

How Effective are Metal Nanotherapeutic Platforms Against Bacterial Infections? A Comprehensive Review of Literature

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Abstract: The emergence of multidrug-resistant bacteria has been deemed a global crisis that affects humans worldwide. Novel anti-infection strategies are desperately needed because of the limitations of conventional antibiotics. However, the increasing gap between clinical demand and antimicrobial treatment innovation, as well as the membrane permeability obstacle especially in gram-negative bacteria fearfully restrict the reformation of antibacterial strategy. Metal-organic frameworks (MOFs) have the advantages of adjustable apertures, high drug-loading rates, tailorable structures, and superior biocompatibilities, enabling their utilization as drug delivery carriers in biotherapy applications. Additionally, the metal elements in MOFs are usually bactericidal. This article provides a review of the state-of-the-art design, the underlying antibacterial mechanisms and antibacterial applications of MOF- and MOF-based drug-loading materials. In addition, the existing problems and future perspectives of MOF- and MOF-based drug-loading materials are also discussed.

Keywords: MOF, nanomaterial, antibacterial, mechanism, application

Introduction

Infectious diseases have for centuries been a tremendous obstacle to human progress and survival. They continue to rank among the world's leading causes of death and disability.¹ Infectious diseases have placed a tremendous financial and health burden on the entire world along with an ongoing background of unabating infections and the intermittent appearance of both new and old diseases. Due to their broad-spectrum antibacterial activities, antibiotics have been used to treat bacterial infections since Fleming discovered penicillin in 1928.² However, the increasing overuse and abuse of antibiotics has been found to have deleterious effects, the most prominent effect being the emergence of antibiotic resistance, which has been recognized as a global crisis, leading to more unfavourable prognoses and higher mortalities.^{3–5} Even now, multidrug-resistant organisms (MDROs) account for up to 50% of the bacterial strains found in health care admission facilities.⁶ Therefore, to overcome this difficult situation, further development of various antibacterial strategies is highly desired.⁵

Nanotechnology has been increasingly used in sterilization and infection control during the past ten years as a result of the development of nanomaterials and nanotechnology. Due to their unique antimicrobial mechanisms, antibacterial nanomaterials were found to be less likely to cause bacterial resistance than conventional antibiotics.⁷ Many nanomaterial agents, including metal nanoparticles (NPs) (eg, Ag-, Cu-, Mn-), metal oxide NPs (eg, CuO, ZnO, Fe₃O₄, TiO₂), and carbon-based nanomaterials (CNMs), have been found to have effective bactericidal functions.^{7–12} The aforementioned antibacterial nanomaterials have impressive antibacterial activities, but they still have unignorable disadvantages. For example, metal NPs and metal oxide NPs have exhibited antibacterial effects by releasing metal ions, but the short duration of efficacy and the possibility of unexpected damage to normal cells due to the fast release of metal ions have limited their application.^{13,14}

Due to their diverse active sites and exceptional properties¹⁵ (high surface area, chemical and thermal stability, tuneable pore sizes, and various functionalities on the internal surface), metal-organic frameworks, a class of microporous polymers made of metal nodes and organic linkers, have been extensively studied and tested for use in a variety of fields, such as the fields of environmental pollution,^{16,17} gas adsorption,¹⁸ catalysis,¹⁹ and sensing platforms.²⁰ Its distinctive biodegradability, biocompatibility, and low toxicity have facilitated a wider range of biomedical applications.^{21–24} Compared with other antibacterial agents, MOFs are unique in the following ways: 1) Their components, pore sizes, and structures can be adjusted according to different requirements to achieve various functions. 2) Their high porosity and specific surface area result in a high efficiency of encapsulation/loading of other agents.²⁵ 3) Their low toxicity and biodegradability ensure the biosafety of their applications in vivo.^{13,25} Thus, MOFs are promising both on their own and as drug delivery systems.

Multiple excellent reviews related to MOFs in the biomedical field were published, some of which discussed the applications of MOF-based materials from a broad perspective, ranging from synthesis and functionalization to wide-ranging biomedical applications,²⁵ others discussed the potential antibacterial action of MOFs as drug carriers.^{26,27} In contrast to these splendid reviews, this review focuses on the up-to-date synthesis methods, discusses potential antibacterial mechanisms from different aspects, and summarizes the current applications of MOF- and MOF-based materials in antimicrobial treatment. In addition, the related future prospects and challenges are discussed. It is hoped that the review will foster a better understanding for researchers of the current situation of MOFs in the antibacterial field.

Synthesis of Metal-Organic Frameworks

The antibacterial effect of nanoparticles is significantly influenced by their particle size and size distribution. Studies have revealed a relationship between the antibacterial action of graphene oxide and its sheet size, which may be because the edge of the graphene oxide sheet causes damage to the bacterial cell membrane through direct physical contact.²⁸ Nanoparticle synthesis techniques have an impact on particle size and size distribution. The steps involved in the formation of nanoparticles according to the LaMer model and the Gibbs-Tompson crystal nucleation theory can be summarized as follows: 1. The monomer concentration increases continuously. 2. The monomer concentration exceeds the nucleation concentration, and nucleation occurs. 3. The monomer concentration decreases, and crystal growth occurs. Generally, nucleation time and crystal growth rate are two factors that can be adjusted to control the nanoparticle size. Microwaves, for example, generate heat quickly, depleting monomers and producing nanoparticles with a smaller size distribution.²⁹

Metal-organic framework materials are a class of organic-inorganic hybrid materials composed of organic ligands and metal ions or clusters, which can be constructed into one-dimensional, two-dimensional, or three-dimensional materials as required.³⁰ They are generally formed by the self-assembly of metal ions and organic ligands through coordination bonds under mild conditions.²⁷ With the development of technology and the increasing application of MOFs, their synthesis methods have become increasingly diversified. The existing synthetic methods include the hydrothermal method,³¹ solvothermal method,^{32,33} ionothermal synthesis,^{34,35} ultrasonicated method,³⁶ spray drying synthesis,^{37,38} and microwave-assisted hydrothermal synthesis.^{39,40} Different synthesis techniques have various benefits and drawbacks. The reactions of hydrothermal synthesis and solvent-thermal synthesis occur under high temperature and high pressure, resulting in a high thermal stability of the obtained products. The ultrasonic method allows materials to nucleate evenly and form small crystals, but the purity of the material is inconsistent. Compared with the traditional hydrothermal/solvothermal method, the microwave heating method has a reaction efficiency that is greatly improved, and the prepared materials have high purity. Electrochemical synthesis has a low yield and is prone to the development of by-products. The properties of the produced crystals differ according to the synthetic conditions, which means that the selection of proper synthesis methods in different fields is crucial. For example, Qian et al synthesized MOF-5 by three different methods (hydrothermal synthesis, direct addition method, and adding H₂O₂ in the direct method) in 2018 and studied the effects of different synthesis methods on the structure, morphology, and other properties. The results showed that crystals with regular cubic structures were synthesized by hydrothermal synthesis, while the crystals synthesized by the direct addition method and the direct method with the addition of H₂O₂ were larger and had an irregular morphology. Table 1 provides a summary of recent MOF structures and the synthesis techniques employed by researchers.

Table I Synthesis Methods of MOFs in Recent Years

Synthesis Methods	Metal Ions	Organic Ligands	T Inlet (T Coil) / Time	Shapes	Reference
Hydrothermal synthesis	Ni ²⁺	TMBDC DABCO	120°C for 48 h	–	[31]
	Fe ³⁺	BTC	150°C for 12 h	Octahedron shape	[41]
	Ni ²⁺ Co ²⁺	2-MIM	120°C for 8h	Sphere and various sheets	[42]
	Zr ⁴⁺	PTA	120°C for 24 h	Uniform aggregated particles	[43]
	Zn ²⁺	2-MIM	140°C for 24h	Rhombic dodecahedron	[44]
	Cr ³⁺	TPA	218°C for 18h	Octahedral shape	[45]
Solvothermal synthesis	Zn ²⁺	2-MIM	Room temperature for 1 h	Dodecahedron	[46]
	Co ²⁺	2-MIM	Room temperature for 1 h	–	[46]
	Zr ⁴⁺	PTA	80 °C for 24 h	–	[46]
	Zr ⁴⁺	BDC-NH ₂	120°C for 24h	–	[32]
	Fe ³⁺	BDC-NH ₂	110°C for 24h	Sharp-ended rod-like shape	[33]
	Fe ³⁺	TPA	90–120°C for 4h	Spherical	[47]
	Zn ²⁺	H ₃ BTC	85°C for 2d	Polyhedral	[48]
	Cu ²⁺	NDCA	120°C for 24h	Irregular flake-like structures	[49]
	Mg ²⁺	H ₄ DHTP	125°C for 4–24h	Hexagonal columnar	[50]
Ultrasound-assisted synthesis	Cu ²⁺	BTC	130°C for 24h	Octahedral	[51]
	Zr ⁴⁺	BDC	130°C for 24h	Cube	[52]
	Eu ³⁺	2,6-Pyridinedicarboxylic acid	40°C for 21min	Uniform particle	[53]
	Cu ²⁺	2,6-Pyridinedicarboxylic acid	25°C for 10min	Hollow, spherical	[54]
	Cu ²⁺	BTC	5–60min	Spherical	[55]
	Al ³⁺	H ₂ BDC	150–220°C for 6–24h	Non-uniformly structures	[56]
	Al ³⁺	FUM	2h	Prismatic central portion tips pyramidal end portions	[57]
Microwave-assisted synthesis	Zn ²⁺	BDC	120°C for 1h	Cubic	[58]
	Cr ³⁺	TPA	220°C for 15min 300mW	Without any specific shape	[45]
	Zn ²⁺	2-MIM	120°C for 2h	Uniform approximately rhombic dodecahedron	[59]
	Eu ³⁺	BTC	150°C for 20min	–	[39]
	Cu ²⁺	CA	120°C for 10min	Spherical	[60]

(Continued)

Table I (Continued).

Synthesis Methods	Metal Ions	Organic Ligands	T Inlet (T Coil) / Time	Shapes	Reference
Spray drying synthesis	Cu ²⁺	BTC	2h	Hollow, spherical	[38]
	Fe ³⁺	FUM	5min	Hollow, spherical	[38]
	Zn ²⁺	BDC	20min	Hollow, spherical	[38]
	Zn ²⁺	2-MIM	180°C	Beads	[61]
	Co ²⁺	2-MIM	180°C	Beads	[61]
	Zn ²⁺ Co ²⁺	2-MIM	180°C	Beads	[61]
	Zr ⁴⁺	BDC-NH ₂	150°C (90°C)	Spherical beads	[62]
	Zr ⁴⁺	FUM	140°C (90°C)	Spherical beads	[62]
	Cu ²⁺	POA	150°C	Hollow, spherical	[63]
	Cu ²⁺	H ₃ BTC	100°C	Hollow, spherical	[64]
	Zr ⁴⁺	BDC	180°C (115°C)	Spherical beads	[65]
Spray-drying continuous-flow synthesis	Zr ⁴⁺	BDC	180°C (115°C)	Spherical beads	[66]
	Zr ⁴⁺	BDC Br-BDC	180°C (115°C)	Spherical beads	[66]
	Zr ⁴⁺	BDC Br-BDC NH ₂ -BDC	180°C (115°C)	Spherical beads	[66]
	Fe ³⁺	BTC	180°C (115°C)	Spherical beads	[66]
Electrochemical synthesis	Cu ²⁺	BTC	0.2–4mAcm ⁻² 1–48h	Octahedral	[67]
	Zn ²⁺	BDC BZIM	40–80mA 1–2h	Small particles	[68]
	Cu ²⁺	BTC	30V 2.5h	Octahedral	[69]
	Zr ⁴⁺	BDC-NH ₂	–	Granular	[70]

How Do Antibacterial Nanotherapeutics Work?

The antibacterial activity of MOFs is mainly reflected by the possibility of degradation of the structure with the release of the active components in the form of metal ions and organic ligands. In addition, the shape and size of the MOF particles, the existence of metal active centres, and other mechanisms are significant elements that cannot be disregarded.

The antibacterial properties of MOF materials are closely related to the collapse of their structures. At the same time, the release rate of the MOF component depends on its structural stability and subsequently determines its antibacterial effect. For instance, the MOF structure is less stable when soft acids interact with hard bases, and this combination is more likely to cause structural collapse and the release of components, according to Pearson's HSAB theory. Various materials have different stabilities due to their coordination bonds, which affect how they exert antibacterial effects in vivo. For example, ZIF materials have zeolite-like structures with a tetrahedral topology composed of Zn or Co and imidazole ligands. They have high chemical stability and can maintain their stable frame structures in high-temperature and water environments while being sensitive to pH value and easily decomposing in an acidic environment.⁷¹ The pH of the healthy human body ranges from 7.35 to 7.45, which is indicative of an alkaline environment.⁷² Due to bacterial growth and metabolism, the pH of the microenvironment at the infected location decreases during bacterial infection and

becomes acidic. Ge et al constructed an intelligent drug delivery system for the treatment of osteomyelitis by using ZIF-8 as a carrier to load celecoxib with the characteristic of PH response of ZIF materials.⁷³ When they are delivered to specific locations, they disintegrate and release drugs, which avoids the loss of drugs and improves drug utilization. Additionally, the release of antibacterial metal ions caused by the collapse of the structure can also induce antibacterial activity.^{74–76} The antimicrobial mechanisms of the different components are discussed separately below.

What is the Role of Metal Ions in Antibacterial Nanotherapeutics?

MOFs are regarded as metal ion reservoirs because of their structural features, which enable them to release metal ions steadily and sustainably.⁷⁷ Metal ions with excellent antibacterial activity should be the first component taken into account when choosing metal particles for MOF materials. Toxicity during transportation and after degradation is another issue to take into account. Therefore, metal ions should have at least the following two characteristics: antibacterial activity and minimal toxicity.

Many metals are indispensable for the biochemistry and metabolism of life. However, when these necessary metals are present in excess, the harm they cause to cells can be fatal.¹⁴ The trace elements found in the highest concentrations in the human body are iron, zinc, and copper. They participate in important cellular metabolic activities, such as catalysis and electron transport.¹⁴ Due to their potent antibacterial qualities and low toxicity, zinc, copper, and silver are frequently utilized in the field of biomedicine.

Silver Ions

Silver has been demonstrated to have a high antibacterial activity against both gram-positive and gram-negative bacteria. The different inhibitory effects on gram-positive bacteria and gram-negative bacteria are attributed to their different cell wall compositions and material interactions with the cell membrane (as shown in Figure 1).^{78,79}

The release of silver ions plays a major role in the antibacterial characteristics of silver, and the mechanisms are basically as follows: 1) Negatively charged bacteria are drawn to positively charged silver ions, which interact with the sulfur-containing proteins in the bacterial cell wall and cause structural damage and cell wall rupture. 2) Silver nanoparticles not only increase membrane permeability and cross the cell membrane but also enter the cell and interact with the contents of the cell, altering their structure and functions. 3) Due to their size and charge, silver nanoparticles can affect metabolic pathways, membranes, and even genetic material by interacting with biological components.⁸¹

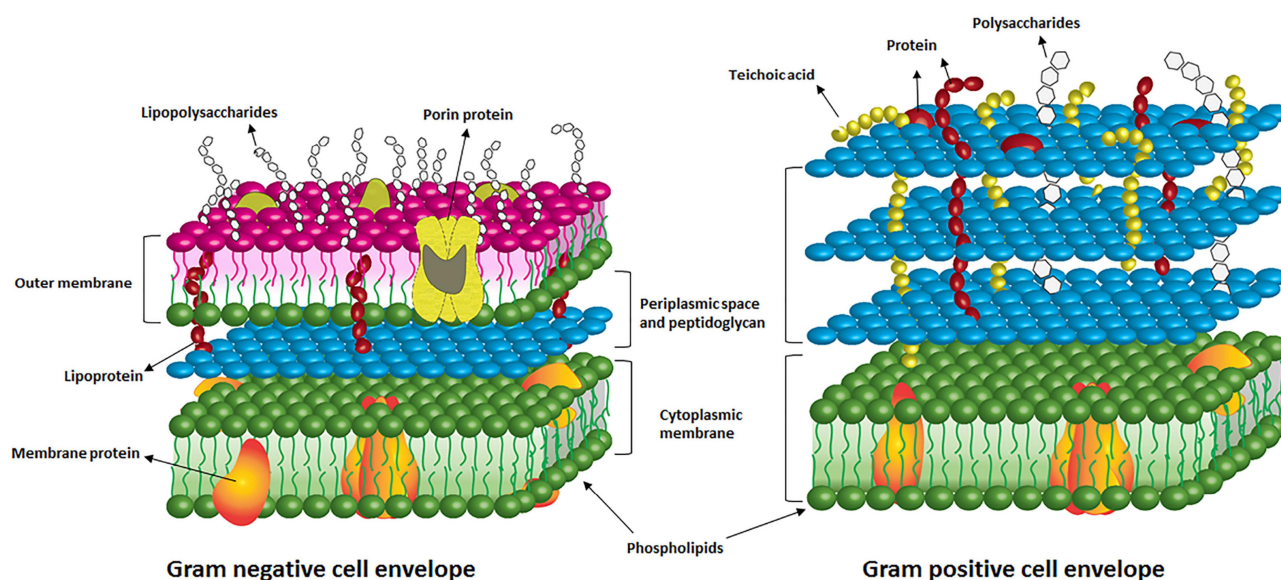


Figure 1 Schematic diagram of the cell membrane of gram-positive and gram-negative bacteria.

Notes: Reproduced from Liu Y, Qin R, Zaat SAJ, Breukink E, Heger M. Antibacterial photodynamic therapy: overview of a promising approach to fight antibiotic-resistant bacterial infections. *J Clin Transl Res*. 2015;1(3):140–167. This is an open-access article distributed under the terms of the Creative Commons Attribution License. (<http://creativecommons.org/licenses/by/4.0/>).⁸⁰

Copper Ions

Studies have shown that the promising antibacterial and antifungal capabilities of copper nanoparticles are due to both the nanoparticles themselves and the released copper ions, which can interact with proteins that contain sulfur and render them inactive.^{82,83} Copper has a lower toxicity and antibacterial activity than silver.

The antibacterial activity of copper suggests that the following mechanisms may cause bacterial mortality, similar to that of other metal ions: 1) Through electrostatic contact, copper ions are adsorbed on bacterial cell membranes, influencing the structural integrity and biological activity of the membrane and associated proteins. 2) Some proteins have a strong affinity for copper ions. The normal metabolism of bacteria may be impacted when the concentration of copper ions increases because replacement reactions with elements in proteins or enzymes may result in the inactivation of proteins and enzymes.¹⁴

Zinc Ions

Strong bactericidal capabilities against both gram-positive and gram-negative bacteria have been exhibited by zinc nanoparticles.^{84,85} Additionally, zinc nanoparticles have excellent antifungal properties. Devanand Venkatasubbu et al developed a drug delivery method for treating bone infections using hydroxyapatite and zinc-doped hydroxyapatite, and they demonstrated that the antibacterial property was enhanced with increasing drug concentration and zinc content.⁸⁴

Due to its role as a crucial cofactor for numerous enzymes, zinc is a trace element that is vital for all living things and has a low harmful effect. Zinc ions at high concentrations have an obvious killing effect on bacteria.⁸⁶ Despite the scarcity of research, the following three theories dominate the current understanding of zinc's antibacterial mechanism: 1) Zinc ions released from zinc nanoparticles impair the function of the cell membrane by causing ion concentration differences, which block material transport. 2) Through the positive charge on the bacterial surface, zinc ions directly bind to bacteria on negatively charged cell membranes, where they denature proteins by reacting with functional groups. 3) A large number of free radicals, including OH^- , H_2O_2 , and O_2^- , can be produced by the activation of zinc oxide (ZnO) by UV or visible light. H_2O_2 can destroy the bacterial cell wall and enter the bacterial body to facilitate sterilization.

Iron Ions

Iron is a trace element that is necessary for life and functions as a cofactor for enzymes in numerous biological pathways, including the transfer of oxygen and carbon dioxide by haemoglobin. However, too much iron can kill bacteria and organisms, and it can also trigger Fenton reactions, which break down proteins, lipids, and DNA.^{14,87} In TEM images of Fe NP-treated S.li, Lee et al noticed a significant rupture of cell membranes and subsequent leakage of intracellular contents. Because iron has powerful reductive capabilities, the authors hypothesized that iron causes the reductive degradation of functional groups in proteins and outer-membrane lipopolysaccharides. By producing reactive oxygen species, the reaction of Fe^{2+} with intracellular oxygen or hydrogen peroxide induced by Fe NPs may also cause oxidative stress.⁸⁸

Other Metal Ions

In addition to the numerous metal ions mentioned above, which have been extensively researched and used in the antibacterial field, there are other relevant metal ions, such as Mn and Co ions. Although the precise antibacterial processes of these metal ions are not fully understood, they have also been proven to have antibacterial effects,^{89,90} and we hypothesize that these metal ions' antibacterial mechanisms are comparable to those described above, particularly in the following aspects: 1) Because nanoparticles themselves have positive charges, they can adhere to bacteria by electrostatic adsorption and cause the bacterial surface to disintegrate. 2) Metal NPs release metal ions into bacteria to elicit a toxic effect. 3) The generation of oxidative stress, which results in bacterial death. The antibacterial mechanism of metal ions is shown in Figure 2.

What is the Role of Organic Ligands in Antibacterial Nanotherapeutics?

The release of organic ligands with antibacterial effects by MOFs can induce antibacterial activity, synergizing with the effect of the released antibacterial metal ions.¹³ There are several reports of the antibacterial properties of metal ions and chemical ligands. Based on the diversity of MOF components, MOFs can be fabricated from components with antibacterial properties to achieve antibacterial function.^{14,82,91–94}

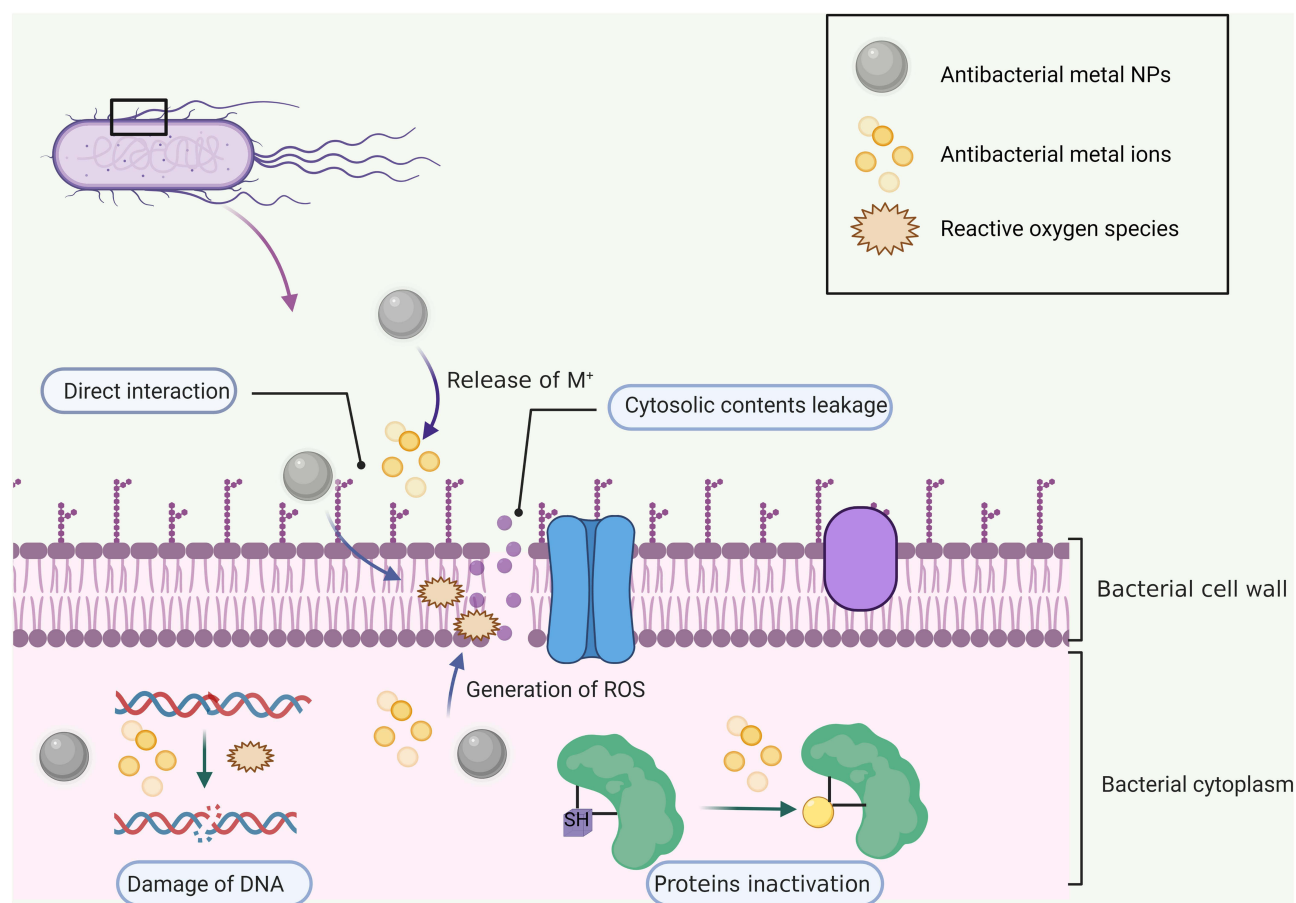


Figure 2 Diagram of bactericidal mechanism of metal nanoparticles and metal ions.

The antibacterial activity induced by ion release is also influenced by ligand design. Ligand design is one of the important factors affecting the diversity of MOFs, and ligands can affect the topology, stability, and porosity of MOFs.⁹⁵ MOF-5 ($[\text{Zn}_4\text{O}(\text{BDC})_3(\text{DMF})_9]$) and Zn-MOF ($[\text{Zn}_3(\text{BDC})_3(\text{H}_2\text{O})_3]_4\text{DMF}$) were developed by Nakhaei et al using the same metal ion and several ligands. This result may be explained by the higher stability of tetranuclear zinc acetate clusters in MOF-5 compared to that of the 2D layered structure in Zn-MOF, which makes it more challenging to release Zn^{2+} from MOF-5.⁹⁶

Numerous organic substances, including metallo-organic antimicrobial compounds, organic halogenates, aldehydes, phenols, acyl anilines, heterocyclic acids, and salts, have antibacterial properties. Depending on their actual use, these antibacterial agents can be classified as bactericides, antiseptics, and antimildew agents. Their antibacterial capabilities can be explained in part by the interactions of naturally occurring antibacterial substances with negatively charged bacteria, which changes the permeability of bacterial cell walls and damages their cell membrane. By altering vinyl chloride with trimethylamine, which endows polyvinyl chloride with antibacterial properties, Wu et al fabricated a quaternized polyvinyl chloride (QPVC) ultrafiltration membrane. When the solution was 50 °C, the QPVC membrane's antibacterial rate increased to 74.2%.⁹⁷

However, Kihak Gwon asserts that the ligand is not as important as the central metal and the MOF structure in determining the antibacterial effect, but the antibacterial ligand released after the collapse of the MOF structure still has a certain antibacterial effect.⁹⁸ An antibacterial Zn-MOF containing hydrazine benzoate linkers was developed by Restrepo et al and was highly effective against *S. aureus*. It had long-lasting antibacterial properties because of the ligand's regulated release.⁸⁶ A new BioMIL-5 made of Zn^{2+} and azelaic acid (AzA), both of which have intriguing

antibacterial effects, was developed by Tamames-Tabar et al. They calculated the MIC/MBC values for AzA and Zn^{2+} , respectively, and reported that this material had additive rather than synergistic antibacterial activity.⁹⁹

Other Possible Mechanisms

The particle size of a substance is a very important factor in determining its properties. When the particle size of the material is reduced to the nanometre scale, the particle has a significant surface effect due to its small surface area and large surface area, thus allowing better performance.¹⁰⁰ Numerous studies have demonstrated that nanomaterials exhibit higher antimicrobial activity than conventional materials and that the antibacterial properties of nanomaterials improve with decreasing particle size.^{100–102}

MOFs can be combined with other substances to elicit corresponding effects in addition to the antibacterial effect they have on their own due to their physical and chemical characteristics. These materials are further discussed in the section on antibacterial applications that follows.

What are the Potential Applications of Metal Nanotherapeutic Platforms in the Antibacterial Field?

According to the explanation of the antibacterial mechanism provided above, the MOF's constitution determines its outstanding antibacterial characteristics. In addition, outstanding researchers have used MOF materials as drug carriers to continuously develop new nanocomplex materials that exhibit a significant antibacterial effect of “1 + 1 > 2”. Below, we discuss examples of MOF antibacterial applications from the following two aspects: pure MOFs as antibacterial agents and MOF-based compounds as antibacterial agents.

Pure Metal Organic Frameworks

Ag-Based MOFs

$\text{Ag}_3(1)$, composed of 3-phosphonobenzoic acid and Ag^+ ions, was developed by Berchel et al. According to the Pearson HSAB hypothesis, 3-phosphonobenzoic acid is a hard base with carboxylic and phosphoric acids. When combined with Ag^+ ions, $\text{Ag}_3(1)$ becomes stable, which is beneficial for the gradual release of Ag^+ . The minimum bactericidal concentration was determined, and the results showed that $\text{Ag}_3(1)$ had broad-spectrum antibacterial activity (including multidrug resistant strains) against three *Staphylococcus aureus*, one *Escherichia coli* and two *Pseudomonas aeruginosa* strains.¹⁰³

Lu et al synthesized two three-dimensional Ag-based MOFs, $[\text{Ag}_2(\text{O-IPA})(\text{H}_2\text{O})\cdot(\text{H}_3\text{O})]$ and $[\text{Ag}_5(\text{PYDC})_2(\text{OH})]$ and tested their antibacterial activity against *E. coli* and *S. aureus* by measuring the minimum inhibitory concentration (MIC) and inhibition zone (ZOI). After the experiment, it was concluded that the MICs of $[\text{Ag}_2(\text{O-IPA})(\text{H}_2\text{O})\cdot(\text{H}_3\text{O})]$ and $[\text{Ag}_5(\text{PYDC})_2(\text{OH})]$ were in the range of 5–10 ppm and 10–15 ppm for *Escherichia coli* and 10–15 ppm and 15–20 ppm for *Staphylococcus aureus*, which indicated that $[\text{Ag}_2(\text{O-IPA})(\text{H}_2\text{O})\cdot(\text{H}_3\text{O})]$ and $[\text{Ag}_5(\text{PYDC})_2(\text{OH})]$ had better antimicrobial activity than most silver-based antimicrobial materials with MICs of 10–40 ppm. The inhibition zones of $[\text{Ag}_2(\text{O-IPA})(\text{H}_2\text{O})\cdot(\text{H}_3\text{O})]$, $[\text{Ag}_5(\text{PYDC})_2(\text{OH})]$, commercial Ag-NPs, and pure ligands were measured by the authors. The results showed that the ZOIs of $[\text{Ag}_2(\text{O-IPA})(\text{H}_2\text{O})\cdot(\text{H}_3\text{O})]$ and $[\text{Ag}_5(\text{PYDC})_2(\text{OH})]$ were larger than those of commercial Ag-NPs, and the diameter of the ZOI of pure ligands was similar to that of filter paper, indicating that they had almost no antibacterial activity. This indicated that the antibacterial activity of Ag-based MOFs is not related to the ligand but depends on the release of the central metal ion. The Ag^+ release of $[\text{Ag}_2(\text{O-IPA})(\text{H}_2\text{O})\cdot(\text{H}_3\text{O})]$, $[\text{Ag}_5(\text{PYDC})_2(\text{OH})]$ and Ag-NPs was also measured by the author. The concentration of Ag^+ was 18.76–25.10 ppm in the Ag-MOF solution on the fifth day compared to 6.685–5.942 ppm in the Ag-NP solution, proving that the release of Ag^+ was the origin of the antibacterial activity of Ag-based MOFs.¹⁰⁴

Cu-Based MOFs

A Cu/ H_3BTC MOF was developed by Shams et al. Its antibacterial properties against *S. aureus* and *E. coli* were tested by ZOI. The ZOI diameters against *S. aureus* and *E. coli* were 22 mm and 16 mm, respectively, and the antibacterial activity increased with increasing Cu/ H_3BTC concentration. By comparing SEM images of the bacteria in the control group,

which had a firm and complete cell wall, to those of the bacteria exposed to increasing concentrations of Cu/H₃BTC, it was found that the severity of bacterial cell membrane destruction rapidly increased. Therefore, the authors hypothesized that the observed bacteriostatic activity may have been caused by Cu²⁺ release, which resulted in cell wall and membrane rupture.¹⁰⁵

Rauf et al synthesized copper-based coordination polymers [Cu(HBTC)(H₂O)₃], which were macroscopically nanofibers, by microwave-assisted hydrothermal synthesis. Antibacterial activity was determined by assaying samples for colony count assays against *E. coli* and *S. aureus*. The mics of commercial Cu NPs were larger than 250 µg/mL, whereas the mics of nanofibers against *E. coli* and *S. aureus* were 200–250 µg/mL and 250–300 µg/mL, respectively. At a concentration of 250 µg/mL, the nanofibers were effective against *E. coli* and *S. aureus*. The inhibition rates were 99.9% and 99.1%, compared to 24% for commercial copper NPs at the same concentration. The ligand H₃BTC had no obvious inhibitory effect on bacteria, which indicated that the copper-based coordination polymer [Cu(HBTC)(H₂O)₃] released copper ions to facilitate sterilization.¹⁰⁶ Studies have demonstrated that copper-based material treatment can produce ROS, which cause oxidative stress and inhibit bacterial growth.^{107,108} The ROS produced by commercial Cu NPs and nanofibers were compared by the authors, who discovered that the output of the former was much lower than that of the latter.¹⁰⁶

Zn-Based MOFs

For the first time, a Zn-MOF was developed by Akbarzadeh et al using the ultrasound-assisted reverse glue method. They then tested the effectiveness of the Zn-antibacterial MOF on six different bacterial strains, including *Staphylococcus aureus*, *Escherichia coli*, *Salmonella enterica*, *Klebsiella pneumoniae*, *Bacillus subtilis*, and *Acinetobacter baumannii*, and the results showed that the Zn-MOF had a good antibacterial effect against the tested bacteria.¹⁰⁹

Fe-Based MOFs

Due to its limited antibacterial action under dark conditions, MIL-101 is frequently utilized as a carrier.^{110,111} Peng et al synthesized MIL-101(Fe) and tuned the unsaturated iron site ratio to increase the potential to produce ROS, making it extremely effective for sterilization in the dark. Experiments showed that when the proportion of unsaturated iron sites was increased, obvious antibacterial activity was observed, and the iron ion leaching experiment confirmed that its antibacterial activity was not determined by the leached iron ions.¹¹¹

Photodynamic Antibacterial Agents

Antibacterial photodynamic therapy (APDT) is a promising alternative to anti-infective therapy that is proposed for photosensitization based on bacteria and photosensitizers (PSs). The mechanism of APDT is as follows: after being exposed to resonant wavelength light, photosensitizers produce reactive oxygen species (ROS), which have a high potential to kill bacteria (as shown in Figure 3).⁸⁰ ROS can act on multiple bacterial targets, thereby providing more opportunities for killing bacteria, and they are less likely to induce drug-resistant bacteria than antibiotics.^{112,113}

It has been observed that MOFs, which are self-assembling porous coordination polymers made of metal ions and organic ligands, have photodynamic antibacterial capabilities similar to ZIF-8 and show promise in the treatment of drug-resistant bacterial infections. Due to the designability of MOF components, metal cluster or organic linker tuning can improve the photocatalytic performance of MOFs.¹¹⁴ Combining MOFs and PSs is one strategy that might be used to take full advantage of the benefits of APDT. The surface of MOFs can be modified with photosensitizers, or MOFs can be used as the carrier to load the photosensitizer and transport it to the bacteria to induce antibacterial activity, and the antibacterial metal ions or organic ligands released from MOFs can also have a synergistic antibacterial effect.^{76,115,116} This point is explained later in this review.

Porphyrins are macromolecular heterocyclic compounds with unique photophysical properties that can produce ROS under irradiation with 660 nm light.^{117,118} Because of their good biological properties, porphyrins have been widely used as photosensitizers for PDT.¹¹⁹ Sun synthesized a porphyrin-based MOF PCN-224 composed of Zr₆ clusters and the TCPP (tetrakis (4-carboxyphenyl)-porphyrin) ligand, which demonstrated great biomedical potential for PDT. A portable band-aid made of chitosan and PCN-224 with the capacity to generate ROS for sterilization when exposed to light

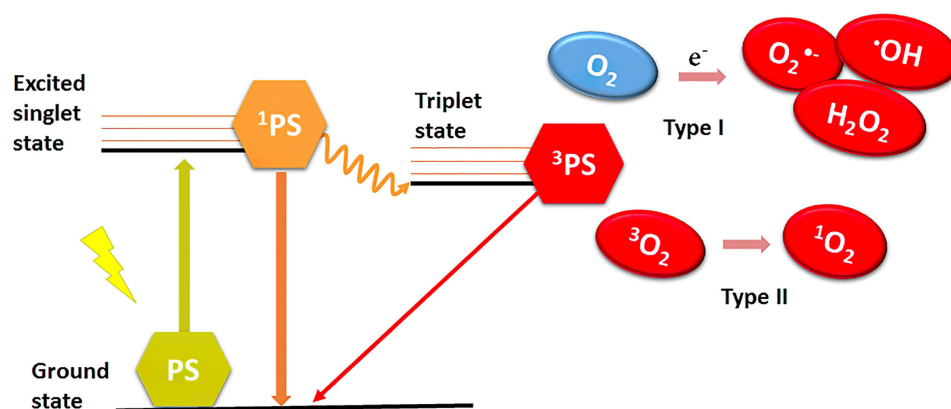


Figure 3 Mechanism of APDT to generate ROS.

Notes: Reproduced from Liu Y, Qin R, Zaat SAJ, Breukink E, Heger M. Antibacterial photodynamic therapy: overview of a promising approach to fight antibiotic-resistant bacterial infections. *J Clin Transl Res*. 2015;1(3):140–167. This is an open-access article distributed under the terms of the Creative Commons Attribution License. (<http://creativecommons.org/licenses/by/4.0/>).⁸⁰

irradiation was developed. Moreover, an experiment showed that the combination of PDT and chemotherapy had a strong synergistic effect on killing drug-resistant *E. coli*.¹¹³

Donglin Han introduced Cu^{2+} into PCN-224 through hydrothermal synthesis to obtain a CuMOF that exhibited a high photodynamic bactericidal efficiency of 99.71% against *S. aureus* and 97.14% against *E. coli* under light irradiation at 660 nm within 20 minutes. The doped Cu^{2+} improved the photocatalytic property of the material by enhancing its capacity to capture photogenerated electrons. The d-d transition of Cu^{2+} also improved the heat-generation ability of the material.¹²⁰

Bimetallic PCN-224(Zr/Ti) was developed by Chen et al through cation exchange. The inclusion of Ti dramatically improved photocatalytic performance and prevented ultraviolet light damage to healthy tissues by efficiently extending PCN-224's light response into the visible region. Studies revealed that PCN-224(Zr/Ti) had a significantly greater antibacterial efficiency than PCN-224. In addition, they created a PLGA-based dressing loaded with PCN-224(Zr/Ti) NPs for use in animal wound models, which showed that the dressing promoted wound healing by killing bacteria and controlling inflammation.¹²¹

Yang et al designed an Ag-doped MOF derivative (C-Zn/Ag) with a graphitic-like carbon structure, which was reported to be capable of broad-spectrum optical absorption and efficient photo-to-thermal conversion. The bacteria-killing rate of C-Zn/Ag under near-infrared irradiation was 76%, while the bacteria-killing rate of C-ZIF with only zinc ion release was 43%, showing that the synergy enhanced the antibacterial performance.¹²²

Li et al reported that ZIF-8 exhibited an excellent inactivation efficiency of 99.9999% against *E. coli* in saline under 2 h of simulated solar irradiation, and they proved that the antibacterial effect depended on the intact ZIF-8 rather than the release of zinc ions in the presence of light irritation because the concentration of zinc ions (2.65 mg L^{-1}) released from ZIF-8 did not reach the minimum inhibitory concentration (MIC, 31.25 mg L^{-1}). They developed a MOFilter mask and proved it was more effective than some commercial masks, providing new ideas for the development and application of porous photocatalytic antibacterial materials. (as shown in Figure 4).¹¹⁴

Metal Organic Frameworks-Based Compounds

As indicated by the above discussion, we know that pure MOF has a certain bactericidal effect, but its antibacterial effect is relatively limited compared to MOF-based composites. For instance, ZOIs of Zn-MOF $\text{Zn}_2(\text{BDC})_2(\text{DABCO})$ and gentamicin-loaded $\text{Zn}_2(\text{BDC})_2(\text{DABCO})$ against *S. aureus* and *E. coli* were studied by Nabipour et al ($\text{Zn}_2(\text{BDC})_2(\text{DABCO})$: ZOI 8 mm for *E. coli*, 6 mm for *S. aureus*. Gentamicin loaded $\text{Zn}_2(\text{BDC})_2(\text{DABCO})$: ZOI 9 mm for *E. coli*, 16 mm for *S. aureus*).¹²³ Therefore, at present, MOFs are mostly combined with other antibacterial materials to induce a greater bactericidal effect. The large pore size and high specific surface area of MOFs provide a perfect platform for the loading of additional antibacterial substances.

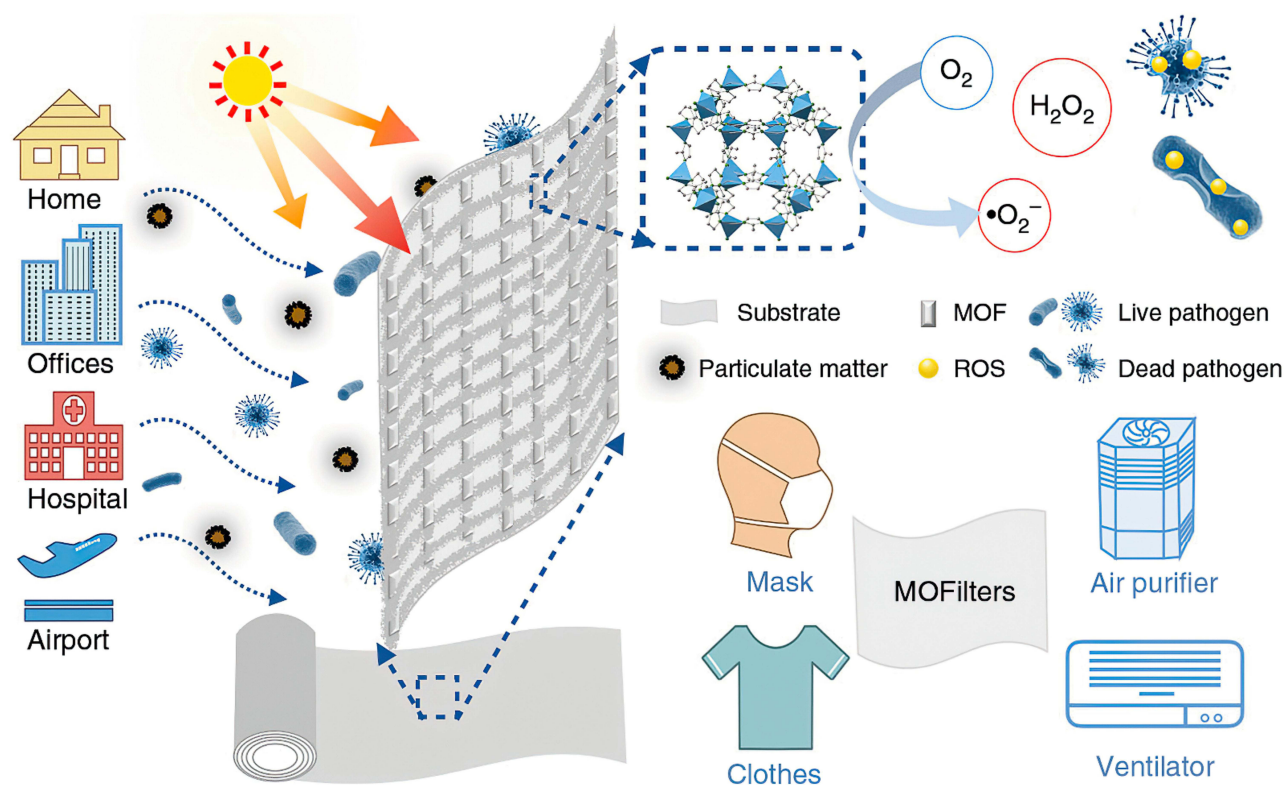


Figure 4 Schematic diagram of MOF-based filter.

Notes: Reproduced from Li P, Li J, Feng X, et al. Metal-organic frameworks with photocatalytic bactericidal activity for integrated air cleaning. *Nat Commun.* 2019;10(1):2177. This article is licensed under a Creative Commons Attribution 4.0 International License. (<http://creativecommons.org/licenses/by/4.0/>).¹¹⁴

Metal Organic Frameworks Act as Carriers to Load Antibiotics in Antibacterial Therapy

As a class of organic antibacterial agents, antibiotics have been commonly used for the treatment of bacterial infections.¹²⁴ However, the concentration of antibiotics reaching the infection site is occasionally insufficient to kill germs and cure the infection, as antibiotics are carried in the blood and metabolized by the human body. It has been proposed to use MOF-based materials as carriers to transport antibiotics to the infection site, which can allow the release of drugs through different mechanisms to achieve bactericidal and anti-infection effects. It has been reported that this new antibacterial strategy can induce a synergistic antibacterial effect and lower the dose of antibiotics required to reduce the emergence of bacterial resistance.

An example of a MOF is UiO-66, which is composed of Zr ions and terephthalic acid and may absorb antibiotics into its pores or surface through electrostatic and hydrophobic interactions.¹²⁵ Nasrabadi et al prepared UiO-66 by the solvothermal method and loaded ciprofloxacin (CIP) into UiO-66 to test its drug loading and antibacterial activity.¹²⁶ The research results revealed that UiO-66 had a very high CIP loading rate of up to 84% and displayed significant antibacterial activity against *S. aureus* and *E. coli*. The inhibitory zone of UiO-66-CIP against *S. aureus* was 24 mm, and the inhibitory zone against *E. coli* was 22 mm. *S. aureus* was resistant to CIP, and the inhibitory zone of CIP against *E. coli* was 14 mm, suggesting that the controlled release system eliminated the drug resistance of *S. aureus* and had enhanced antibacterial activity against *E. coli*.¹²⁶

ZIF-8, composed of zinc ions and dimethylimidazole, was employed to construct a pH-responsive drug delivery system due to its stability in neutral aqueous solution and disintegration in an acidic environment.¹²⁷ Nabipour et al encapsulated CIP in ZIF-8 through the nanoprecipitation method and compared the drug release rate under different pH values. It was concluded that the amount of CIP encapsulated in ZIF-8 was 21 (w/w) %, and the antibacterial activities were higher than those of ZIF-8 (CIP-ZIF-8: ZOI 46 mm for *E. coli*, 49 mm for *S. aureus*. ZIF-8: ZOI 14 mm for *E. coli* and 12 mm for *S. aureus*). At pH 5.0, the release rates of CIP were faster than those at pH 7.4, indicating that ZIF-8 is a pH-responsive DDS, and it may be a useful antibiotic delivery system for the treatment of infections.¹²⁸

Due to its large pore size, noticeable surface area, and capacity for the incorporation of backbone functional groups, the MIL family of MOFs, which are composed of trivalent metal centres and carboxylic acid bridging ligands, show tremendous promise for drug delivery.²⁷ Simon et al used MIL-100 as a carrier of isoniazid to overcome its poor solubility and bioavailability, thereby offering an improvement upon the hepatotoxicity, peripheral neuritis, and emergence of drug-resistant strains that may be caused by long-term isoniazid treatment. They evaluated the physicochemical features of MIL-100 and the adsorption and release of isoniazid. The findings demonstrated that MIL-100 exerted an effective, controlled release of isoniazid and that there were no burst release phenomena during the release process. Moreover, MIL-100 had good biocompatibility, and the above findings suggest that MIL-100 is a promising isoniazid drug delivery system.⁴¹

Metal Organic Frameworks-Metal/Metal Oxide Antibacterial Agents

Metal and metal oxides have excellent antibacterial effects on both gram-positive and gram-negative bacteria. Metals, however, have the propensity to agglomerate or oxidize, which reduces their surface area and lessens their antibacterial action.¹²⁹ Due to their desirable characteristics of large pores, high porosity, and high surface area, MOFs have been extensively studied as templates for immobilizing metal NPs to create MOF-based composites.^{130,131} For instance, to increase the stability and dispersity of silver nanoparticles, Duan et al immobilized the particles on the surface and in the pores of HKUST-1. The combination of copper ions in HKUST-1 and carboxyl groups in carboxymethylated fibres (CFs) allowed the particles to be uniformly fixed on the fibre surface to form Ag NPs@HKUST-1@CFs. The antibacterial activities of HKUST-1, Ag NPs@HKUST-1 and Ag NPs@HKUST-1@CFs were determined using the shake flask method, and the results showed that Ag NPs@HKUST-1@CFs had the highest antibacterial activity. The authors asserted that the Ag NPs and the gradual release of copper ions by HKUST-1 were responsible for its antibacterial action.¹³⁰

Metal Organic Frameworks-Photosensitizer Antibacterial Agents

Bagchi et al developed a dual-stimuli-responsive therapeutic platform against drug-resistant bacteria with hydrophobic PS squaraine (SQ) embedded in a zeolitic imidazolate framework (ZIF-8). The encapsulation of SQ within ZIF-8 limited the aggregation of SQ and improved ROS generation capacity. Moreover, because ZIF-8 is sensitive to pH, hydrolysis in acidic environments enabled SQ to be specifically transported to the site of infection, reducing the likelihood of damaging normal tissues. Furthermore, an experiment demonstrated that ZIF8-SQ had a superior antibacterial effectivity against MRSA even at a very low concentration range under red-light irradiation.¹¹⁵

Some researchers developed a NIR/pH dual stimulus-responsive antibacterial formulation by encapsulating antibiotics in photosensitizer-modified MOFs (Van@ZIF-8@PDA). Polydopamine (PDA) had a high antibacterial impact due to its thermal effect when exposed to near-infrared light, which was synergized with the degradation of ZIF-8 to release zinc ions and loaded medicinal drugs (as shown in Figure 5).⁷⁶

UiO-66 is an ideal drug carrier that can be functionalized with amino groups, nitro groups, etc. In addition, it can electrostatically and hydrophobically attract antibacterial compounds to its pores and surfaces. Lv et al combined UiO-66 with the photosensitizer zinc phthalocyanine to construct an efficient drug-loading system. By electrostatic adsorption and molecular interactions, the chemical antibacterial agent linezolid and lysozyme were successively loaded on the inside and outside of its pores to produce (Li@UiO-66-H₄Pc)@lysozyme. Antibacterial experiments were carried out on UiO-66-NH₂, UiO-66-H₄Pc, Li@UiO-66-H₄Pc, and (Li@UiO-66-H₄Pc)@lysozyme in the dark and in the light. Li@UiO-66-H₄Pc and (Li@UiO-66-H₄Pc)@lysozyme both showed various antibacterial activities in the absence of light, whereas UiO-66-NH₂ and UiO-66-H₄Pc exhibited no apparent antibacterial effects. UiO-66-H₄Pc, Li@UiO-66-H₄Pc, and (Li@UiO-66-H₄Pc)@lysozyme all had apparent dose-dependent antibacterial responses when exposed to laser radiation. These results indicated that antimicrobials and zinc phthalocyanine synergistically kill most bacteria under light. A possible antibacterial mechanism is the destruction of the bacterial cell wall by lysozyme, making it easier for nanomaterials to enter the bacteria to exert a better bactericidal effect. Additionally, the ROS generated under light can kill stubborn bacteria through multiple targets to achieve synergistic photodynamic and chemical antibacterial effects.¹²⁵

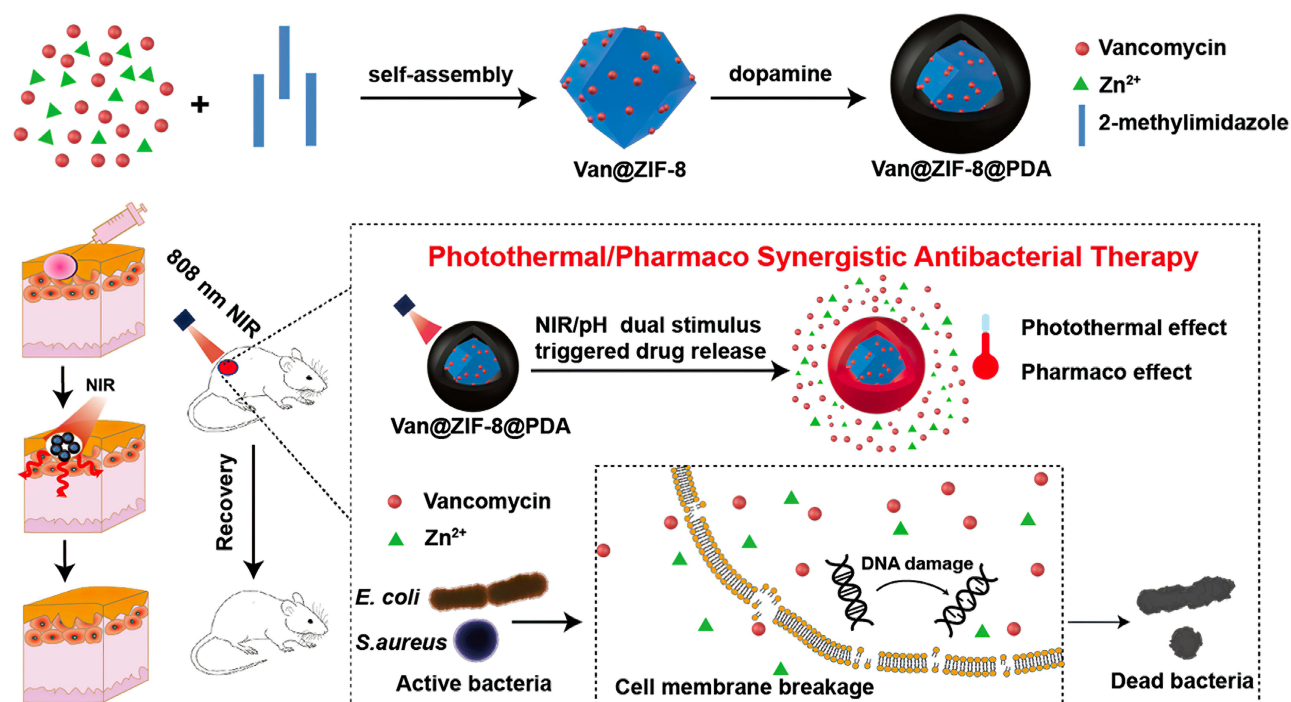


Figure 5 Schematic diagram of photothermal synergistic drug antibacterial.

Notes: Reprinted from *Acta Biomater*, 122, Xiao Y, Xu M, Lv N, et al. Dual stimuli-responsive metal-organic framework-based nanosystem for synergistic photothermal/pharmacological antibacterial therapy. 291–305. Copyright (2020), with permission from Elsevier.⁷⁶

The addition of a photosensitizer endows MOFs with photodynamic antibacterial activity, and MOFs also have a favorable impact on the additional photosensitizer. Li et al, for instance, proposed a photosensitizer-modified ZIF-8 nanocomposite that killed MRSA with high efficiency through the potential synergistic antibacterial effect of the metal ions and photosensitizer. The combination of Ce6 (Chlorin e6) and ZIF-8 made the absorbance intensity of Ce6 more stable and enhanced its ability to generate ROS.¹¹⁶

Other

MOF-Chlorine Disinfectant

In the past two years, there has been a global pandemic of coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).¹³² The World Health Organization (WHO) suggested the global use of face masks to prevent COVID-19 infection. SARS-CoV-2 can exist on the surface of various objects, including textile-based materials, such as face masks, for several days, which can produce contamination sources to result in a more widespread infection, so it is urgent to develop personal protective equipment with the ability to kill pathogenic microorganisms.¹³³

Cheung et al designed multifunctional N-chlorine-based textiles coated with UiO-66 and loaded with N-chlorine biocide to develop a material with rapid biocidal activity. Antibacterial experiments showed that the UiO-66-NH-Cl-PET composite demonstrated a rapid bactericidal effect on both gram-positive and gram-negative bacteria, and the sterilization effect reached 10^7 – 10^8 CFU/mL within 5 minutes. Obvious deformation and membrane collapse of treated bacteria were observed under a scanning electron microscope. Due to the presence of a layer of lipopolysaccharide outside the cell wall of gram-negative bacteria, UiO-66-NH-Cl-PET had a lesser antibacterial effect on gram-negative bacteria than on gram-positive bacteria. Additionally, UiO-66-NH-Cl-PET exhibited potent biocidal activity against SARS-CoV-2 and the selective degradation of sulfur mustard and its chemical simulant 2-chloroethyl ethyl sulfide, suggesting that the composite has great potential to be prepared as multifunctional protective wear that can prevent pathogenic microorganisms and sulfur-based chemical warfare agents.¹³³

MOF-Iodine

Teng et al designed a composite coating composed of ZIF-8 and iodine on orthopaedic implants, which not only had a synergistic antibacterial effect but also enhanced the osseointegration of the coated implants. In this study, ZIF-8 functioned as a carrier for povidone-iodine to control its release and induce its antibacterial activity while also using its capacity to produce ROS under infrared radiation to kill bacteria. This suggests the application potential of povidone-iodine as a feasible antibacterial agent for orthopaedic applications.¹³⁴

MOF-Dimethyl Fumarate

Antibacterial composite materials based on MOFs are also appropriate for industrial uses in food, heating, water, and other fields.^{135,136} For example, Huang et al combined carboxymethyl chitosan (CMCS) and HKUST-1 to fabricate an ecofriendly, recyclable, long-acting, and intelligent antibacterial agent carrier for loading dimethyl fumarate, which is a nontoxic preservation material with antimicrobial capability. The porosity of the MOFs and the characteristics of polymer processing were fully utilized in the fabrication of the MOF-CMCS composite. Since the active groups such as $-\text{COOH}$, $-\text{NH}_2$, and $-\text{OH}$ of CMCS may be intimately coupled with the copper ions in HKUST-1, no copper ions are left in the release matrix, avoiding any potential biological safety issues and environmental pollution caused by metal ions. When employed in the food industry, MOF-CMCS can efficiently control the release of dimethyl fumarate to induce a long-term antibacterial effect and extend the storage time of food (as shown in Figure 6).¹³⁵

Among the MOF-based compounds applied as antibacterial agents listed above, MOFs and other materials were combined and complemented each other to achieve a synergistic antibacterial effect of “1+1>2”. The diversity of MOF components makes it possible for them to have synergistic antibacterial effects. In addition to the synergistic effect with other materials, MOFs themselves also exhibit interesting phenomena. For example, some MOFs exhibit antibacterial activity superior to that of their corresponding ligands and exhibit antibacterial activity without ligand release, which may be explained by Tweedy’s chelating theory.^{137,138} The chelation effect allows the metal ion to share a partial positive charge with the ligand and the possible presence of delocalized electrons during the chelation process, which increases the lipophilicity of the metal and makes it easier for them to cross the lipid-like layer of the bacterial cell membrane to achieve enhanced antibacterial activity.¹³⁷ For instance, complexes of 2-(5-chloro/nitro-1H-benzimidazol-2-yl)-4-bromo/nitro-phenols (HL_x ; $x=1-4$) and zinc (II) nitrate were synthesized, and paper diffusion experiments were performed to

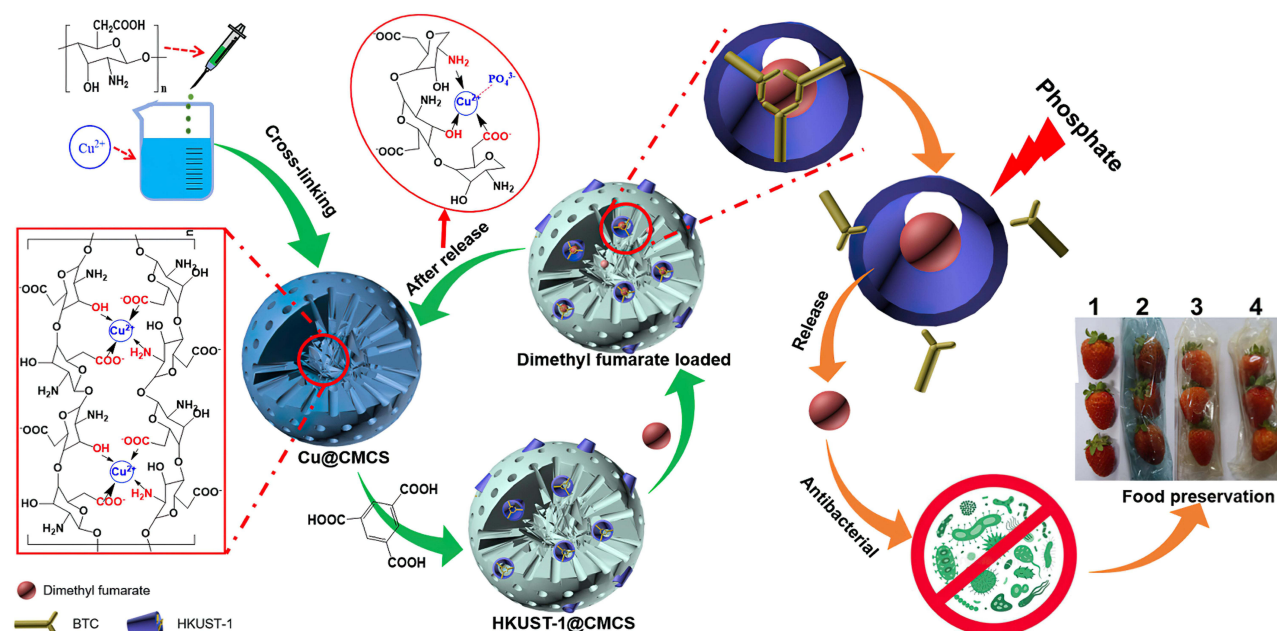


Figure 6 Schematic diagram of the synthesis and antibacterial application of HKUST-1@CMCS.

Notes: Reprinted from *Carbohydrate polymers*, 233, Huang G, Li Y, Qin Z, Liang Q, Xu C, Lin B. Hybridization of carboxymethyl chitosan with MOFs to construct recyclable, long-acting and intelligent antibacterial agent carrier. 115848. Copyright (2020), with permission from Elsevier.¹³⁵

assess their antibacterial activity. It was discovered that $[\text{Zn}(\text{L}_1)_2] \cdot \text{H}_2\text{O}$ exhibited strong antibacterial activity, whereas the ligand and zinc nitrate alone did not exhibit antibacterial activity.¹³⁹

In addition to antibacterial applications, MOFs could also be promising in other fields. Tumour therapy is a developing field in which MOFs have great application potential. Substances with pharmacological activity can be chosen as ligands or metal ions for direct assembly to obtain MOFs with therapeutic functions due to the modifiability of the MOF component.¹⁴⁰ Surface modification of MOFs can also be performed to avoid their clearance by the immune system, protect the delivered drugs, etc.¹⁴¹ Additionally, MOF-based drug delivery systems have been developed significantly in a number of therapeutic modalities, including chemotherapy, photodynamic therapy, radiation, and immunotherapy, all of which have shown promising therapeutic effects.^{140,142}

Conclusions and Future Prospects

In addition to harming human health, the regional spread of infectious illnesses has a significant negative economic impact because the fear of infection can impede many industries, including consumption, entertainment, and tourism industries.¹⁴³ In the above discussion, we summarized the various antibacterial mechanisms and applications of various MOFs, which indicated that the application of MOFs and MOF-based materials is a promising therapeutic approach for refractory illnesses caused by resistant bacteria. In terms of infection control, timely and accurate diagnosis of bacterial infections is just as crucial as the subsequent infection therapy.

Monitoring of the corresponding inflammatory indicators, such as C-reactive protein¹⁴⁴ and calcitoninogen,¹⁴⁵ is the traditional method used for the clinical diagnosis of bacterial infections, particularly deep infections. However, changes in these inflammatory indicators always occur after the development of the infection. H_2S is a metabolite of many microorganisms that can alter the peri-infective microenvironment. Many bacterial strains have been found to be protected by H_2S , which lessens the damage that antibiotics may cause to them.¹⁴⁶ One study used BI-MOF to monitor H_2S in the microenvironment by taking advantage of the strong affinity of Bi for H_2S , and the two reacted to produce Bi_2S_3 , which can be triggered by a laser with deep tissue penetration and signalling.¹⁴⁷ This can allow the early monitoring of bacterial infections and offers a promising diagnostic tool for the rapid and precise diagnosis of infections. The monitoring function of MOFs was employed in a range of sensors for tracking viruses, microorganisms in drinking water, etc., in addition to assisting in the early identification of bacterial illnesses.^{148–150}

Although MOFs have many advantages compared with other antimicrobial materials, such as the tunability of the composition structure and drug loading capacity, as mentioned above, there are still some factors that limit their practical application. First, MOFs must be synthesized under stringent conditions. Variations in time, temperature, and environment might result in various MOF shapes and sizes, which directly affect the physicochemical characteristics of MOFs. Second, the powder state of MOFs limits its further application, and future research should concentrate on developing MOF-based macrocomposites employing techniques such as electrostatic spinning. Third, the conclusions of studies on MOF toxicity are not clear. The majority of the investigations being conducted right now include short-term cellular or animal tests, and proof of the hazardous consequences of long-term MOF application is insufficient. In addition, MOF toxicity is influenced by their composition, size, shape, and tolerance in living tissues, necessitating a thorough evaluation of the toxicity of various MOFs.

In summary, this paper provides a review of the current research progress of MOFs from the perspective of their applications in the antimicrobial field, including the synthesis, antimicrobial mechanism, and application of MOFs and MOF-based materials. Although significant progress has been achieved, this progress is insufficient, and there are still no studies available on the long-term toxicity of MOFs and real-world therapeutic MOF applications. It is hoped that the antibacterial qualities of MOFs will garner more interest in the fields of water and environmental treatment, biomedical science, and materials science, leading to more research and practical applications of MOFs.

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Disclosure

The authors report no conflicts of interest in this work.

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