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Review Article

Research status and prospects of covalent organic frameworks in the antibacterial field

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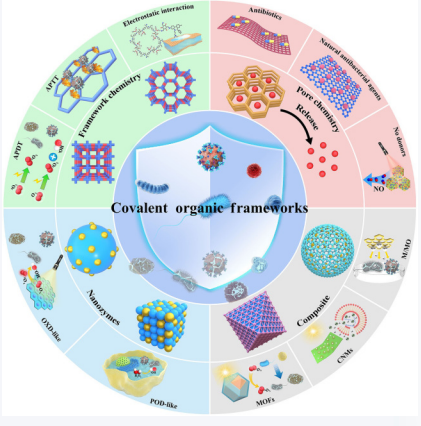
ABSTRACT: Covalent organic frameworks (COFs), as an emerging class of crystalline porous polymeric material, process large surface area, ordered pore structure, good biocompatibility, excellent chemical stability, and low toxicity, making it an excellent candidate for nanotherapeutics. In this article, the recent research progress of COFs was reviewed in the antibacterial field. We introduced the antibacterial potential of COF materials themselves, covering framework structures and pore chemistry. Moreover, the synergistic antibacterial effects of COF composites were discussed, which were formed by the combination of COF with other nanomaterials. In addition, the excellent performances of COFs as nanozymes were investigated in antibacterial applications. Currently, COF-based high-efficiency antibacterial agents face great challenges and prospects in practical applications. The review will provide new COF-based methods for resolving drug-resistant bacterial issues.



KEYWORDS: covalent organic frameworks, antibacterial potential, framework chemistry, pore chemistry, composite material, nanozymes

1 Introduction

Bacteria are the pathogens of many diseases. They mainly spread diseases in organisms through respiration, contact, digestive tract, mosquito bites, etc. They are highly infectious and harmful, affecting the health of millions of people around the world [1]. As one of the most common sterilization methods, antibiotic therapy is widely used in clinical practice. However, the inappropriate use of antibiotics soon led to cytotoxicity and bacterial resistance, which caused a crisis in the use of antibiotics and led to another serious crisis in human health [2, 3]. Therefore, it is crucial to develop new and efficient antibiotic-free antibacterial drugs.

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Antibacterial therapy based on bio-nanomaterials is currently receiving a lot of attention as a promising alternative strategy to conventional antibiotics. Unlike conventional antibiotics, nanomaterials have structural and functional designability, such as size and dimension, surface environment, and stimulus response, to establish specific interactions with bacteria. As a result of these interactions, nanomaterials provide unique sterilization mechanisms and excellent antibacterial properties, such as antibacterial broad-spectrum, long-lasting efficacy, and effective resistance to the development of drug-resistant bacteria [4–6]. Currently, a variety of nanomaterials, including metal and metal oxide nanoparticles (M/MO) [7, 8], antibacterial peptides [9, 10], carbon-based nanomaterials (CNMs) [11, 12], metal-organic framework nanomaterials (MOFs) [13, 14], and polymeric nanomaterials [15, 16] have been demonstrated to possess superb antibacterial properties through *in vitro* and *in vivo* experiments. While nanomaterials demonstrate outstanding antibacterial performance, they currently suffer from several defects (Table 1). These defects encompass, but are not limited to: poor chemical

Table 1 The advantages and disadvantages of current antibacterial nanomaterials

Materials	Advantages	Disadvantages
M/MO	1. Broad-spectrum; 2. High efficiency	1. Poor biocompatibility; 2. Concentration dependence; 3. Easy agglomeration; 4. Large environmental burden; 5. High cost
Peptides	1. Broad-spectrum; 2. Anti-drug resistance	1. Short duration of half-life; 2. Protease degradation; 3. Adverse effects; 4. High cost
CNMs	1. Broad-spectrum; 2. Good biocompatibility; 3. Environment-friendly	1. Poor dispersion; 2. Difficult recovery and post-processing; 3. Uncertain long-term biosafety
Polymers	1. Excellent carrier of antibiotics; 2. Biodegradability	1. Limited antibacterial ability; 2. Fuzzy aggregation mechanism
MOFs	1. Structural diversity and designability; 2. Slow-release metal ions; 3. Excellent carrier of antibiotics.	1. Poor chemical/thermal stability; 2. Potential biological toxicity
HOFs	1. No metal; 2. Flexibility and reversibility	1. Poor chemical/thermal stability; 2. Difficult to synthesize accurately; 3. Lack of functional groups, difficult to post-modification
SOFs	1. No metal; 2. Flexibility and reversibility	1. Poor chemical/thermal stability; 2. Difficult to synthesize accurately; 3. High cost

stability, easy agglomeration, toxic side effects, high manufacturing cost, and etc. These defects seriously limit their wide application, and they are still far from being a real antibiotic replacement agent.

Covalent organic frameworks (COFs) are a new class of crystalline porous polymeric materials assembled by covalent bonding with organic small molecules as building blocks, also known as "organic zeolites". The highly ordered pore structure, good chemical stability, and tunable functionality make COFs materials have a wide range of applications in the fields of catalysis, sensing, electrochemistry, adsorption and separation, energy, and nanomedicine [17–22]. COFs with large specific surface area and porosity have attracted much attention in the biomedical field, and the large number of pores not only makes COFs excellent carriers for hydrophobic drugs but also helps the reactive oxygen species (ROS) generated by photothermal diagnostics to diffuse from the interior to the surface. In addition, imine-bridged COFs are usually more sensitive to acidic conditions and can serve as potential biodegradable carriers in the tumor microenvironment. As a highly crystalline material, the ordered structure in COFs can give them a better photothermal effect [23]. These unique properties of COFs make them an excellent material that has attracted much attention in fields ranging from energy to biomedicine [24–26].

Based on the fact that COFs are highly customizable and excellent materials for designing antibacterial agents, antibacterial active groups can be introduced into the framework of COFs or antibacterial drugs can be loaded by the pores as a way to develop COFs materials with their antibacterial activity. For example, photosensitizers (e.g., porphyrin, triazine, acridine, boradipyrrolidine (BODIPY), etc.) were introduced into the framework of COFs to prepare photosensitized COFs, which could kill bacteria by generating cytotoxic ROS under the conditions of light irradiation and the presence of O_2 [27]. Guanidine and quaternary ammonium salts, etc. were introduced to prepare cationic COFs, which can adsorb on the surface of anionic bacterial membranes through electrostatic interactions, disrupting their potential and leading to the leakage of metabolites, thus killing bacteria [28]. Similarly, based on the porous nature and uniform pore size of COFs, antibiotics, and other antibacterial drugs can be loaded in the pore channels to realize intelligent controlled release of drugs and ensure long-term antibacterial effects [29]. In addition, COFs can be integrated with other antibacterial nanomaterials (e.g., metallic NPs, CNMs, MOFs, etc.) to enhance their antibacterial activity [30]. In addition, as an emerging porous crystalline material, COFs have high physical/chemical stability, are easy to synthesize, and do not contain unstable and harmful metals or metal oxides, which provides a high degree of safety and utility in biomedical applications, and thus the value of COFs materials for antibacterial applications has been continuously developed. This paper reviews the latest research progress of COFs in the field of antibacterial and firstly summarizes the antibacterial activity of COF materials themselves. After that, the synergistic antibacterial effect of COFs composite with other antibacterial nanomaterials is summarized. Next, the antibacterial progress of COF-based nanozymes is presented. Finally, current challenges and perspectives for practical applications of COFs are discussed.

2 Antibacterial activity of COFs materials themselves

2.1 Framework chemistry

Currently, there are two main strategies for the synthesis of functionalized COFs, bottom-up synthesis and post-synthesis modification [31]. Therefore, the selection of organic molecules containing antibacterial active groups as the building block monomers for direct synthesis or the post-modification of pre-synthesized COFs with antibacterial active groups can be used to obtain the desired COFs antibacterial agents (Fig. 1). Specific antibacterial properties of COFs, such as photodynamic, photothermal, and electrostatic interactions, can be conferred by designing different introduced moieties.

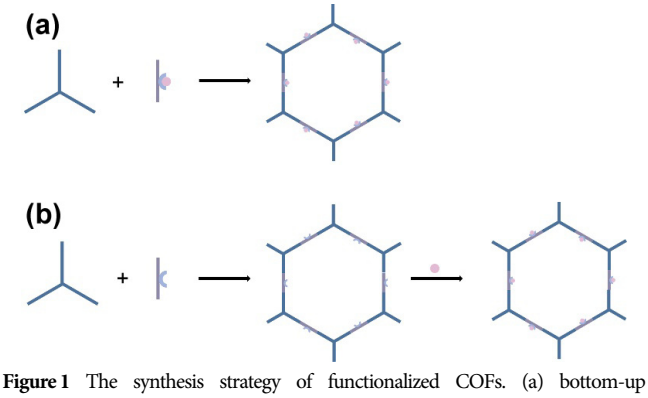

Figure 1 The synthesis strategy of functionalized COFs. (a) bottom-up synthesis, (b) post-synthesis modification [31].

2.1.1 *Photodynamic*

Photodynamic therapy (PDT) has received widespread attention as a clinical treatment with significant results [32, 33]. PDT was divided into type I and type II. Upon photoactivation, the photosensitizer (PSs) was transformed from the ground state (S_0) to the excited singlet state (S_1), and then to the electron-excited triplet state (T_1). In type I PDT, T_1 involves in a process of hydrogen- or electron transfer to interact with a biological substrate, forming free radicals. The radicals will react with triplet oxygen ($^3O_2$) and water to get superoxide anions ($\cdot O_2^-$) and hydroxyl radicals (·OH). In type II PDT, the triplet state converts $^3O_2$ to $^1O_2$ by direct energy transfer (Fig. 2) [34–36]. Antibacterial photodynamic therapy (APDT) can effectively resist the emergence of drug-resistant bacteria and has become one of the most promising modes of research against drug-resistant bacteria because of its easy spatial control and low invasiveness [37]. Currently reported PSs, such as methylene blue, porphyrin, phthalocyanine, BODIPY etc., can be used to inhibit bacterial growth or kill bacteria under specific wavelength laser irradiation [38]. However, conventional PSs often suffer from easy agglomeration, low reactive oxygen species production, short lifetime, and small action range, which seriously reduce the antibacterial efficiency [39]. Previous studies have shown that the introduction of PSs into nanomaterials can improve the dispersion of PSs, the generation of ROS, and the antibacterial effect [40, 41]. COFs with an extended π-conjugated structure can allow for a wide range of light absorption, whereas the porous nature with a uniform pore size can effectively promote the diffusion of O_2 and ROS, increase the efficiency of ROS action [42], and thus improve the antibacterial effect. The introduction of PSs (e.g., porphyrin, triazine, acridine, BODIPY, etc.) into the framework of COFs can construct COFs with antibacterial activity.

In recent years, covalent triazine frameworks (CTFs) have been demonstrated excellent photocatalysis activity due to their structural advantages such as abundant nitrogen content, visible photosensitivity, high stability, nontoxicity, and complete conjugation [43–45]. However, photocatalytic antibacterial based on CTFs are poorly studied and urgently need to be explored. In 2017, Zhang et al. synthesized two examples of triazine COFs (COF-SDU1 and COFs-Trifr-Benz) from tri-(4-formacylphenoxy)-1,3,5-triazine and benzidine or p-phenylenediamine under solvothermal conditions. The triazine COFs consisted of irregular schistose morphologies. Due to their extensive π-conjugation and porous structure, the two examples of triazine COFs have excellent photodynamic activity (Fig. 3(a)), and the singlet oxygen ($^1O_2$) generated under visible light irradiation effectively kills both Gram-positive (*S. aureus*) and Gram-negative (*E. coli O86*) bacteria (Figs. 3(b) and 3(c)) [46].

Porphyrins and their derivatives are widely used as an effective PSs for PDT. Porphyrins, when activated by visible light (600–800 nm), can undergo a photo-induced reaction with molecular oxygen to produce ROS, which can be used for therapeutic purposes to kill pathogens [47]. Although existing porphyrin PSs have been shown to be effective for antibacterial photodynamic therapy (APDT), these molecules tend to self-aggregate, resulting in a loss of photosensitizing activity, which hampers their clinical application. An effective strategy to overcome these obstacles is the synthesis of solid porphyrin-based PSs that can modulate their stability and therapeutic efficacy [48, 49].

In 2018, Lang et al. prepared an example of 3D porphyrin-based COFs (3D-TPP) by Schiff base condensation using porphyrin and tetrakis(4-aminophenyl)methane as the building blocks, which is a COFs material that can effectively inhibit the inactivation of $^1O_2$ due to porphyrin aggregation, with photostability, broad spectral efficiency and excellent dispersibility. Particularly, 3D-TPP can produce a higher concentration of localized singlet oxygen under visible light irradiation compared to 2D-TPP (Fig. 3(d)), which can effectively kill *P. aeruginosa* and *E. faecalis* (Figs. 3(e) and 3(f)) [50].

Notably, the conjugation range of PSs is also related to the ROS generation ability. A larger conjugation range improves the electron-leaping probability, which in turn results in a red-shifted and broader spectral response of the ultraviolet–visible (UV–vis) spectrum [51–53]. The conjugation of 2D COFs can be improved by using conjugated monomers as building blocks. In 2021, Yan et al. proposed a conjugated regulation strategy. Three highly photosensitive porphyrin-based covalent organic frameworks (COF-366, DhaTph, JNU-2) were prepared by the condensation of terephthalaldehyde (Da), 2,5-dihydroxyterephthalaldehyde (Dha), and 2,5-diethoxyterephthalaldehyde (Deta) with different degrees of conjugation, and 5,10,15,20-tetrakis(4-aminophenyl) porphyrin (Tph), respectively (Fig. 4(a)). The three Por-COFs were all sheet-like morphology. Compared with Da, Dha and Deta with higher degree of conjugation further extend the conjugation range of DhaTph and JNU-2 upon the formation of a two-dimensional extended π-conjugated structure, which in turn leads to enhanced photosensitivity. JNU-2 with intra-layer p-π conjugation has the highest degree of conjugation, and accordingly presents the highest photosensitivity, which can effectively kill *S. aureus* (99.1%) and *E. coli* (96.8%) (Figs. 4(b)–4(e)) [41].

Protoflavin, also known as 3,6-diaminoacridine, is a DNA intercalator widely used in the biomedical field as an antibacterial agent against a wide range of Gram-positive bacteria. Protoflavin has a wide range of light absorption from ultraviolet to near-infrared region, and can efficiently produce biotoxic ROS under visible light irradiation, thereby killing pathogens [54, 55]. In 2021,

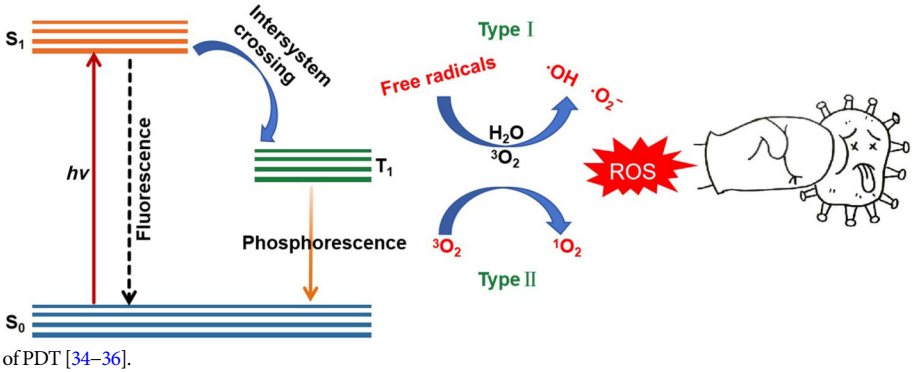

Figure 2 The mechanism of PDT [34–36].

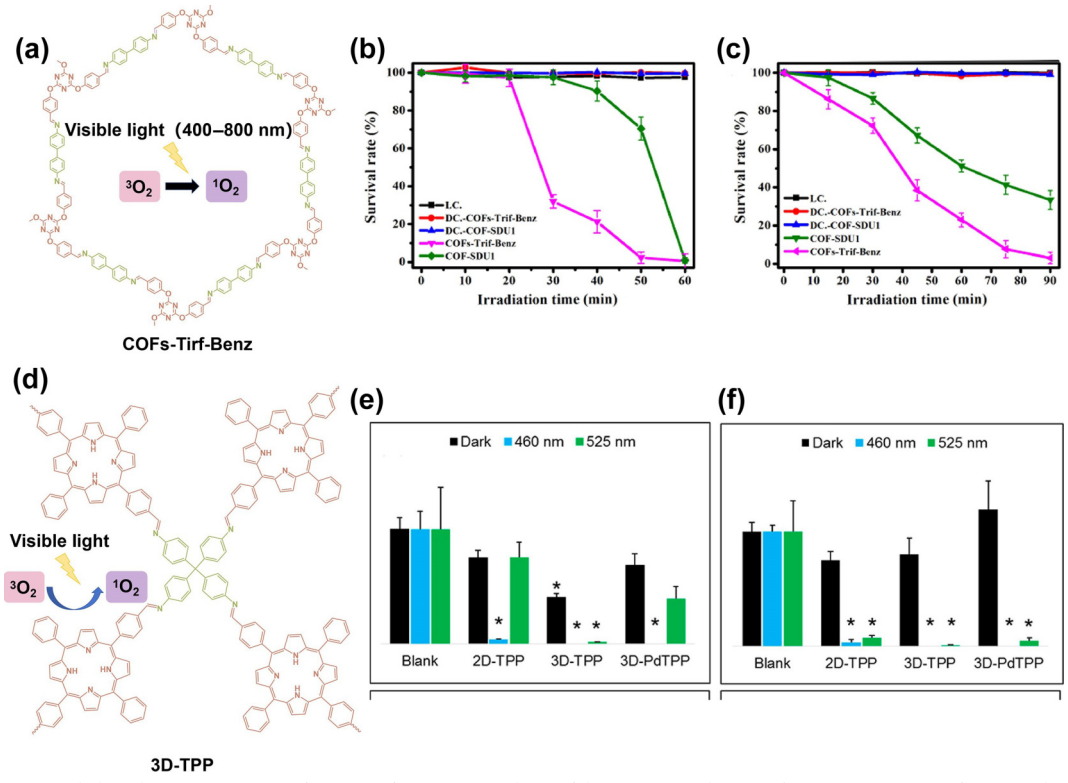

Figure 3 (a) Structure and photodynamic properties of COFs-Trifr-Benz. Survival rate of (b) *S. aureus* and (c) *E. coli O86* using COFs-Trif-Benz as photosensitizer under irradiation with visible light over 60 min. Reproduced with permission from Ref. [46], © Published by Elsevier B.V. 2017. (d) Structure and photodynamic properties of 3D-TPP. Antibacterial activity of 3D-TPP against (e) *P. aeruginosa* and (f) *E. faecalis*. Reproduced with permission from Ref. [50], © American Chemical Society 2018.

Yan et al. synthesized a COF photosensitizer (TPDA) using 2,4,6-triformylphloroglucinol (TFP) and 3,6-diaminoacridine (DAA) as building blocks. The morphology of TPDA was long cross-linked. Compared with DAA, TPDA showed enhanced photosensitive activity, which was due to the increase of the conjugate range after the connection of TFP and DAA (Fig. 5(a)). Interestingly, TPDA can be attached to the surface of bacteria through electrostatic interaction, and the reactive oxygen species generated under irradiation can directly damage the bacterial cell membrane and lead to its death. *In vitro* antibacterial experiments showed that TPDA almost completely killed Gram-negative bacteria (*E. coli*) and Gram-positive bacteria (*S. aureus*) within 10 min (Figs. 5(b) and 5(c)). In addition, the cytotoxicity of TPDA was evaluated by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay, and it was found that TPDA almost did not affect the relative proliferation rate of mouse fibroblasts (L929), which proved its good biocompatibility. A fish skin infection model was constructed to study the therapeutic effect of TPDA, and it was found that the antibacterial efficiency could reach 85%. This confirmed that TPDA could effectively protect fish from skin bacterial infection by generating ROS in water under light [56].

The structural core of BODIPY and its derivatives is a planar conjugated structure composed of a methylene bridge bond, boron bridge bond, and two pyrrole rings. As a common photosensitizer, BODIPY has excellent optical characteristics including high fluorescence quantum yield, high molar absorption coefficient, and good photostability, and has attracted much attention in the biomedical field [57–60]. The typical integrating strategy of COF and BODIPY is to introduce BODIPY into the COF framework through post-synthetic modification to exert its biological activity [61, 62], but there are few studies on the synthesis of COFs using BODIPY as a direct building unit. In 2022, Qiu et al. constructed TAPP-BDP using two photosensitizers, porphyrin and BODIPY, which can be used for photodynamic/photothermal/peroxidase-like activity synergistic antibacterial therapy under near-infrared light irradiation (Fig. 5(d)). TAPP-BDP had a uniform capsule morphology with an average size of 350 nm. The extended π-conjugated skeleton and unique conjugated donor-acceptor (D-A) structure of TAPP-BDP enable excellent photodynamic activity and efficient photothermal conversion. Moreover, TAPP-BDP showed high peroxidase-like activity under acidic conditions (pH = 4), which could convert H_2O_2 into ·OH with biological toxicity. Under the synergistic effect, TAPP-BDP could effectively kill *E. coli* (99.3%) and *S. aureus* (99.6%) (Figs. 5(e)–5(g)). In addition, the *in vitro* hemolysis assay and cytotoxicity assay confirmed that TAPP-BDP had good blood compatibility and low cytotoxicity. *In vivo* wound healing experiments showed that TAPP-BDP could effectively promote skin wound healing without any adverse reactions. All of these showed that TAPP-BDP had high biosafety [63]. Similarly, Liu et al. prepared $COF_{BDP/CD-S-3}$ by Schiff-base condensation reaction using BODIPY and carbon quantum dots (CD-S-3) as building blocks, and then loaded AgNPs into the pores of $COF_{BDP/CD-S-3}$ by *in-situ* reduction method to obtain nanocomposite $COF_{BDP/CD-S-3-Ag}$. $COF_{BDP/CD-S-3-Ag}$ was mainly uniform sphere with the size of 700–800 nm. $COF_{BDP/CD-S-3-Ag}$ shows good photodynamic and photothermal properties, which can effectively capture and kill bacteria. *In vitro* hemolysis assay further confirmed the biocompatibility of $COF_{BDP/CD-S-3-Ag}$ [64].

2.1.2 *Photothermal*

In recent years, photothermal therapy (PTT), as a non-invasive

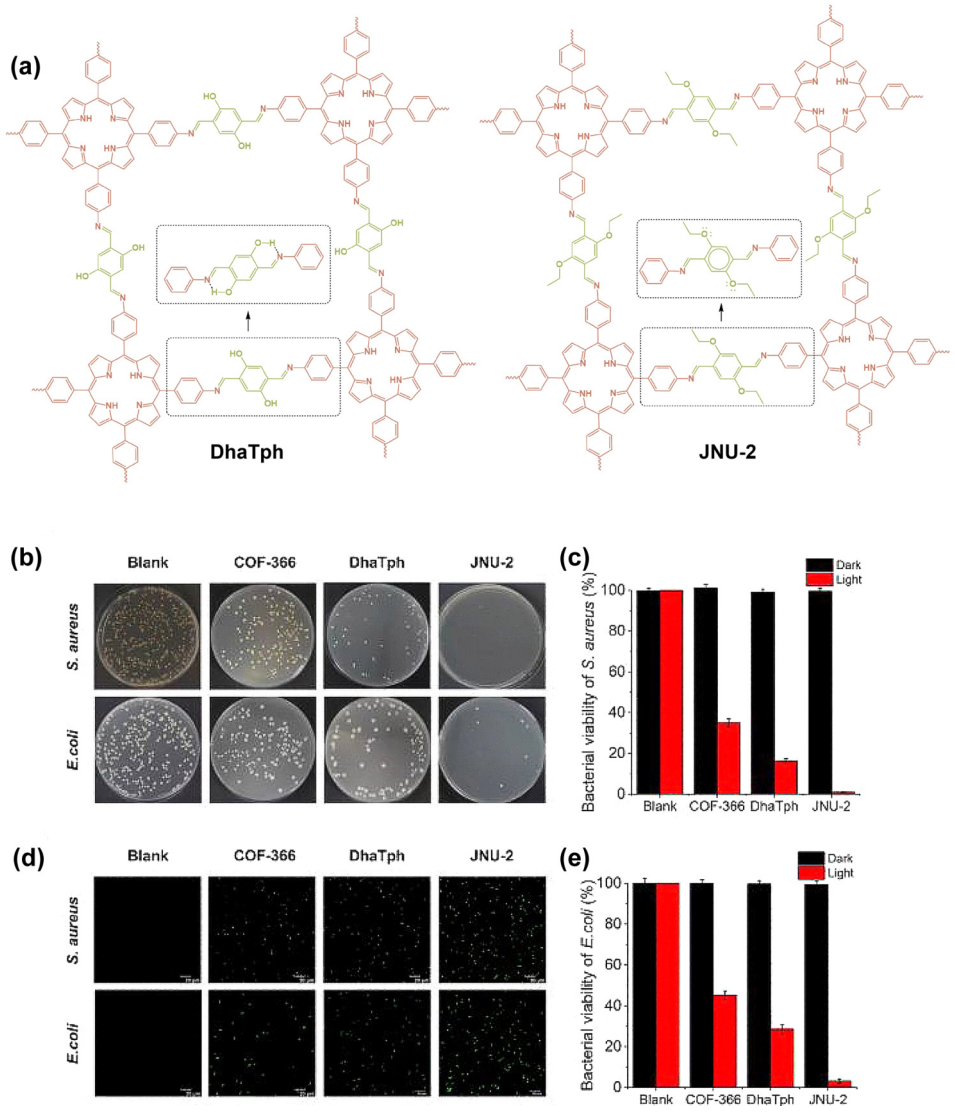

Figure 4 (a) The Por-COFs (DhaTph and JNU-2) were designed and synthesized by conjugate regulation strategy. (b) Photographs of bacterial colonies treated with Por-COFs under white LED light irradiation. The survival rate of (c) *S. aureus* and (e) *E. coli* treated with Por-COFs. (d) Representative confocal laser scanning microscope (CLSM) images for 2',7'-dichlorodihydrofluorescein diacetate (DCFH-DA) stained bacteria either with Por-COFs. Reproduced with permission from Ref. [41], © Elsevier B.V. All rights reserved. 2021.

treatment method with higher efficiency and lower side effects, has been becoming one of the most promising treatment methods in the treatment of tumors or infectious diseases [65–67]. Antibacterial photothermal therapy (APTT) is a method that utilizes materials with photothermal conversion properties to convert light energy into heat energy, breaking the bacterial cell membrane through a thermal ablation mechanism, thus killing bacteria. It can also effectively avoid the emergence of bacterial resistance, showing a good *in vivo* application prospect [68–70]. However, due to the low photothermal conversion efficiency of the material, weak interaction with bacteria, and poor specificity, the further clinical application of antibacterial photothermal therapy is seriously hindered [71]. Therefore, developing photothermal materials with high photothermal conversion efficiency and strong specificity is still a major challenge.

Currently, the photothermal effect alone cannot achieve a powerful germicidal effect, and the high temperatures may also cause unnecessary damage to the surrounding tissues of the skin. Therefore, combining photothermal therapy with other treatments can help to achieve a more optimal germicidal effect [72–75].

2.1.3 *Electrostatic interaction*

Cationic antibacterial peptides can efficiently kill a broad spectrum of bacteria without inducing resistance [76–78]. Inspired by this, it has been found that cationic antibacterial agents can be adsorbed on the surface of anionic bacterial membranes through electrostatic interactions, which can easily disrupt the potential of the bacterial membranes, change the permeability of the membranes and lead to the leakage of metabolites, and ultimately kill the bacteria [79, 80]. In recent years, ionic COFs (iCOFs) have been one of the research hotspots in the field of antibacterial.

Guanidinium antibacterial agents, as cationic antibacterial agents, have the advantages of high antibacterial efficiency, broad-spectrum and biosafety, which make them one of the research hotspots in the field of antibacterial [81–83]. Although polymeric materials based on substituted guanidinium have good antibacterial properties,

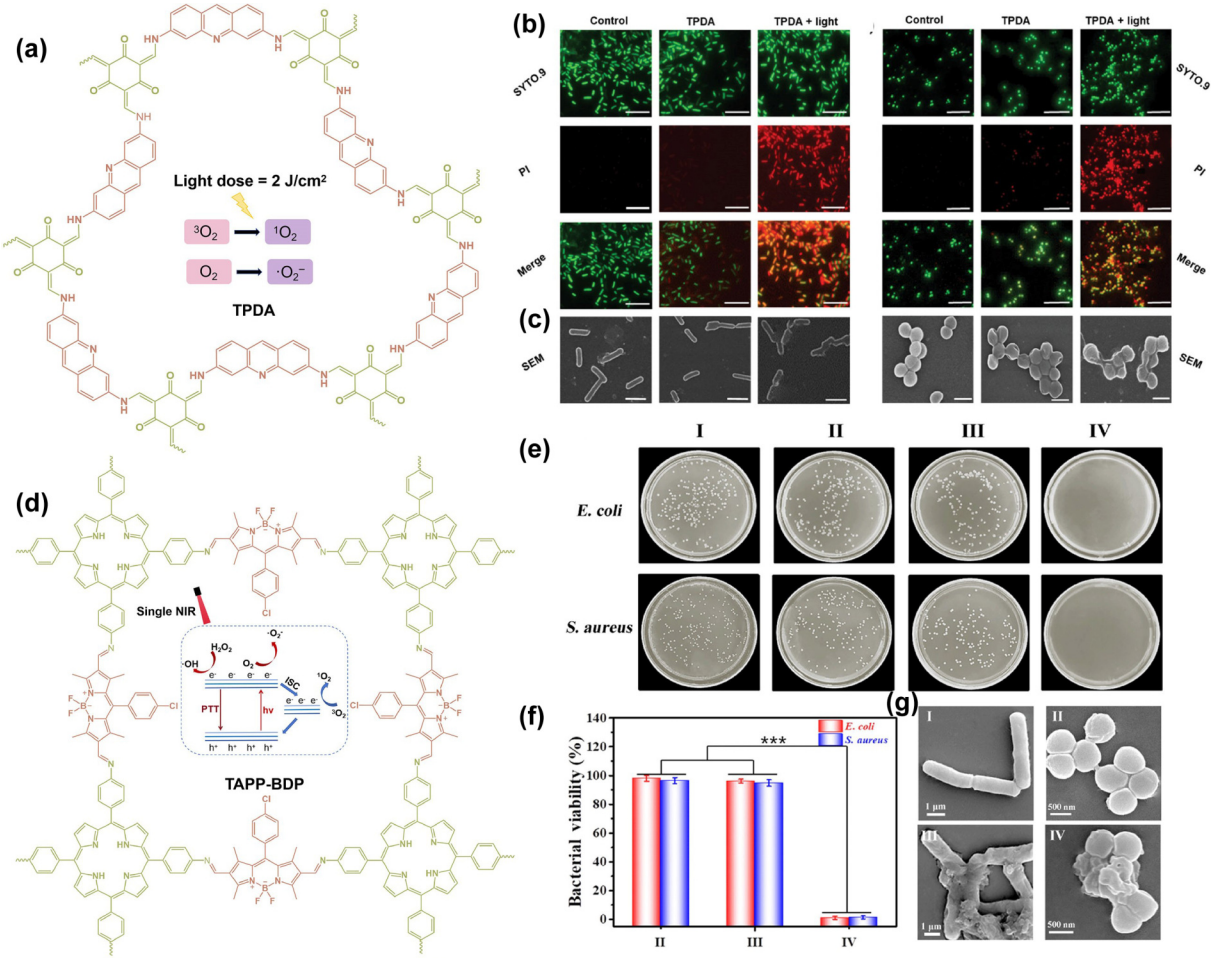

Figure 5 (a) Structure and photodynamic properties of TPDA. (b) Fluorescence imaging and (c) scanning electron microscope (SEM) images of *E. coli* and *S. aureus* at 50 μg/mL TPDA concentrations with/without irradiation. Reproduced with permission from Ref. [56], © Wiley-VCH GmbH 2021. (d) The triple synergistic effect of PDT/PTT/nanozyme of TAPP-BDP under single near infrared (NIR) light irradiation. (e) Photos of bacterial colonies, (f) bacteria viabilities and (g) SEM micrographs under different conditions. Reproduced with permission from Ref. [63], © American Chemical Society 2022.

their solubility severely limits their practical application in non-homogeneous water-resistant antibacterial coatings [84]. Ionic covalent organic nanosheets (iCONs) containing substituted guanidinium with antibacterial properties and insolubility can effectively expand their antibacterial applications in biomedicine. In 2016, Banerjee's group developed 2D cationic covalent organic nanosheets (2D-iCONs) with a thickness of 2–5 nm by introducing guanidinium halide into the framework of 2D-COFs. The cationic guanidinium-based part can promote the stripping of 2D-iCONs in water and also disrupt the negatively charged bacterial cell membranes, leading to a better antibacterial effect (Fig. 6(a)). These guanidinium chloride-based cationic 2D-iCONs significantly reduced the colony formation of both Gram-negative and Gram-positive bacteria in a dose-dependent manner, suggesting their potential application in bio-antibacterial coatings [28].

In addition, quaternary ammonium salts are the most widely studied organic cationic antibacterial materials, which have the advantages of good bactericidal effect, sample preparation as well as low production cost [85, 86]. Recent studies have shown that quaternary ammonium salt antibacterial agents can be compounded with other functional materials to improve their solubility, antibacterial properties, biocompatibility, etc [87–89]. Propidium iodide, as a quaternary cationic antibacterial agent, is commonly used as a topical antiseptic in the biomedical field for treating wounds, sterilizing utensils, etc. In 2019, Ajayaghosh et al. prepared a self-peeling ultrathin 2D-iCONs (PI-TFP) based on propidium iodide. The supramolecular host-guest interaction between cucurbit[7]uril (CB[7]) and 1-adamantylamine hydrochloride (AD) competing for quaternary ammonium groups is used to reversibly control the exfoliation and surface charge of iCONs. Atomic force microscopy (AFM) images confirmed the nanosheet structure of PI-TFP with an average layer thickness distribution of 1.6 nm. The positively charged PI-TFP can disrupt the phospholipid bilayer of negatively charged bacterial membranes, leading to efflux of intracellular metabolites and bacterial death. After the addition of CB, the PI-TFP restacked, which reduces the availability of surface charge, leading to bacterial regrowth. Since AD has an affinity for CB, this process can be reversed by adding AD, which promotes the re-stripping of iCONs and improves the availability of surface charge, thus restoring the antibacterial properties (Fig. 6(b)) [90].

In addition to its antibacterial activity, cationic antibacterial therapy can also effectively promote the antibacterial effect of other therapies. For example, the action range of ROS and PTT is very limited, and the existence of electrostatic interactions can effectively shorten the distance of the action, which fully ensures that the generated ROS and heat can directly contact the bacteria, thus significantly improving the antibacterial effect [91–94]. Therefore, it

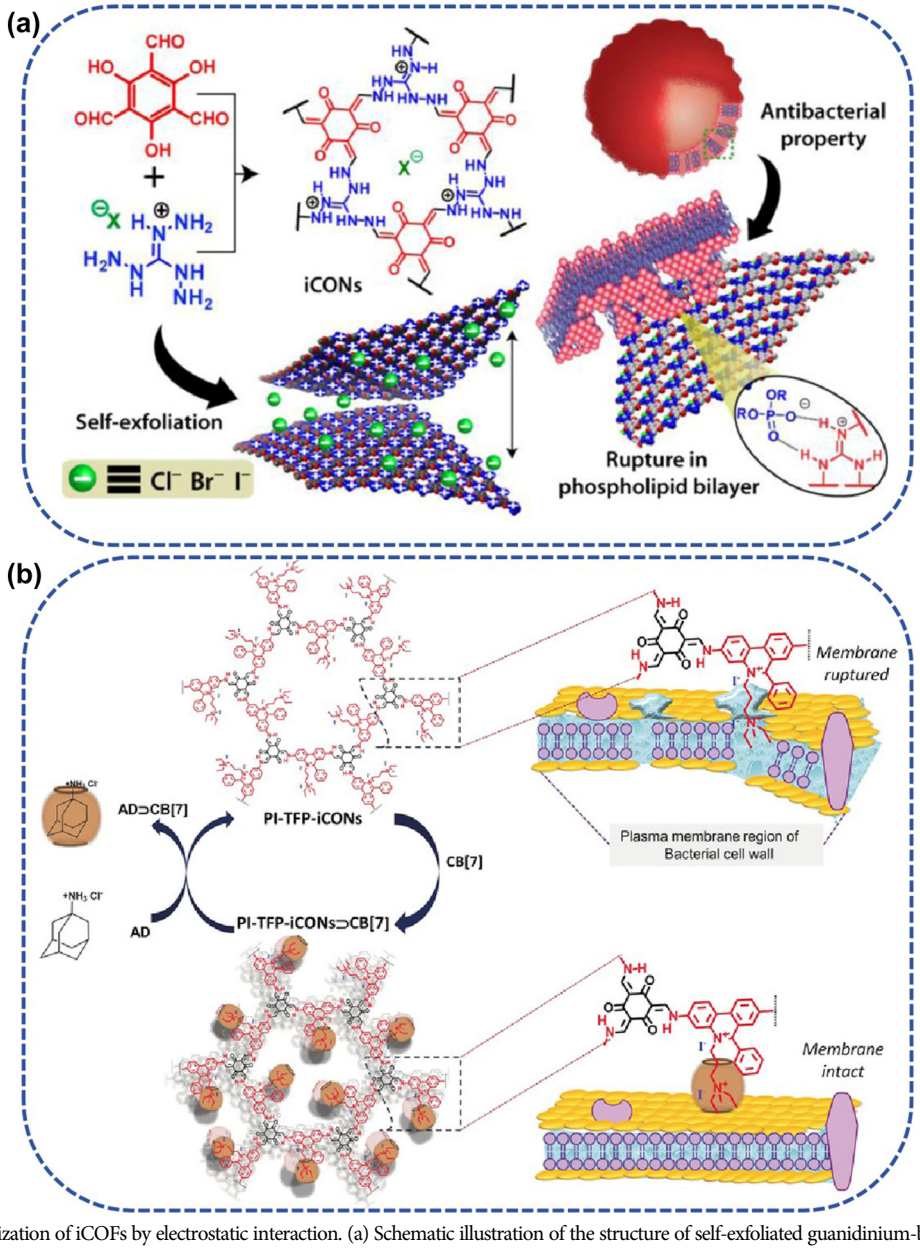

Figure 6 Schematic sterilization of iCOFs by electrostatic interaction. (a) Schematic illustration of the structure of self-exfoliated guanidinium-based iCONs and its mode of action with bacteria. Reproduced with permission from Ref. [28], © American Chemical Society 2016. (b) Schematic illustration of surface charge-tunable PI-TFP-mediated controllable bacterial growth. Reproduced with permission from Ref. [90], © Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim 2019.

is of fatal research significance to construct an intelligent platform to organically coordinate electrostatic interactions and other therapies to achieve synergistic antibacterial effects. Antibacterial agents for COFs containing pyridinium, imidazolium and viologen cations have been shown to combine with other antibacterial therapies, such as PDT, PTT, gas therapy, and nanozyme activity, to achieve excellent synergistic antibacterial effects [92].

2.1.4 *Others*

Benzoxazines are a class of heterocyclic compounds containing nitrogen-oxygen heteroatoms with good biological activity, which is one of the research hotspots in the field of pharmaceutical research and widely used in antibacterial and antitumor applications [95–97]. In 2021, Qian et al. firstly synthesized a hydroxyl-containing imine COF by solvothermal method using 2,4,6-tris(4-aminophenyl)-1,3,5-triazine (TAPT) and 2,5-dihydroxy-1,4-phthalaldehyde (DHNDA) as raw materials. Then, a new benzoxazine-linked COF was successfully obtained by reduction and cyclization reaction. The COF was an ellipsoidal morphology with needle-like structures. Compared with the imine COF, benzoxazinyl-linked COF showed excellent thermal stability and antibacterial activity. The bacterial DNA replication was inhibited by inhibiting the activity of bacterial topoisomerase, and the bacterial inhibition rates against *E. coli* and *S. aureus* were more than 99% [98].

Among various biological agents, biologically active α-aminophosphonates have been widely explored for their antibacterial, antifungal, antiviral, anti-tumor, and as human immunodeficiency virus (HIV) protease and phosphatase inhibitors [99–103]. In 2022, Dong et al. reported the preparation of α-aminophosphonate-linked COFs containing porphyrin moieties (APCOF-1) at room temperature using a three-component *in situ*

Kabachnik-Fields reaction. Due to the coexistence of α-aminophosphonate bioactive groups and porphyrin photosensitizers, APCOF-1 exhibits good photo-driven antibacterial activity. In addition, a spiral tube flow sewage purification device based on APCOF-1@chitosan composite aerogel (50 wt.% APCOF-1) was also prepared. APCOF-1@chitosan aerogel had a macroporous structure, indicating its seamless interconnected morphological characteristics. Driven by natural light, APCOF-1@chitosan aerogel can be used for large-scale removal of hazardous substances (Fig. 7) [104].

COF framework chemistry mainly concentrates on incorporating one or two antibacterial functional units into the framework, which enhances the antibacterial properties and synergistic effect of COFs. However, the development of multi-component COFs presents an opportunity to introduce a wider array of antibacterial groups into their structures. The approach is expected to further enhance synergistic performance and functional diversity. By incorporating a variety of antibacterial groups, COF-based antibacterial agents will exhibit more complex and comprehensive mechanisms against bacteria, thereby more effectively eliminating them.

2.2 Pore chemistry

COFs are good carriers for loading guest molecules based on their inherent pores and stable structure, and have become excellent candidates for drug storage and delivery [105–108]. COFs materials, as a kind of porous adsorbent, can improve the solubility and bioavailability of drugs, protect the controlled release of drugs from the external environment, and improve drug targeting and specificity, which is of far-reaching and long-term significance in the drug delivery system. Currently, loading antibiotics, natural antibacterial agents or NO donors into the pores of COFs for intelligent controlled release gradually distinguish themselves and succeed in the antibacterial field (Table 2) [29, 92, 109–118].

Antibiotics, if misused, can lead to the emergency of cytotoxic and drug-resistant bacteria and loss of therapeutic efficacy [119, 120]. COFs can be used as carriers to control the release of antibiotics and reduce the use of antibiotics. In 2021, Qiu et al. firstly introduced kanamycin into COFs and prepared a novel amidoxime-functionalized multifunctional adsorbent with antibacterial properties (AF-Anti-COF) (Fig. 8(a)). The material had excellent anti-fouling properties and could inhibit the growth of over 90% of marine bacteria (Fig. 8(b)) [109]. Compared with single-antibiotic delivery, dual-antibiotic delivery is favorable for improving antibacterial activity, expanding antibacterial range, and reducing the development of drug resistance [121]. However, drugs with different compatibility often cannot be delivered simultaneously [122, 123]. Therefore, it is of great significance to develop a co-delivery system for hydrophilic and hydrophobic drugs. In 2023, Han et al. reported an imine COF (DEG-HEP-COF) with alternately arranged heterogeneous environmental pore structures, which can simultaneously load hydrophobic levofloxacin (Lev) and hydrophilic vancomycin (Van) antibiotics (Fig. 8(c)). MTT assay confirmed that DEG-HEP-COF@Lev&Van had no cytotoxicity. Then, DEG-HEP-COF@Lev&Van loaded polycaprolactone/gelatin (PG) membranes (PG-DEG-HEP-COF@Lev&Van membranes) were prepared by electrospinning. The *in vitro* antibacterial effect and *in vivo* antibacterial effect of the wound dressing showed that PG-DEG-HEP-COF@Lev&Van membranes had good synergistic antibacterial activity (Fig. 8(d)), and had good ability to promote granulation regeneration, increase collagen content and accelerate wound healing [113]. When a ruptured wound or trauma occurs on the skin, it is often accompanied by bacterial infection and inflammation, which disrupts the bacterial healing process. Therefore, the development of wound dressings with synergistic antibacterial and anti-inflammatory efficacy would be effective in accelerating wound healing [124–127]. In 2021, Dai et al. reported a wound dressing (ENR-FM-COF-TPU) that can simultaneously load the antibiotic enrofloxacin and the anti-inflammatory drug flunixin meglumine. The composite membrane has porous structure, continuous fiber morphology, random orientation and smooth surface. The inhibition rate of ENR-FM-COF-TPU fiber membrane against *S. aureus* and *E. coli* was more than 99%, which could last for 50 h. Meanwhile, it can significantly accelerate and promote wound healing by down-regulating the expression of inflammatory factors interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α) and up-regulating the expression of growth factors vascular endothelial growth factor (VEGF) and epidermal growth factor (EGF). Cell viability test and histopathological results showed that ENR-FM-COF-TPU fibrous membranes had good biocompatibility *in vitro* and *in vivo* [110].

Natural antibacterial agents are ideal alternatives to antibiotics, possessing the following advantages: (1) Extensive sources, pure

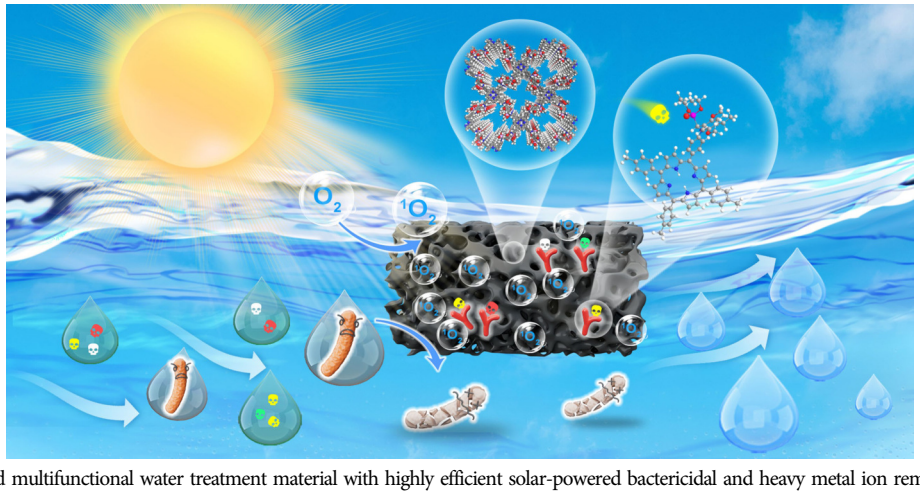

Figure 7 APCOF-1-based multifunctional water treatment material with highly efficient solar-powered bactericidal and heavy metal ion removal abilities. Reproduced with permission from Ref. [104], © Elsevier B.V. All rights reserved 2022.

Table 2 Research progress on the loading of antibiotics, natural antibacterial agents or NO donors in the pores of COFs and their antibacterial efficiency

Entry	Guest	Classification	Host-Guest	Bacteria	Antibacterial efficiency (%)	Ref.
1	Kanamycin	Antibiotic	AF-Anti-COF	*B. subtilis* *B. cereus* *V. alginolyticus* *P. aeruginosa*	> 80% > 80% > 95% > 80%	[109]
2	Enrofloxacin	Antibiotic	ENR-FM-COF-TPU	*E. coli* *S. aureus*	99% 99%	[110]
3	Curcumin	Antibiotic	CUR@COF	*E. coli* *S. aureus*	61.5% 69.2%	[29]
4	Trimethoprim	Antibiotic	TMP@COF	*E. coli* *S. aureus*	87% 75%	[111]
5	Daunorubicin	Antibiotic	DNR@$CoFe_2O_4$@St@COF (DtTb)-HA	*E. coli* *S. aureus*	1500 μg/mL 750 μg/mL (MICs)[b]	[112]
6	Levofloxacin/Vancomycin	Antibiotic/ antibiotic	DEG-HEP-COF@Lev& Van	*Methicillin-resistant S. aureus*	—[a]	[113]
7	Nisin	Natural antibacterial agent	nisin@COFs	*Cerevisiae* *L. brevis*	100% 100%	[114]
8	Thymol	Natural antibacterial agent	THY@COF/ PCL films	*E. coli* *S. aureus*	89.41% 100%	[115]
9	Capsaicin/ Chitosan	Natural antibacterial agent/natural antibacterial agent	CAP@CS/ TpPa-1	*S. aureus* *P. aeruginosa*	91.68% 92.84%	[116]
10	Honokiol	Natural antibacterial agent	COFTAPB-FPBA@ Honokiol	*E. coli* *S. mutans*	—[a] 58%	[117]
11	BNN6	NO donor	TP-PorCON@ BNN6	*E. coli* *S. aureus*	100 μg/mL 150 μg/mL (MICs)[b]	[118]
12	Sodium nitroprusside	NO donor	DC-COF-SNP	*E. coli* *S. aureus*	0.28% ± 0.19% 0.41% ± 0.59%	[92]

[a] It has antibacterial activity, but does not indicate a clear antibacterial efficiency; [b] the minimum inhibition concentrations.

natural, and low cost; (2) high biosafety, no side effects, no *in vivo* residues, and no pollution; and (3) no bacterial resistance. However, natural antibacterial agents still suffer from poor chemical stability, poor water solubility, and low antibacterial efficiency, which severely limit their applications [128, 129]. In 2022, Zhang et al. prepared *in-situ* curcumin-loaded COF (CUR@COF) using a one-pot method. Through electrospinning technology, a nano-composite fiber membrane (CUR@COF/PCL NFMs) was prepared by incorporating CUR@COF into polycaprolactone (PCL), which can be used as an intelligent pH-responsive drug release platform for wound dressings. The composite membrane showed good thermal stability and mechanical properties, and the loading of CUR could be as high as 27.68%. Interestingly, under acidic conditions (pH = 5), C=N in CUR@COF was protonated, which reduced the hydrophobic interaction with CUR, thereby promoting the release of CUR and showing intelligent pH-responsive drug release. Compared with PCL NFMs, CUR@COF/PCL NFMs showed significantly enhanced antibacterial and antioxidant activities, as well as good biocompatibility. *In vivo* wound healing and tissue regeneration analysis showed that CUR@COF/PCL NFMs accelerated wound healing and skin tissue regeneration by continuously releasing CUR with antibacterial, anti-inflammatory and antioxidant effects [29]. Similarly, in 2023, Chen et al. reported an example of THY@COF/PCL membrane loaded with plant essential oil thymol (THY) for active food packaging. The loading amount of THY on the membrane was 30.35%, and the average diameter of the fiber increased to 446.2 nm. The *in vitro* cytotoxicity test confirmed that the THY@COF/PCL film had low cytotoxicity and excellent biocompatibility. In addition, the THY@COF/PCL film exhibits excellent antibacterial properties, which can destroy the bacterial cell membrane, leading to leakage of intracellular substances and causing death. More importantly, the film has a temperature-responsive THY intelligent control release function, which is particularly critical for the preservation of food in a warm environment [115]. According to recent studies, COFs loaded with natural antibacterial agents such as capsaicin, chitosan and hydroxyapatite exhibited good responsive release performance and excellent antibacterial activity, indicating their great potential in the field of antifouling coatings and biomimetic mineralization [16, 117].

In recent years, nitric oxide (NO) has received wide attention as a promising broad-spectrum antibacterial agent. NO can react with endogenous superoxide during bacterial respiration to generate NO radicals (NO·), peroxynitrite ($ONOO^-$), and nitric oxide (N_2O_3), which can exert antibacterial effects through oxidation or nitrosation and avoid drug resistance. However, there are some problems including low NO loading, short release time, and uncontrollable release time and space. Therefore, NO donors still need suitable carriers to store and control the release of NO [130, 131]. In 2021, Shen et al. reported an example of porphyrin COF nanosheets (TP-Por CON@BNN6) loaded with NO donor-BNN6. The thickness of TP-Por CON@BNN6 was about 5.4 nm, and the

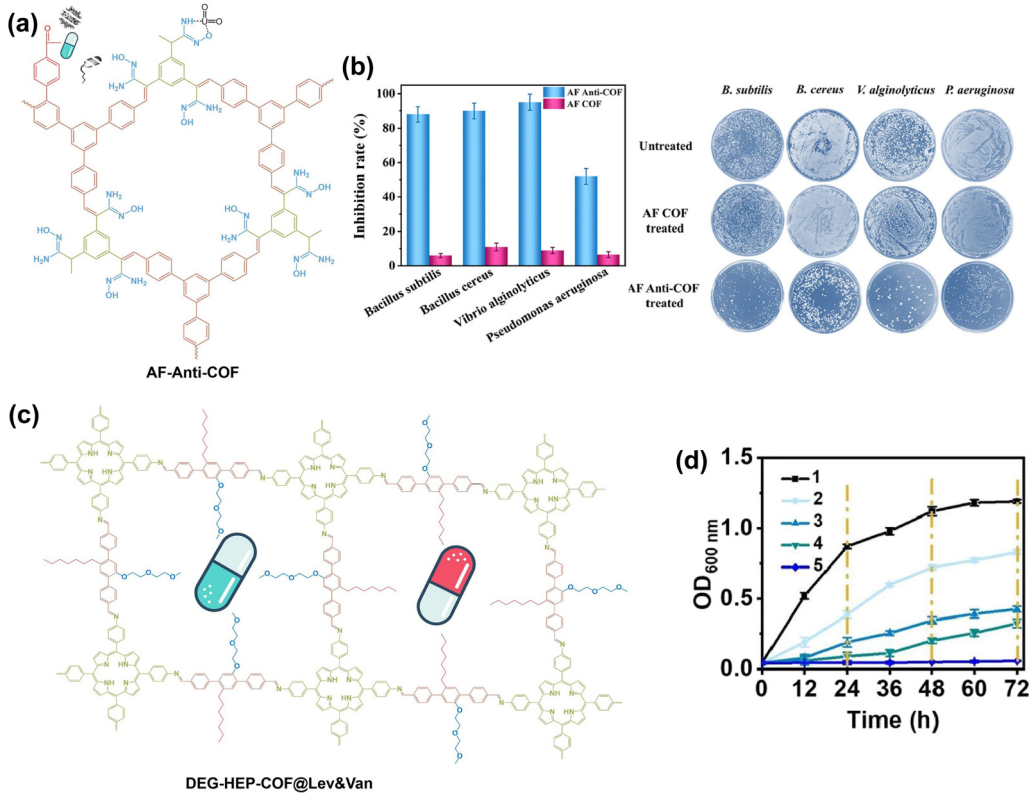

Figure 8 COFs loaded with antibiotics for antibacterial applications. (a) Structure and antibacterial activity of AF-Anti-COF. (b) Antibacterial activity of AF-Anti-COF for typical bacteria. Reproduced with permission from Ref. [109], © Y. D. Wu, et al. under exclusive licence to Springer Nature Switzerland AG part of Springer Nature 2021. (c) DEG-HEP-COF with alternatively arranged hetero-environmental pore structure can simultaneously load hydrophobic levofloxacin (Lev) and hydrophilic vancomycin (Van) antibiotics. (d) Antibacterial activity of DEG-HEP-COF@Lev&Van. Reproduced with permission from Ref. [113], ©W. Ji, et al. 2023.

rigid sharp edge could damage the bacterial surface. Under infrared light irradiation, TP-Por CON@BNN6 could synergize with PDT/PT/NO therapy to effectively inhibit the growth of *E. coli* and *S. aureus*. Meanwhile, TP-Por CON@BNN6 had good biocompatibility and biodegradability. A mouse wound model infected with *S. aureus* was established. The results showed that TP-Por CON@BNN6 could effectively inhibit the early inflammatory response, promote the formation of collagen fibers and angiogenesis, and accelerate wound healing in mice (Fig. 9) [118]. Similarly, in 2022, Zhou et al. reported an example of a multifunctional COFs platform (DC-COF-SNP) loaded with NO donor-sodium nitroprusside (SNP). DC-COF-SNP was a block with a 3D network structure and interconnected macropores. Under laser irradiation, DC-COF-SNP could realize the synergistic sterilization of PTT/cation/NO. Through ion exchange, the negatively charged SNP can be strongly adsorbed in the DC-COF pores, avoiding the self-decomposition of SNP. Under intermittent laser irradiation, DC-COF-SNP could realize the controlled release of NO. Based on the multimodal synergistic antibacterial effect, DC-COF-SNP resulted in excellent antibacterial activity by reducing the colony counts of *S. aureus* and *E. coli* to 0.41% ± 0.59% and 0.28% ± 0.19%, respectively [92].

Pore chemistry benefits from the high designability of COFs, allowing for the precise adjustment of pore size, topological structure, and microenvironment via design. Research reports have indicated that antibacterial agents can be incorporated into the pores of COFs via various mechanisms, including physical adsorption, hydrogen bonding, and covalent bonding, which will enhance the efficiency of antibacterial drugs, achieve intelligent sustained release, boost antibacterial efficacy, reduce drug toxicity, etc.

3 COFs composite antibacterial materials

The development of antibacterial nanocomposites with multimodal synergism has attracted significant attention because single antibacterial material cannot satisfy the demands of practical antibacterial applications [132–138]. COFs can not only play an antibacterial role alone but also be employed as a platform in combination with materials such as metals and metal oxides (M/MO), carbon-based materials (CNMs) and MOFs. Furthermore, the complementary advantages and functional integration of different materials are realized, as well as multi-mode synergistic high-efficiency and long-term antibacterial (Table 3) [30, 64, 139–148].

3.1 Metals and metal oxides (M/MO)

Metal and metal oxide nanoparticles (M/MO NPs) have been widely studied for their wide range of antibacterial activities [7, 8]. However, M/MO NPs often suffer from poor biocompatibility, high concentration dependence, easy agglomeration, and large environmental burden, which greatly limit their clinical applications [149–151]. In order to solve these problems, an effective strategy is to encapsulate them in nanomaterials for dispersion and immobilization to enhance their antibacterial effects [30, 141, 143].

AgNPs have attracted much attention due to their broad spectrum and excellent antibacterial activity. They can release positively charged Ag^+, destroy bacterial membranes through

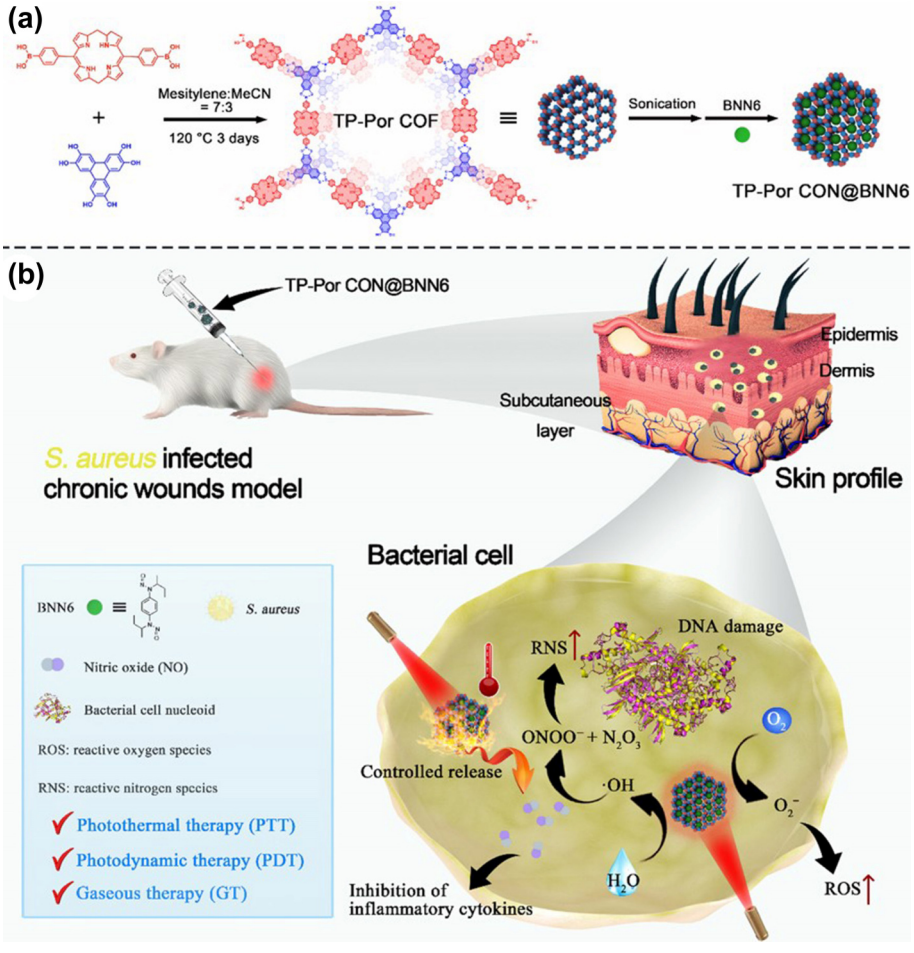

Figure 9 COFs loaded NO donors for antibacterial applications. (a) The synthesis schematic illustration of TP-Por CON@BNN6. (b) TP-Por CON@BNN6 can achieve synergistic antibacterial effect of PDT/PTT/NO therapy. Reproduced with permission from Ref. [118], © American Chemical Society 2021.

electrostatic interactions, and interfere with DNA/RNA replication to kill bacteria [152, 153]. In addition, recent studies have shown that AgNPs exhibit localized surface plasmon resonance properties that can enhance photothermal efficiency. Interestingly, when AgNPs are combined with PSs, the $^1O_2$ produced by PSs can promote the degradation of AgNPs to release more Ag^+, achieving a long-lasting bacterial inhibition effect [154–156]. In 2022, Dong et al. reported a case of reusable self-sterile COFs masks. Firstly, AgNPs were combined with porphyrin PSs to successfully construct AgNP-loaded, quinoline carboxylic acid-linked nanoporphyrin COFs composites (Ag@DhaTph-COOH). Then, the Ag@DhaTph-COOH@M mask was prepared by spraying the dispersion of Ag@DhaTph-COOH covalently crosslinked with polyurethane oligomer onto the outer layer of PET non-woven fabric. The mask realizes the effective functional integration of AgNPs and porphyrin PSs. Under sunlight irradiation, Ag@DhaTph-COOH@M exhibits efficient solar self-disinfection performance through a triple-modal chemo/PDT/PTT synergy, with excellent antibacterial and antiviral activity, and can be recycled (Fig. 10) [140].

In addition, gold nanoclusters (AuNC) are a class of PSs with unique optical properties that produce ROS and emit fluorescence stably under light irradiation [157–160]. In 2022, Li et al. synthesized AuNC *in situ* in the pores of imine COF using 1-vinylimidazole as a reducing agent to obtain COF/AuNC nanocomposites. COF/AuNC had a spherical morphology with an average particle size of 122 nm. The fluorescence of COF/AuNC was significantly enhanced with the increase of AuNC content. Meanwhile, under visible light irradiation, COF/AuNC could efficiently generate cytotoxic $^1O_2$, $\cdot O_2^-$, and ·OH, which is due to the charge transfer and separation of photogenerated electron-hole pairs between COF and AuNC. In addition, COF/AuNC-3 exhibited low dark toxicity and high photocidal efficiency against *E. coli* under visible light irradiation [143].

3.2 Carbon-based materials (CNMs)

COFs, as organic semiconductors, have higher exciton binding energies compared with inorganic semiconductors, which indicates that COFs are very limited by tuning the structure and bandgap to enhance the separation and migration rates of photogenerated electron-hole pairs [161–163]. Therefore, maximizing carrier extraction from photoexcited COFs is one of the most important aspects to achieve an efficient photooxidation reduction reaction. CNMs (e.g., carbon nanotubes, MXene, and carbon dots) exhibit excellent photocatalytic performance in antibacterial applications, and combining with semiconductors to form heterojunctions can effectively improve the carrier separation efficiency and lifetime, and enhance the photocatalytic activity [164–166]. However, their bactericidal effect and biosafety are relatively limited, which seriously limits their wide application [11]. Therefore, combining CNMs with COFs may greatly improve the photocatalytic performance of COFs.

MXene is a novel transition metal carbide or carbon nitride

Table 3 Research progress of COFs composite antibacterial materials

Entry	Nanocomposite	Mechanism	Bacteria	Antibacterial efficiency (%)	Ref.
1	Ti_3C_2/TpPa-1/Ag	Ag^+ release /PDT/mechanical damage	*S. aureus* *P. aeruginosa*	99.60% 99.78%	[139]
2	Ag@DhaTph-COOH@M	Ag^+ release /PDT/PTT	*E. coli* *S. aureus*	99% 99%	[140]
3	COFs-AgNPs	Ag^+ release	*E. coli* *S. aureus*	60 μg/mL 60 μg/mL (MICs)[b]	[141]
4	Ag/COFTGTp	Ag^+ release /cation-interaction	*E. coli* *S. aureus*	100 μg/mL 50 μg/mL (MICs)[b]	[30]
5	Ag-TA-CON@ EBS@PEG	EBS release /Ag^+ release	*E. coli* *S. aureus*	50 μg/mL 25 μg/mL (MICs)[b]	[142]
6	COFBDP/CD-S-3-Ag	Ag^+ release /PDT/PTT	*E. coli* *S. aureus* *MRSA* *Monilia albican*	160 μg/mL 310 μg/mL 310 μg/mL 310 μg/mL (MICs)[b]	[64]
7	COF/AuNC	PDT	*E. coli*	85%	[143]
8	Mt/COF-CuO/Cu_2O	Cu^{2+} release	*E. coli* *B. subtilis*	—[a] —[a]	[144]
9	Ti_3C_2/TpPa-1/Cu_2O	Cu^+ release /PDT/mechanical damage	*S. aureus* *P. aeruginosa*	98.90% 99.62%	[145]
10	COF@CDs	PDT	*E. coli*	95%	[146]
11	OCNT@COF-Fe @Gel	Enzyme/PDT/PTT	*E. coli* *S. aureus* *MRSA*	100% 100% 100%	[147]
12	ZIF-8@iCOF	PDT	*S. aureus*	99.99999%	[148]

[a] It has antibacterial activity, but does not indicate a clear antibacterial efficiency; [b] the minimum inhibition concentrations.

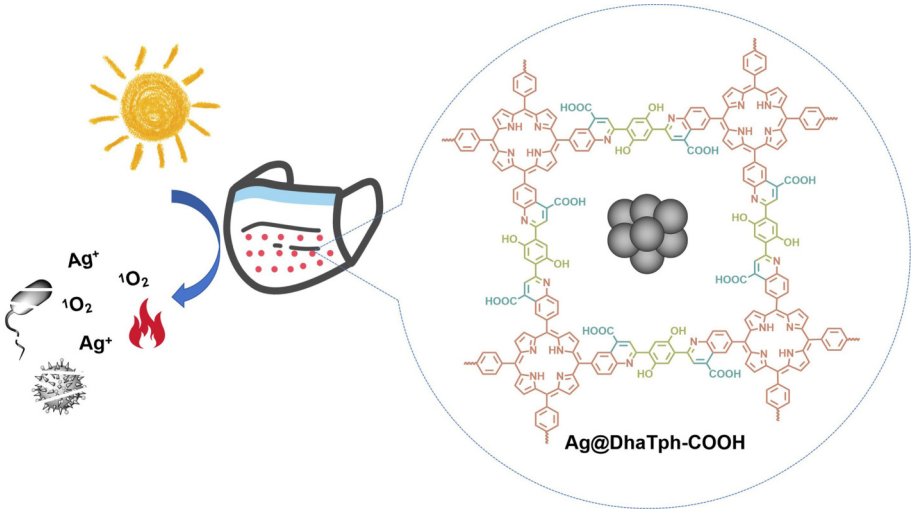

Figure 10 The multifunctional self-sanitizing face masks Ag@DhaTph-COOH@M can be utilized through chemo/PDT/PTT synergistic antibacterial and antiviral [140]. Reproduced with permission from Ref. [140], © The Royal Society of Chemistry 2022.

material with a 2D layered structure and good electrical conductivity, which is widely used as a co-catalyst in photocatalysis [167, 168]. In 2021, Chen et al. constructed a Ti_3C_2/TpPa-1/Cu_2O nanocomposite with excellent photocatalytic antibacterial activity. TpPa-1 and Cu_2O formed a heterojunction, so that the photogenerated electrons and holes migrate to TpPa-1 and Cu_2O, respectively. As a co-catalyst, Ti_3C_2 effectively improves the carrier mobility and the separation efficiency of electron-hole pairs, generates more ROS, and improves its photocatalytic antibacterial performance. The copper ions released by ROS and Cu_2O played a synergistic antibacterial effect, almost killing *S. aureus* (98.90%) and *P. aeruginosa* (99.62%). Compared with TpPa-1-COF, the inhibition rate was increased by 50% and 33%, respectively (Fig. 11) [145].

In 2022, Zhang et al. constructed a binary efficient photocatalytic antibacterial system (COF@CDs) composed of D-A type COF and carbon dots (CDs). COF@CDs exhibited a 2D sheet-like COF stacked layer by layer, with an ultra-thin 2D layered π-interaction

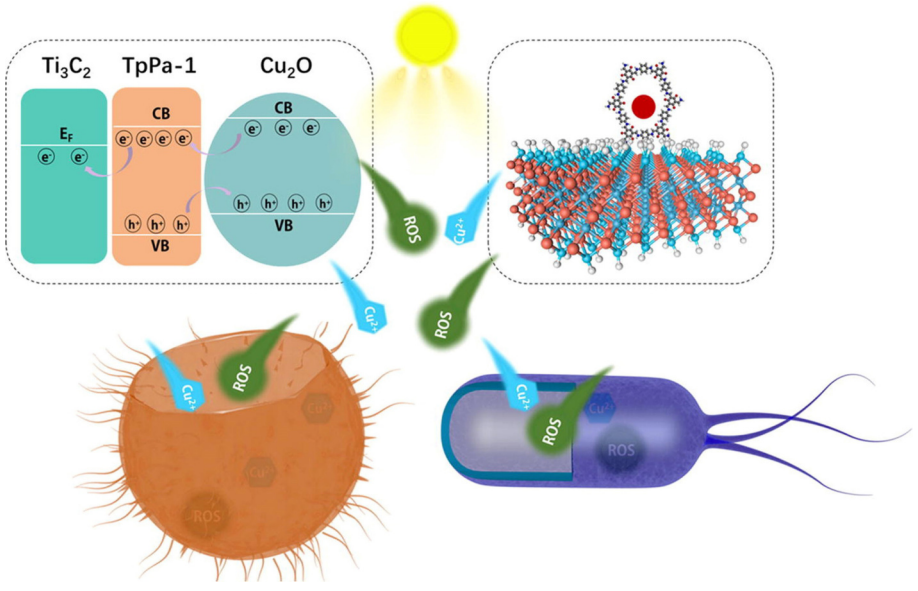

Figure 11 Schematic of the sterilization mechanism of Ti_3C_2/TpPa-1/Cu_2O. Reproduced with permission from Ref. [145], © Elsevier B.V. All rights reserved 2022.

structure. CDs acted as both an electron extractant and a storage medium. When the CDs are loaded into the COF, the π-electrons in the D-A type COF semiconductor are extracted and accumulated in the CDs through hydrogen bonds. The high water solubility of CDs increases the probability of contact between the catalyst and dissolved oxygen in water, resulting in a redox reaction to produce more ROS, which significantly enhanced the photocatalytic antibacterial performance. Under visible light irradiation for 60 min, the killing efficiency of COF@CDs on *E. coli* was higher than 95%, and the bacterial survival rate was 8.3 times lower than that of pure COF [146].

In addition, the unique structure and properties of carbon nanotubes (CNTs) give them good light absorption properties and high thermal conductivity. The photothermal properties of CNTs have a wide range of applications in biomedical fields, such as tumor therapy and bactericidal [169–173]. However, the poor dispersion and biocompatibility of carbon nanotubes due to van der Waals forces severely limit their applications. Therefore, enhancing the dispersibility and biocompatibility of carbon nanotubes by modification is one of the current research hotspots [174, 175]. In 2023, Wang et al. reported a multifunctional hydrogel (OCNT@COF-Fe@Gel) coated on carbon nanotubes by iron-doped COF, which can comprehensively treat bacterial diabetic wounds. OCNT acts as an intermolecular charge transfer channel, and Fe^{3+} acts as an electron acceptor and substrate (O_2 and H_2O) adsorbent, thereby narrowing the energy band gap, enhancing light absorption, and increasing ROS ($\cdot O_2^-$, ·OH, and H_2O_2) production capacity. At the same time, due to the pH response of Fe^{3+} to peroxidase (POD) and catalase (CAT) activity, H_2O_2 can be converted to ·OH, which also supplements $\cdot O_2^-$. In addition, due to the presence of OCNT, O@CF exhibits a concentration-dependent photothermal performance. A significant enhancement of the photothermal properties of O@CF occurred with the degradation of the COF coating under acidic conditions. O@CF possesses a synergistic photothermal combination of multiple photodynamic properties for bactericidal and hypoxia relief (Fig. 12). O@CF was

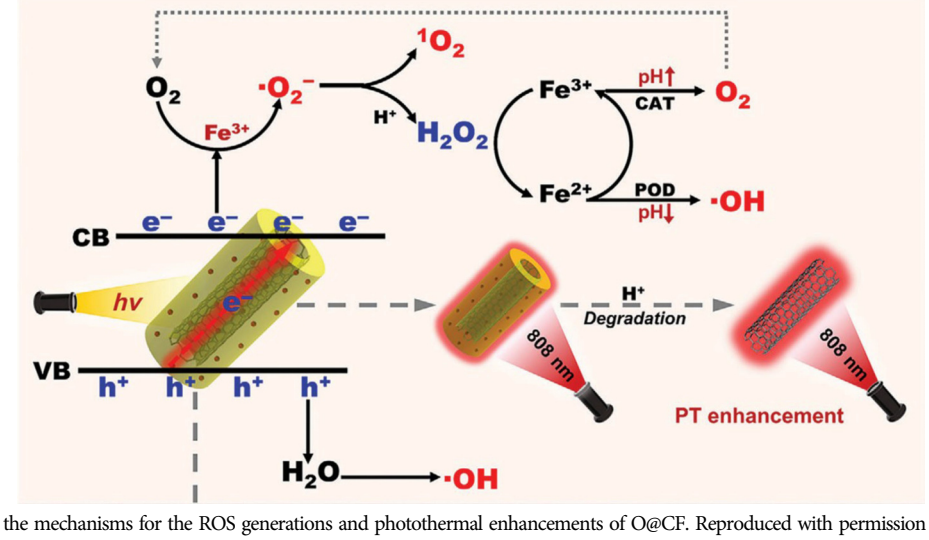

Figure 12 Schematic of the mechanisms for the ROS generations and photothermal enhancements of O@CF. Reproduced with permission from Ref. [147], © Wiley-VCH GmbH 2023.

introduced into the Schiff base hydrogel by covalent cross-linking to obtain a multifunctional conductive hydrogel OCNT@COF-Fe@Gel (O@CF@G). The hydrogel maintains the multifunctional photoactivity of O@CF and enhances the processability of the hydrogel. It can be used as a wound dressing for bacterial diabetes, which has multiple effects such as hemostasis, sterilization, hypoxia relief and intercellular electrical signal transduction to accelerate wound healing [147].

3.3 Metal organic frameworks (MOFs)

As a universal drug carrier, MOFs nanomaterials can achieve more accurate, diversified and efficient antibacterial targets by adjusting the functional groups of organic ligands or modifying the surface sites [13, 176]. However, MOFs have inherent defects such as low antibacterial efficiency, poor chemical stability, and the release of large amounts of metal ions and original connecting ligands, resulting in toxic and side effects on cells and tissues, which seriously limits their application [177]. Therefore, it is of great significance to improve the stability and antibacterial effect of MOFs. In 2023, Xie et al. reported a core-shell nanocomposite (ZIF-8@iCOF), as a photocatalytic filter for pathogenic bioaerosols, which was driven by white light or sunlight. The obtained ZIF-8@iCOF nanocomposites had a uniform core-shell structure with a particle size of about 140 nm. Photoactivity experiments demonstrated that the heterogeneous interface within the ZIF-8@iCOF nanocomposites features a narrow optical band gap and enhanced intersystem crossing of excitons. Under white light or sunlight irradiation, the production of $^1O_2$ was significantly increased by 220%. And after 15 min of irradiation, the antibacterial efficiency can reach 99.99999%. The ZIF-8@iCOF/PAN fibrous membrane was prepared by combining ZIF-8@iCOF with polyacrylonitrile (PAN) by electrospinning, which had bactericidal performance under white light or sunlight irradiation (Fig. 13). In addition, *in vitro* safety evaluation experiments confirmed that ZIF-8@iCOF and its fibrous membranes exhibited excellent cell compatibility, and could maintain long-term stability in a complex salt and protein environment without toxicity due to decomposition products, meeting the basic safety requirements for long-term exposure [148].

COFs composites overcome the limitations encountered when employing a single nanomaterial, such as unsatisfactory antibacterial effects and high costs. By combining COFs with other nanomaterials, the unique advantages of various materials can be fully utilized, making up for the deficiencies of individual components, thereby enhancing the comprehensive performance and application value. Various nanomaterials possess distinct antibacterial mechanisms. When integrated with COFs, these can work synergistically, resulting in more potent antibacterial effects.

4 Nanozymes

As an artificial synthetic enzyme, nanozymes has unique advantages such as good stability, highly customizable, large-scale preparation, low cost, and repeatable recovery. As a substitute for natural enzymes, nanozymes have been widely used in biosensing and imaging, antioxidant, antibacterial and anticancer therapy [178, 179]. Among them, nanozymes that can mimic *in situ* catalytic generation of reactive oxygen species such as oxidases (OXD) and peroxidases (POD) are considered as novel antibacterial agents with promising applications [180–183]. COFs with extended π-conjugated structure, well-defined porosities and regular distribution of active sites are ideal platforms for simulating natural enzymes [184–186]. However, the research of nanozymes based on COFs in the field of antibacterial is still in its infancy, and the number of related reports is small. This is a new field that needs to be studied urgently.

4.1 Peroxidase-like activity (POD-like)

Nanozymes with POD-like can catalyze the conversion of endogenous H_2O_2 into biotoxic ·OH, thereby killing bacteria [187]. In 2021, Jing et al. developed an ionic covalent organic framework nanozyme (GFeF) with self-enhancing antibacterial effect and good biocompatibility. This nanozyme is designed as a glucose-triggered cascade catalyst that can be used to treat bacterial wound infections.

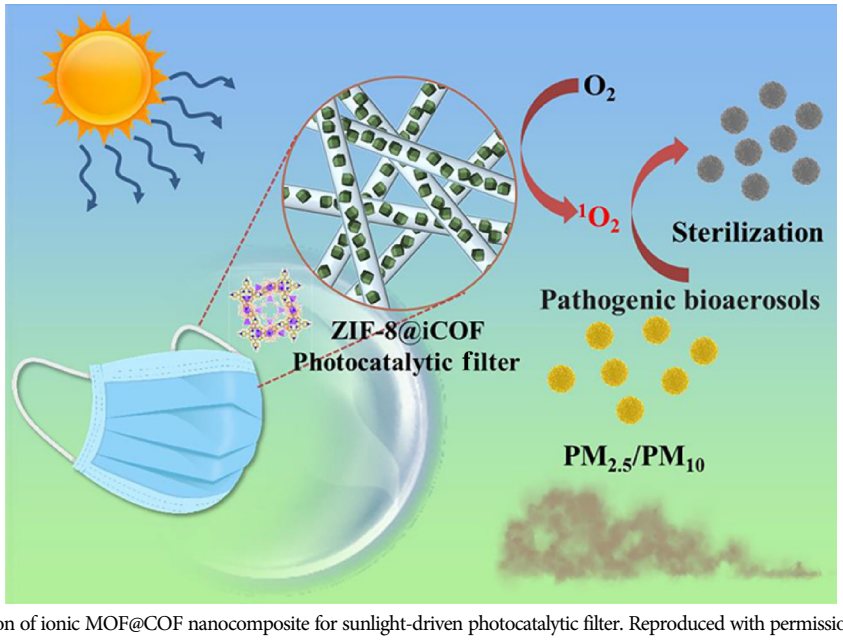

Figure 13 Schematic illustration of ionic MOF@COF nanocomposite for sunlight-driven photocatalytic filter. Reproduced with permission from Ref. [148], © American Chemical Society 2023.

iCOF was synthesized in three main steps: Firstly, iCOF was synthesized from 5,10,15,20-tetra(4-pyridyl)-21H,23H-porphine (TPyP) and p-xylylene dibromide. The iron porphyrin-based ionic covalent organic framework (Fe-iCOF) with peroxidase-like activity was obtained by chelating iCOF with ferrous chloride. Finally, Fe-iCOF was loaded with glucose oxidase (GOX) by electrostatic interaction to obtain GFeF. As an initial catalyst, GOX catalyzes the reaction of glucose with O_2 to produce gluconic acid and H_2O_2. Fe-iCOF with POD-like will convert the generated H_2O_2 into more toxic ·OH. The positively charged GFeF can be adsorbed on the surface of the negatively charged bacterial membrane to ensure that the generated ·OH radicals can direct contact with the bacteria, thereby efficiently killing the bacteria. The indirect production of H_2O_2 by glucose can significantly reduce harmful side effects. At the same time, the adhesion between GFeF and bacterial membrane can enhance the wound healing effect and can be used for wound healing in diabetic patients (Fig. 14) [91].

4.2 Oxidase-like activity (OXD-like)

Nanozymes with OXD-like can catalyze the redox reaction between one or more substrate molecules and O_2, and produce a large number of free radicals in a short time, which can effectively kill a variety of drug-resistant bacteria. Compared with POD-like, OXD-like do not need to add unstable H_2O_2 as a co-substrate, reducing the inevitable test errors [181, 188]. In 2023, Bajda et al. prepared polyethyleneimine-modified covalent organic framework nanosheets (PEI-COF NSs) by hydrothermal method using melamine and 1,4-phthalaldehyde as raw materials, PEI as dispersant and stabilizer. COF NSs with a large number of amino groups can be combined with citrate-coated gold nanoparticles (C-AuNPs) by electrostatic interactions to form PEI-COF NSs@C-AuNPs. The morphology of PEI-COF NSs@C-AuNPs was ultra-thin, transparent, polygonal, and highly dispersed. The large surface area of PEI-COF NSs increases the contact with dissolved oxygen, improves the photoresponsive OXD-like catalytic activity of C-AuNPs, and also enhances the antibacterial ability. PEI-COF NSs@C-AuNPs with OXD-like can convert dissolved oxygen into $\cdot O_2^-$ and ·OH under photocatalysis. PEI-COF NSs@CAuNPs were post-modified by thiol polyethylene glycol functionalized folic acid (FA-PEG-SH), which can be used to detect cancer cells with overexpression of folic acid receptors. In addition, PEI-COF NSs@C-AgNPs could effectively inhibit the growth of *E. coli* and *S. aureus* under visible light irradiation. The minimum inhibitory concentrations were 17 and 34 ng/mL, respectively, and the diameters of the inhibition zones were 2.1 and 1.8 g/mL, respectively [189].

COFs nanozymes maintain the high antibacterial activity while significantly enhancing chemical and thermal stability. Given the increasing concern over bacterial resistance, leveraging the designable properties of COFs nanozymes will lead to the development of personalized antibacterial strategies. According to the bacterial infection category, infection level, and individual physiological characteristics of patients, nanozyme materials can be tailored with specific properties, thereby improving the efficacy and safety.

5 Conclusions and outlooks

COFs, as a new type of crystalline nano-antibacterial agent, offer numerous advantages over traditional antibacterial methods. It has resistance to drug resistance, exhibits excellent designability to address different antibacterial scenarios, possesses a slow-release function to solve frequent dosing, demonstrates synergistic action of multiple mechanisms to enhance antibacterial effects, and boasts good thermal/chemical stability to reduce deactivation risks. Therefore, we summarize the latest research progress of antibacterial COFs in this review.

The antibacterial strategies of COFs can be summarized as follows: (1) Based on the high customization of COFs, the introduction of building blocks or post-modification elements with antibacterial activity can obtain COFs materials with their antibacterial activity, including photodynamic, photothermal, and electrostatic interactions. (2) Due to the inherent pores and stable structure of COFs, it is an advantageous nanoplatform for antibacterial drug delivery. The reversible bond of COFs not only increases its biodegradability, but also ensures the intelligent controlled release of antibacterial drugs to achieve the goal of long-

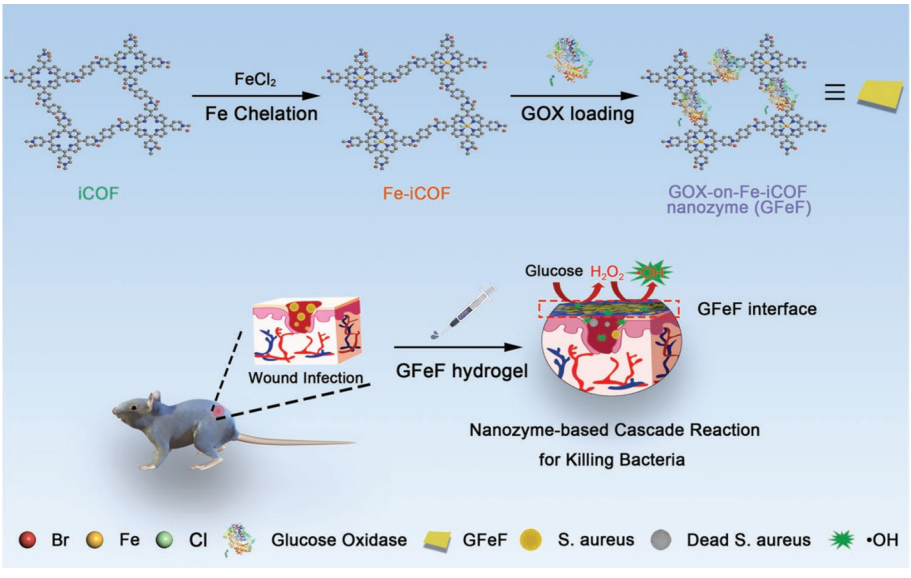

Figure 14 Schematic representation of preparation and *in vivo* antibacterial application of GFeF nanozyme and its hydrogel form via cascade reaction. Reproduced with permission from Ref. [91], © Wiley-VCH GmbH 2021.

term antibacterial. (3) The composite of COFs with other antibacterial nanomaterials is also a promising antibacterial strategy, which can not only overcome the disadvantages of single materials but also achieve better antibacterial effects in synergy. For example, the composite of COFs and metal nanoparticles can improve the dispersion and controlled release of metal nanoparticles, and improve their stability, biosafety, and long-term antibacterial properties. (4) The efficient antibacterial properties of COFs nanozymes cannot be ignored and need to be developed. Above all, COF-based antibacterial agents have shown great potential in practical applications such as wound dressing, masks, food preservation, antibacterial coatings, and water treatment.

However, despite the numerous advantages, COF-based antibacterial agents still have many limitations. The first is the nanocrystallization and large-scale preparation of COFs antibacterial agents. The solvothermal method is one of the most commonly used methods for the synthesis of COFs. However, harsh and complex synthesis conditions severely limit its large-scale preparation. At the same time, the COFs obtained by the solvothermal method have problems such as easy aggregation, poor dispersibility and difficulty in controlling the size, which seriously limit the antibacterial performance. In contrast, the room temperature synthesis method makes it easier to realize the size nanocrystallization and large-scale preparation of COFs. However, the mild synthesis conditions are not suitable for most COFs. Therefore, the study of the scale-up synthesis of nanosized COF-based antibacterial agents under mild conditions is necessary to realize their practical applications. Meanwhile, various antibacterial strategies based on COFs are emerging as a focal point of current research endeavors. While COFs have demonstrated efficacy in photothermal, photodynamic, and synergistic antibacterial effects, the exploration of additional antibacterial approaches remains underdeveloped. For instance, the potential of SDT or PDT/SDT effects has yet to be realized in COFs-based antibacterial field [190]. Moreover, the antibacterial mechanism is difficult to be mapped out, which may cause certain side effects in the face of complex application environments. Therefore, the development of simple, safe and efficient COF-based antibacterial agents is urgently needed, as well as some challenges should be addressed. The biosafety and biocompatibility of COF-based antibacterial agents still need to be further explored. At present, COFs antibacterial agents mainly focus on *in vitro* antibacterial experiments, while *in vivo* antibacterial experiments are relatively few. The effects on normal tissues and organs still need further study, and toxicology and clinical studies still need to be carried out. In addition, COFs antibacterial agents mostly combat against common Gram-positive bacteria (*S. aureus*) and Gram-negative bacteria (*E. coli*), while new pathogenic bacteria emerge one after another every year. It is imperative to investigate the antibacterial mechanism and antibacterial effect of COFs antibacterial agents on new pathogenic bacteria. In short, COFs are excellent candidates for antibacterial clinical trials, and the challenge is the driving force. With the deepening and optimization of research, COF-based antibacterial agents will have a broader application space.

Data availability

Not applicable.

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Declaration of competing interest

All the contributing authors report no conflict of interests in this work.

Author contribution statement

W. X. W.: Literature collection, writing manuscript, and creation of figures and tables. W. Z. L.: Literature classification, writing manuscript. Y. Y. J.: Project administration, funding acquisition. Z. W.: Funding acquisition. Y. R. G.: Technical supports. J. Y. N.: Software. X. G.: Manuscript revision. W. S. L.: Project administration. J. B. S.: Project administration, supervised and revised the manuscript. All the authors have approved the final manuscript.

Informed consent

Not applicable.

Ethics statement

Not applicable.

Use of AI statement

None.

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