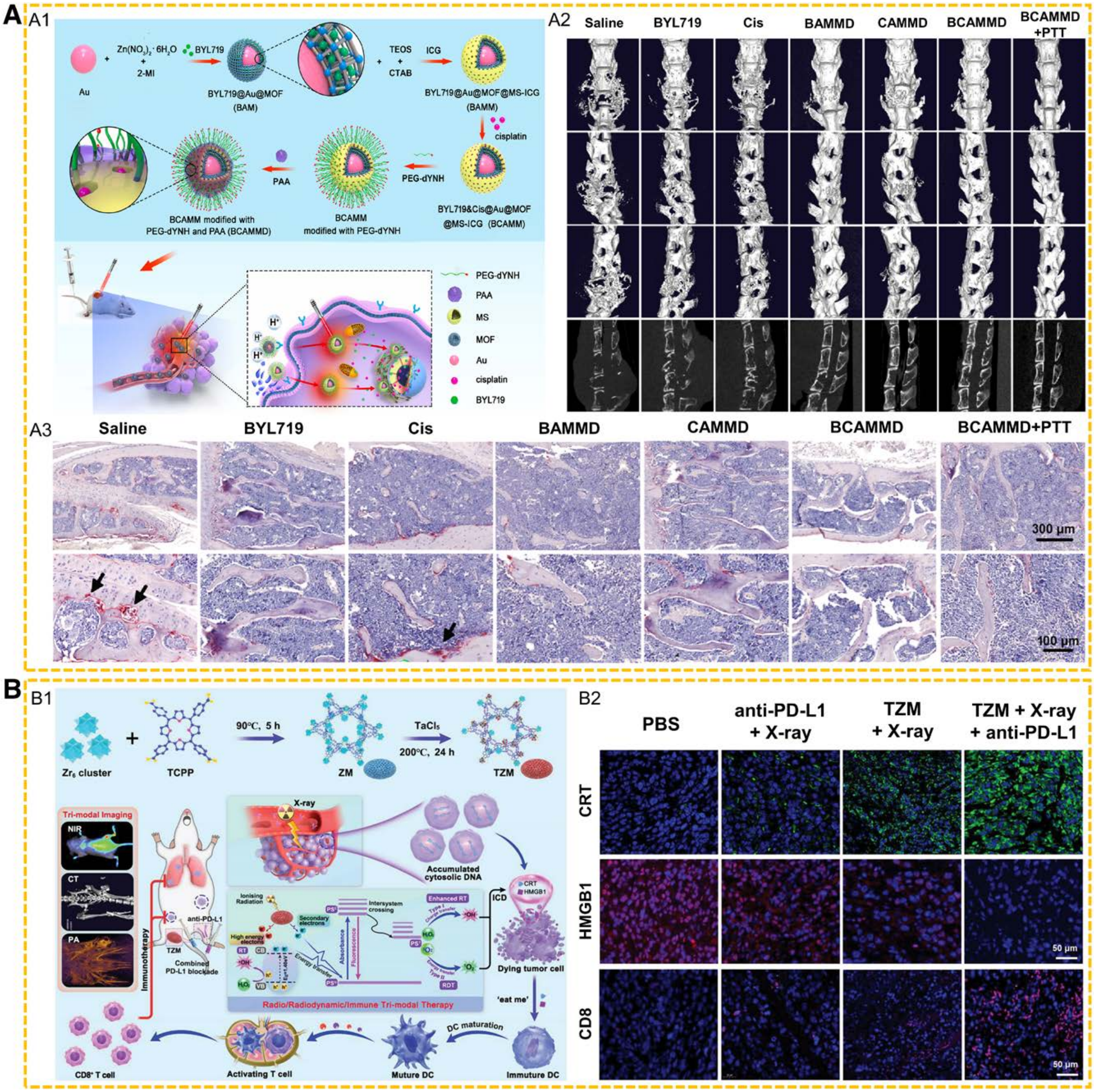

Figure 7. (A1) Synthesis process and antitumor mechanism of a nano platform composed of Au nanoparticle core, MOF double shell, and mesoporous silica loaded with alpelisib (BYL719) and cisplatin in tumor cells. (A2) Microscopic CT images of spinal metastasis specimens from different groups. (A3) TRAP staining images of spinal tumors in each group. (B1) Preparation diagram of TZM and its mechanism as a radiosensitizer for the treatment of metastatic osteosarcoma. (B2) Expression of CRT and HMGB in tumor sections of mice after 3 days of different treatments and immunofluorescence analysis of tumor-infiltrating CD8 T cells after 5 days of different treatments. CRT, calreticulin; HMGB, high-mobility group box; TZM, Ta-Zr codoped nMOF. Information was adapted and modified from (A)[79] and (B).[80]

about their stability and performance in humans, necessitating comprehensive studies on their response and stability across various biological environments, and their long-term safety and stability in vivo.

Moreover, most in vivo studies do not solely depend on MOF but combine them with other functional materials. Ensuring consistent quality and controllability of these MOF composites during fabrication is a formidable challenge. The effect of MOF composites also varies with size.[91] Additionally, as drug carriers, nano-MOF must ensure stable and efficient drug release, prevent accumulation in biological media,[92] and manage the complex interactions between drugs and MOF.[51] The behavior, metabolism, and decomposition of MOF within the human body remain incompletely understood, making it challenging to develop techniques for accurate assessment and monitoring within organisms.

Finally, our literature review revealed no studies or reports on the use of MOF materials in orthopedic clinical settings. Thus, there is a need for more extensive research, support from preclinical trial data, and technological advancements to ensure the safe and effective use of MOF materials in clinical orthopedics.[93]

### 4.3 Future prospects of MOF materials in orthopedic applications

#### 4.3.1 Enhancement of MOF material applications through international and institutional collaboration

Our analysis of publication data reveals a dominant role of China in MOF materials research within orthopedics, both in terms of publication volume and international collaboration strength. Notably, partnerships have expanded with countries such as the United States, the United Kingdom, Germany, Australia, and Singapore, enhancing knowledge and expertise exchange. Institution-level analysis underscores the pivotal contributions of the Chinese Academy of Sciences, Sichuan University, and Shanghai Jiao Tong University, underlining their leadership in this field. Examination of author collaboration networks has identified key authors and clusters, highlighting the importance of these collaborations in advancing research. Looking forward, enhanced cross-institutional and international collaborations are anticipated to further propel the field, driving innovation and facilitating knowledge sharing.

#### 4.3.2 Multidisciplinary field linkage to accelerate MOF in clinical application

Despite extensive research has been conducted on MOF materials in orthopedics, the translation of these findings into clinical applications remains a lengthy process. The development of MOF materials requires interdisciplinary expertise, encompassing materials science, chemistry, engineering, biomedical science, and clinical medicine, as evidenced by the diversity of author research areas in relevant literature.[20,26,69,72,94–96] For successful clinical application, a collaborative effort is essential: first, to tailor MOF materials to specific clinical needs; second, to evaluate their safety and efficacy in living organisms; and third, to conduct preclinical studies in a clinical context to assess their practical viability. This necessitates subsequent material adjustments and optimizations for clinical utility.[51] Consequently, a multidisciplinary collaborative approach will not only expedite the development and application of MOF materials in orthopedics but also facilitate their transition from laboratory to clinical settings. Such collaboration will broaden the scope of MOF applications in orthopedics, offering new therapeutic options and potentially enhancing patient quality of life. Moreover, this collaborative model may yield numerous applications across various disciplines.[93,97,98]

Our study faces certain limitations, it is confined to a single database, WOSCC, potentially leading to an incomplete collection of relevant literature. Nevertheless, WOSCC is among the world's most extensive and comprehensive databases, offering a substantial volume of literature that adequately represents the current state of research in this field and is widely utilized by scholars. Additionally, the impact of recent high-quality publications may be underestimated due to low citation rates. Furthermore, our analysis exclusively includes articles published in English.

## 5. Conclusion

The utilization of MOF in orthopedics, particularly in the realms of bone regeneration, repair, and tissue engineering, represents a burgeoning field of research. While numerous in vivo studies highlight MOF diverse benefits and functions in this domain, extended research and innovative advancements are essential for a deeper understanding of MOF before their clinical application. Continued investigation and progressive innovation are anticipated to establish MOF as a significant tool in treating orthopedic diseases.

## Conflicts of interests

The authors declare that they have no conflicts of interest.

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## Data availability statement

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

## Author contributions

Wanbo Zhu, Junchen Zhu, and Zheng Su conceived the idea for this study. Yao Yang, Yingjie Wang, and Yuan Chen carried out the data extraction. The statistical analysis was performed by Yao Yang and Yingjie Wang. Image plotting was conducted by Yao Yang, Baoliang Lu, Zheng Su, and Xianzuo Zhang. Yao Yang, Yingjie Wang, and Yanling Zhou drafted the initial manuscript, while all coauthors provided critical feedback and revisions to the final version. Wanbo Zhu and Junchen Zhu provided financial support, Zheng Su and Junchen Zhu provided administrative assistance. All authors reviewed the manuscript.

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