Phototherapy-based combination strategies for bacterial infection treatment

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Abstract

The development of nanomedicine is expected to provide an innovative direction for addressing challenges associated with multidrug-resistant (MDR) bacteria. In the past decades, although nanotechnology-based phototherapy has been developed for antimicrobial treatment since it rarely causes bacterial resistance, the clinical application of single-mode phototherapy has been limited due to poor tissue penetration of light sources. Therefore, combinatorial strategies are being developed. In this review, we first summarized the current phototherapy agents, which were classified into two functional categories: organic phototherapy agents (e.g., small molecule photosensitizers, small molecule photosensitizer-loaded nanoparticles and polymer-based photosensitizers) and inorganic phototherapy agents (e.g., carbo-based nanomaterials, metal-based nanomaterials, composite nanomaterials and quantum dots). Then the development of emerging phototherapy-based combinatorial strategies, including combination with chemotherapy, combination with chemodynamic therapy, combination with gas therapy, and multiple combination therapy, are presented and future directions are further discussed. The purpose of this review is to highlight the potential of phototherapy to deal with bacterial infections and to propose that the combination therapy strategy is an effective way to solve the challenges of single-mode phototherapy.

Keywords: Bacterial infection, Multidrug-resistance, Phototherapy, Combinatorial strategies, Nanomedicine

Graphical abstract
Introduction

Bacterial infections are caused by harmful bacteria invading the host, which may cause severe diseases, including pneumonia, tuberculosis, sepsis, cholera, meningitis and osteomyelitis [1-5]. Although the discovery of antibiotics has been saving millions of lives [6], unfortunately, conventional antibiotics treatment has problems such as a low utilization rate and severe side effects [7-9]. More seriously, the overuse and misuse of antibiotics inevitably increase the prevalence of multidrug-resistant (MDR) pathogenic bacteria [10], which has become a global public health problem in the past decades [6]. According to statistics from the World Health Organization (WHO), nearly 80% of MDR microorganisms have arisen due to the global overuse or misuse of antibiotics, and infection by these strains is accompanied by severe adverse effects such as thrombophlebitis and epidermal necrolysis [11]. Under this circumstance, massive efforts have been made to develop new strategies for efficient bacterial infections therapy without causing drug resistance.

The use of light in modern medicine was introduced in the 19th century. Based on the advances in our understanding of the physical properties of light and light-matter interactions, medical technology has been developed in parallel [12]. A classic example of the early success of light-induced therapy was the treatment of lupus vulgaris with ultraviolet (UV) light, which was discovered by physician Niels Finsen, who won the Nobel Prize in Physiology or Medicine in 1903 for this discovery. A notable milestone in the 1960s was the treatment of severe hyperbilirubinemia using blue-light phototherapy, which subsequently cured millions of infants of this condition [13]. Presently, numerous laser-based diagnostic and therapeutic devices have been widely used in clinical practice.

Over the recent decades, the developments of phototherapy antibacterial strategies, such as photodynamic treatment and photothermal treatment [14], have attracted striking attention in nanomedicine because of their good controllability. Different from conventional antibiotics, phototherapy rarely causes bacterial resistance [15]. Therefore, phototherapy is a minimally invasive and effective
modality that provides a convenient method for ablating bacterial infections using light irradiation in a clinically safe manner [16, 17]. Figure 1A shows that the mechanism of photodynamic treatment or photothermal treatment activity by a phototherapy agent. Despite the rapid progress and distinctive advantage of phototherapy, single-mode phototherapy techniques face several challenges, including limitations in targeting the infection site. Fortunately, combination with chemotherapy, chemodynamic therapy, gas therapy and multiple combination therapy can effectively combat these challenges while maximizing the advantage of each therapeutic mode (Figure 1B). In this review, we aim to present a discussion on the significant research progress in combinatorial strategies using phototherapy. Firstly, we introduced phototherapeutic agents systematically, summarized the development of phototherapy and discussed the challenges of single-mode phototherapy. Furthermore, the advantages of combination therapy for the treatment of bacterial infections were emphasized. Finally, we discussed the major challenges and problems facing therapeutic nanomedicine in bacteria infectious therapy, and propose possible future directions in this field.

**Phototherapy agents for bacterial infection therapy**

Photosensitizers play an important role in phototherapy. The first generation photosensitizers mainly include hematoporphyrin derivatives and porfimer sodium, and their phototherapy performance was limited by the short wavelength of excitation in deep tissues. To solve the disadvantage of the first generation photosensitizers, researchers further developed second generation photosensitizers with near-infrared activation. However, the low cell/tissue specificity of the second generation photosensitizers still prevented them from being used in clinical therapeutics. Over the past few years, novel nanomaterial-based photosensitizers have been received extensive attention and been studied, and these photosensitizers can be divided into organic and inorganic agents. In this part, we will compare the advantages and disadvantages of these two kinds of agents.
Organic phototherapy agents

Small molecule photosensitizers, small molecule photosensitizers-loaded nanoparticles and polymer-based photosensitizers are the three primary classifications of organic phototherapy agents, all of which have several common advantages, including 1) good biocompatibility; 2) structures and performances that are easy to characterize; 3) easy chemical modification.

Small molecule photosensitizers

Recently, the small molecules commonly used as organic phototherapy agents mainly including protoporphyrin IX (PpIX), chlorine e6 (Ce6), indocyanine green (ICG) and other photosensitizers. However, several disadvantages still remain in the use of small molecules phototherapy agents. For example, due to the lack of the ability to target bacteria or infection sites, the enrichment of small molecule phototherapy agents at the infected site was not enough, which would further affect their therapeutic performance. To solve this problem, Wang et al. [18] developed a new molecular probe (Ppa-PLGVRG-Van), including a signal molecule (pyropheophorbide-α, Ppa), an enzyme-responsive peptide linker (Pro-Leu-Gly-Val-Arg-Gly, PLGVRG), and a targeting ligand (vancomycin, Van) (Figure 2A). Figure 2B shows that Ppa-PLGVRG-Van could accumulate at the site of responsive bacterial myositis via the targeting molecule (Van). Then, the peptide linker is cleaved by gelatinase to make the supramolecular form of hydrophobic building blocks, which readily self-aggregates in situ and significantly enhances the photoacoustic signal for detecting the bacterial infection by imaging. Thus, the specific accumulation of Ppa-PLGVRG-Van at the bacterial infection sites leads to a significant function of Ppa in situ. We believe that this strategy of chemically functionalizing phototherapy agents can be expanded to enhance the therapeutic effect of other phototherapy agents in bacterial infections.

Small molecule photosensitizer-loaded nanoparticles

To enhance the therapeutic effect of small molecule photosensitizers, in addition to the above strategies, another approach is to the extend circulation time of
photosensitizers, and enhance the stability at the same time. To achieve this goal, the small molecule photosensitizers can be conjugated with a variety of synthetic biomaterials, or encapsulated into nanoparticles to form small molecule photosensitizer-loaded nanoparticles, such as polymer nanoparticles, liposome, upconversion nanoparticles and other inorganic nanoparticles. All the small molecule photosensitizers-loaded nanoparticles and the corresponding information can be found in Table 1. The payload of conjugated or encapsulated drugs can be enriched in the bacterial infection zone via the enhanced penetration and retention (EPR) effect [38-40], and kill bacteria under light irradiation. Moreover, to reduce the side effects, the components of nanoparticles are also required to be degradable in vivo to guarantee rapid clearance after eradicating bacterial infections [41]. Therefore, biodegradability is one of the important considerations in developing small molecule photosensitizer-loaded nanoparticles. When bacteria infects and invades the host, the expression of enzymes (e.g., phosphatase, phospholipase and protease) at the site of infection will significantly increase, the pH value will decrease to an acidic pH, and the local temperature will increase, thus forming a special microenvironment of bacterial infection [40, 42, 43]. Therefore, the prepared small molecule photosensitizer-loaded nanoparticles, which can respond to the microenvironment of bacterial infected tissues, are the best choices to improve the phototherapy efficacy and helpful to slow down the emergence of side effects. For example, Yan et al. [24] synthesized silica nanoparticles doped with Ce6. This hybrid structure exhibits enhanced photostability and a high antibacterial efficiency towards Staphylococcus aureus (S. aureus) and methicillin-resistant S. aureus (MRSA). Therefore, this work demonstrates an effective platform to improve the efficiency of small molecule photosensitizers for better treatment of wound infections.

In addition, nanosized metal organic frameworks (NMOFs) exhibit an advantage of encapsulating many small molecules due to their highly porous structure. In addition, they can reduce the self-quenching of small molecule photosensitizers and show great photodynamic treatment efficacy. For example, Bagchi et al. [30] prepared a squaraine (SQ)-encapsulated zeolitic imidazolate framework-8 (ZIF-8) NMOF
(ZIF8-SQ) by a postsynthetic strategy. The insertion of SQ within the ZIF-8 cavity could lower the free diffusion of SQ molecules in biological media and limit the SQ aggregation possibilities. *In vitro* antibacterial tests confirmed that ZIF8-SQ could provide unparalleled photodynamic treatment action against MRSA.

In recent years, bioresponsive nanoparticles have achieved remarkable results in the treatment of bacterial infections *via* phototherapy [44, 45]. Sun *et al.* developed pH sensitive nanoparticles combined with ammonium methylbenzene blue for the photodynamic treatment of bacterial infections, showing an efficient biofilm eradication capability [31]. Wang *et al.* [44] designed an antibacterial hydrogel in an acidic environment. The hydrogel loading photothermal agent could cure wounds infected with a MRSA biofilm in a short period of time.

To realize the targeted delivery of photosensitizers, target ligands can be modified on nanoparticles. For example, Zhang *et al.* [22] prepared a pH-tunable ON/OFF nanovehicle with a heteromultivalent and glycomimetic shell for targeting bacterial lectins and an acid-responsive core for the controlled release of phototherapeutic agent at infectious sites. As shown in Figure 3, the shell of the nanovehicle was composed of heteromultivalent glycomimetics, which could bind tightly to bacteria and subsequently inhibit biofilm formation. The core was composed of acid-sensitive polymers that changed from hydrophobic to hydrophilic through protonated effects under an acidic microenvironment. Under physiological conditions, the hydrophobic core of nanotherapeutics was in the “OFF” state and locks the phototherapeutic agent in the cage. Upon arriving at the infection site, the nanotherapeutics were in the “ON” state under an acid microenvironment, promoting the release of phototherapeutic agent which induced oxygen species (ROS) and heat under NIR laser illumination. Therefore, this heteromultivalent ligand-decorated nanovehicle could effectively avoid side effects on normal tissue and the occurrence of bacterial resistance.

On the other hand, the targeting of nanoparticles to bacterial cells can be promoted *via* electrostatic interaction. For example, Shi *et al.* [23] designed and synthesized pH-sensitive mixed-shell-polymeric-micelles (MSPMs) composed of
poly(ethylene glycol)-b-poly(ε-caprolactone) (PEG-b-PCL) and poly(ε-caprolactone)-b-poly(β-amino ester) (PCL-b-PAE). The potential of MSPMs could change from a negative charge to a positive charge due to charge-switching of the PAE blocks at a low pH, which would promote the targeting of MSPMs to bacterial cells via electrostatic interactions. In a murine model, Figure 4 shows that the experimental group administered PpIX-loaded MSPMs exhibited a faster recovery rate after infection with vancomycin-resistant staphylococcal, while the differences in the bacterial eradication efficacies of the groups treated with saline, vancomycin, and PpIX-loaded single shell-polymeric-micelles (SSPMs) composed of PEG-b-PCL were minimal. Taken together, these studies provided promising approaches for the treatment of MDR bacterial infection.

Because upconversion nanoparticles (UCNPs) have the unique ability of upconverting NIR light to UV and visible emissions [46], they are also commonly used in phototherapy. Sun et al. [33] designed and synthesized antibacterial a core-shell UCNPs@SiO$_2$(MB), in which the core was NaYF$_4$:Yb,Er,Gd and the shell was methylene blue (MB)-loaded silica, which could convert NIR light into visible photons to activate MB through fluorescence resonance energy transfer (FRET) and generate ROS to rapidly kill both Gram-positive $S. aureus$ (94.5%) and Gram-negative $E. coli$ (93.2%). To develop highly effective antibacterial UCNPs, Zhou et al. [36] reported a photosensitizer (PS) prepared through the self-assembly of poly(selenoviologen) on the surface of core-shell NaYF$_4$:Yb/Tm@NaYF$_4$ UCNPs. Figure 5 shows a schematic illustration of the main synthetic procedure and synergistic photodynamic treatment and photothermal treatment strategies. The hybrid UCNP/PSeV PS showed a strong ROS generation ability and high photothermal conversion efficiency (~52.5%) under the mildest reported-to-date irradiation conditions ($\lambda=980$ nm, 150 mW/cm$^2$, 4 min) and led to a high efficiency in killing MRSA both in vitro and in vivo.

**Polymer-based photosensitizers**

Polymer-based photosensitizers are in-between small molecules and
nanoparticles. Many conjugated polymers and conjugated polymer nanoparticles (CPNs) have been utilized as photodynamic and photothermal treatment agents for bacterial infection therapy [47-51].

For example, Feng et al. [51] reported photothermal-responsive CPNs for the rapid and effective killing of bacteria. These CPNs are composed of poly[2,6'-4,8-di(5-ethylhexylthienyl)benzo[1,2-b;3,4-b]dithiophenealt-5-dibutyloctyl-3,6-bis(5-bromothiophen-2-yl)pyrrolo[3,4-c]pyrrole-1,4-dione] (PDPP-DBT) and matrix polymer DSPE-PEG2000-MAL. To enhance the interaction of CPNs with bacteria cells, the resulting CPNs were further modified with the positively charged Tat peptide (RKKRRQRRRC) by chemical conjugation between the maleimide groups and thiol groups. In vivo and in vitro experimental results confirmed that CPNs-Tat could enhance the interaction with bacteria cells with the formation of CPN-Tat/bacteria aggregates, and these photothermal-responsive CPNs converts light into heat and produces local hyperthermia to kill bacteria within a few minutes under NIR irradiation. Therefore, this photothermal-responsive strategy offers another rapid and effective modality for combating bacterial infections.

Inorganic phototherapy agents

Compared with organic phototherapy agents, many inorganic phototherapy agents exhibit strong optical absorption and efficient photothermal conversion, and therefore, they are commonly used as photothermal treatment agents (PTTs) to fight bacterial infections. There are many factors influencing the phototherapy performance of inorganic PTTs, including their size, shape, concentration and surface modification. According to the morphology of inorganic PTTs, they can be classified into nanorods, nanocages, nanodots, nanocubes, nanosheets, nanostars, nanoflowers, nanoeggs, nanopopcorn, and numerous other 2D materials [52]. In this part, we classify most PTTs into 4 categories: carbon-based nanomaterials (e.g., graphene derivatives and carbon nanotubes), metal-based nanomaterials (e.g., Au and CuS) [53], composite nanomaterials and other nanomaterials (e.g., quantum dots). In fact, overlaps cannot be avoided in some cases for our classification.
**Carbon-based nanomaterials**

Carbon-based nanomaterials have been widely as phototherapy agents studied in antibacterial therapy because of their relatively high bacterial toxicity, negligible mammalian cytotoxicity and other favourable properties. In recent years, graphene-based nanomaterials (GBNs), such as graphene, reduced graphene oxide (rGO), graphene oxide (GO) and other chemically modified-graphene, have been widely used in antibacterial therapy research. Table 2 shows the carbon-based nanomaterials commonly used in antibacterial therapy.

To achieve the more specific and effective photothermal sterilization of GBNs, they were usually modified with some functional molecules or nanostructures. For example, Qian et al. [54] developed surface-adaptive and biocompatible glycol chitosan-conjugated carboxyl graphene (GCS-CG), which could target to the acidic environments of infected abscesses without damage to healthy tissue (Figure 6). The *in vitro* experimental results demonstrated that the aqueous solution of GCS-CG showed the rapid production of heat energy with NIR irradiation. This kind of GO-based nanomaterial could be applied as a new potential photothermal treatment agent in treating bacterial infection and even MDR bacteria.

**Metal-based nanomaterials**

Metal nanomaterials are the material most commonly used for photothermal treatment due to their broad spectral absorption range and light stability [53, 55]. Figure 7 shows the antibacterial mechanism of the photothermal conversion of metal nanomaterials. In short, the electromagnetic field causes electrons in the conduction band at the surface of the metal nanomaterials to rapidly oscillate [64]. This absorbed energy induces vibrations in the metallic lattice via electron–photon coupling, which is subsequently transferred into thermal energy causing a local temperature increase [65]. In order to kill pathogens specifically, these nanomaterials could target the pathogen by conjugating targeting ligands (such as antibodies) on their surface, which would increase the local temperature around the pathogen and cause cell death through a suite of actions including the denaturation of essential proteins/enzymes,
induction of heat shock proteins, disruption of metabolic signaling and rupture of the cell membrane [54, 66-68]. The commonly investigated inorganic PTTs and their images with corresponding shape are shown in Table 3.

For example, Norman et al. [71] prepared gold nanorods with covalently conjugating primary resistance antibodies, which could selectively target the Gram-negative pathogen, *Pseudomonas aeruginosa*. The subsequent attachment of these gold nanorods to the pathogenic bacterial cell surface could significantly reduce the bacteria cell viability under near-infrared radiation (λ=785 nm). Similarly, Wang et al. [109] prepared oval-shaped gold nanoparticles, with anti-salmonella antibodies bound on their surface (Figure 8). When oval-shaped gold nanoparticles are attached to bacterial cells, the heat locally generated during NIR irradiation (λ=785 nm) could cause irreparable cellular damage of *Salmonella typhimurium* bacteria. The successful bioconjugation of photothermal nanomaterials with targeting ligands shows promise in improving the selectivity to enhance the photothermal treatment effect of metal nanomaterial-based PTTs.

**Composite nanomaterials**

To fully exploit the effect of different types of photothermal agents, increasing numbers of composite-based nanomaterials photothermal agents have been designed and prepared [110]. For example, Feng et al. [111] prepared a rGO and AuNS nanocomposite (rGO/AuNS) via a seed-mediated growth method (Figure 9). The results of *in vitro* experiments confirmed that MRSA could be killed completely when incubated with rGO/AuNS (50 μg/mL) under NIR irradiation (808 nm, 3 W/cm²) for 6 min. Therefore, this indicates that rGO/AuNS can be used as a dual functional photothermal agent for synergistically killing MDR bacteria. Similarly, Luo et al. [112] developed a facile assembly of Au NPs decorated GO/nanocellulose paper, which has an intense antimicrobial activity against both Gram-positive and Gram-negative bacteria due to its excellent photothermal conversion performance. Besides, the satisfactory *in vitro* antibacterial performance demonstrated that these functionalized papers could be applied for skin disinfection or medical device sterilization.
In addition, black phosphorus (BP) nanosheets, a rising star among 2D materials, have recently attracted widespread attention in antibacterial applications owing to their high photothermal conversion efficiency, large surface area-to-volume ratio, excellent biocompatibility, and good biodegradation [126]. In particular, a variety of composite materials based on black phosphorus and metal nanoparticles have been developed and proved to exhibit an excellent antibacterial efficiency [127, 128]. For instance, Aksoy et al. [129] designed and prepared new a BP/Au nanocomposite as a photothermal antibacterial agent to kill an important nosocomial pathogen E. faecalis. In vitro studies have shown that because the BP/Au nanocomposite has a higher photothermal conversion efficiency, it more efficiently destroyed the bacterial cell membrane than bare BP, with a biofilm inhibition rate of 58% achieved under NIR light irradiation. The photothermal composite nanomaterials can be found in Table 4.

Quantum dots

Quantum dots (QDs) have garnered increasing attention as another kind of promising photosensitizers due to their ease-of-synthesis, favourable dispersibility in water, and widely controllable optical properties. Currently, QDs mainly include metal-based (Cd, Pb, and In) semiconductor QDs, carbon QDs and graphene QDs. However, compared with metal-based semiconductor QDs, carbon QDs and graphene QDs are safer, more sustainable, and more biocompatible for potential biomedical applications [130-132]. Most GQDs exhibit photothermal performance [133]. Recently, it has been reported that GQDs have photodynamic characteristics rather than photothermal effects [134]. Carbon QDs (CQDs) can reportedly generate ROS for PDT applications via light absorption [136]. For example, Wei et al. [137] synthesized CQDs from citric acid and 1,5-diaminonaphthalene in ethanol using a one-pot solvothermal method (Figure 10A), and the in vitro antibacterial photodynamic inactivation of both Gram-positive and Gram-negative bacteria are shown in Figure 10B.

Single-mode phototherapy
Photodynamic treatment

Photodynamic treatment is a photochemistry-based technology that relies on the generation of singlet oxygen ($^1$O$_2$) and ROS under light irradiation in the presence of photosensitizers and oxygen [138], and has been reported to be effective in killing both Gram-negative and Gram-positive bacteria [139-141]. It is generally believed that photosensitizers can undergo type I (electron transfer) and/or type II (energy transfer) processes to produce highly reactive ROS under light irradiation [142]. Type I processes produce radical and radical anion species (e.g., $O_2^-$, and -HO), while type II processes generate $^1$O$_2$ [143]. However, antioxidant molecules, for example, glutathione, are present in the complex abscesses site, which could protect bacteria from the toxicity of photodynamic treatment. In addition, the hypoxic microenvironment of an infection site limits the efficacy of oxygen-dependent photodynamic treatment to kill bacteria [144]. Moreover, most existing photosensitizers (e.g., PpIX) often aggregate in aqueous solution because of their large conjugated molecular structures. This aggregation usually results in a lack or low levels of ROS generation due to aggregation-caused quenching, which severely hampers the application of photosensitizers in photodynamic treatment [25]. Herein, Yoon et al. found that boronic acid-functionalized phthalocyanine (PcN4-BA) displays an uncommon phenomenon, an aggregation-enhanced photodynamic effect. The combination of the ability to form uniform nanostructured self-assemblies in water, highly efficient ROS generation and boronic acid-induced targeting cause PcN4-BA to exhibit excellent performances in antimicrobial photodynamic treatment [145].

Photothermal treatment

The mechanism of photothermal antibacterial treatment occurs by producing local high heat through the phototherapy agent, which can cause the irreversible ablation of bacteria by the denaturation of their proteins/enzymes, inhibiting their essential intracellular reactions [146, 147]. Therefore, photothermal nanomaterials have been proposed as a promising solution for the targeted treatment of pathogenic
micro-organisms as they are controllable and can be localized to the immediate area surrounding the nanomaterial [148, 149]. Currently, NIR laser-triggered photothermal treatment based on various nanoagents has become one of the most effective antibacterial strategies due to the high spatial resolution and tissue penetration depth of NIR lasers [104, 150]. Additionally, NIR lasers can be focused on a target area to promote blood circulation and relieve inflammation of tissues. However, there are still some limitations to photothermal treatment alone, whose antibacterial effect is restricted by the following issues: 1) high power density and long-term exposure of NIR lasers can damage healthy tissues [151]; 2) it is difficult to kill the heat-resistant bacteria [152]; 3) the phototherapy agent cannot rapidly and effectively eradicate bacteria due to its poor diffusivity [153]. Photothermal treatment-based synergistic therapy (e.g., a combination with chemotherapy or gas therapy) is a promising strategy for addressing these limitations and integrates the advantages of single modality approaches to shorten antibacterial time and improve antibacterial efficiency [35].

Advantages and disadvantages of phototherapy

Compared to traditional antibiotic therapy, both photodynamic treatment and photothermal treatment have several advantages in bacterial infections therapy. For example, treatment strategy can be adjusted in a timely manner according to the actual situation since the irradiation site and time can be precisely controlled. Notably, the limited irradiation area can reduce side effects and ensure more locally concentrated energy, which would significantly improve the therapeutic effect. However, despite these advantages, there are still disadvantages. For photodynamic treatment, the high concentrations of glutathione and hypoxic microenvironment at the infection site can limit the efficacy of ROS-dependent photodynamic treatment to kill bacteria. For photothermal treatment, it is difficult to kill the heat-resistant bacteria even when treated at high temperatures such as 45 °C. Moreover, so far, a wide range of the clinical application of single-mode phototherapy is limited due to the poor tissue penetration of light source. Fortunately, the second NIR window (NIR-II, 1000–1700
nm) provides a solution for deep-tissue therapy and diagnosis. Therefore, the development of photosensitizers based on the second NIR window may be the focus of future research.

**Combined phototherapy**

To address the intractability of bacteria, single-mode therapy is insufficient for clinical use. Phototherapy combined with other therapeutic methods provides a better alternative for infectious therapy through their respective therapeutic advantages.

**Combination with chemotherapy**

At present, antibiotics used as the main chemotherapy drugs are used in the treatment of bacterial infection [154]. It is well known that oral and intravenous administrations are the two main forms of antibiotic treatment, which may lead to only a small proportion of the drug being concentrated at the site of the lesion, resulting in less effective treatment [44]. In order to maintain the effective treatment concentration of antibiotics at the infected site and ensure the treatment effect, it is often necessary to increase the dosage of drugs or prolong the treatment cycle. However, large dose or long time of drug use would enhance the harmful effects of drugs in the human body and produce severe side effects. The common toxicity and side effects of antibiotics are shown in Table 5, mainly involving the gastrointestinal tract, liver, kidney and other organs. To overcome these difficulties, chemotherapy in combination with phototherapy has been significantly emphasized in many recent studies. Nanosystems offer a clue to solving the drawbacks of chemotherapy while introducing a more advanced therapeutic effect [155-157].

Nanoparticles such as AuNPs, graphene, and other polymer nanoparticles capable of photothermal conversion have been designed to deliver antibiotics to the infected sites for achieving chem-photothermal therapy under NIR irradiation [118, 158,159]. These synergetic strategies can not only fully exploit the advantages of enhancing the antibacterial effect, but also reduce the side effects of antibiotics. For example, Liang et al. [20] developed a smart biocompatible thermo-responsive-inspired drug-delivery nanotransporter (TRIDENT) for the
synergistic eradication of MDR bacteria through combined chemo-photothermal therapy. As shown in Figure 11A, under NIR irradiation, the prepared imipenem (IMP)-loaded IR780 TRIDENT (IMP/IR780@TRN) could increase the local temperature to kill the bacteria under NIR irradiation. IMP/IR780@TRN can melted at temperatures above 43 °C, which causes IMP to be released from the NPs and damage the MDR bacteria. Even low doses of IMP-encapsulated TRIDENT could eradicate clinical MRSA according to *in vitro* and *in vivo* evidence. Therefore, this combination therapy strategy can reduce the use of antibiotics to prevent MDR while ensuring efficacy.

In another report, Wu *et al.* [160] designed a chemo-photothermal combination therapy system (PDA NP-Cip/GC hydrogel, abbreviated as Gel-Cip). As Figure 11B shows, the phototherapy agent polydopamine (PDA) NPs were firstly used to load the antibiotic ciprofloxacin (Cip) via π−π stacking and/or hydrogen bonding interactions, and then the Cip-loaded PDA NPs was mixed with glycol chitosan (GC) to form an injectable hydrogel through Schiff base reaction and/or Michael addition. Both *in vitro* and *in vivo* evidence confirmed that this combination treatment of Gel-Cip and NIR light irradiation could eradicate both Gram-positive and Gram-negative bacteria.

**Combination with chemodynamic therapy**

Although chemo-photothermic combined therapy strategies can significantly improve the effect of photothermal treatment and reduce the dosage of antibiotics, the use of antibiotics has the risk of producing drug-resistant bacteria. To avoid the occurrence of drug-resistant bacteria, and improve the effect of photothermal treatment at the same time, non-antibiotic combined photothermal treatment strategies have been developed. To our best knowledge, the less reactive H₂O₂ can be converted into a highly reactive hydroxyl radical (·OH) through the iron-mediated Fenton chemistry, which will cause the oxidative stress and alteration of biomolecules (*e.g.*, proteins and DNA) [161, 162]. It has been discovered that there is a significant overproduction of H₂O₂ in the microenvironment of bacterial infection site [163]. Therefore, the biofilm formation of bacteria could be prevented by applying
ferromagnetic NPs to produce ·OH [164]. In addition, nanoenzymes are nanomaterials with peroxidase- and oxidase-like properties, and also have been explored as powerful tools to kill bacteria due to their capability to catalyze the formation of ROS [164-167]. For instance, noble metal NPs, such as Au, Pd, and Pt, have attracted extensive attention in the antibacterial field [168-171]. Though this is an inspiring protocol with promising antibacterial outcomes, the existing metal-carrying nanomaterials often have low reaction rates due to the insufficient catalyst ion amount, which results in slow ·OH generation and unsatisfactory chemodynamic therapy outcome [172-175]. Therefore, it is necessary to design multimode antibacterial nanomaterials with chemodynamic therapeutic effects. For example, Zhao et al. [101] combined catalysis with the NIR photothermal effect and developed a biocompatible antibacterial system based on polyethylene glycol functionalized molybdenum disulfide nanoflowers (PEG-MoS$_2$ NFs). In vitro experiments confirmed that this combination therapy system could provide a faster and more effective kill outcome for Gram-negative ampicillin resistant Escherichia coli and Gram-positive endospore-forming Bacillus subtilis than chemodynamic treatment or photothermal treatment alone (Figure 12).

In addition, to address the impact of low oxygen content in the infection microenvironment during antimicrobial photodynamic treatment, Liu et al. [21] utilized manganese dioxide (MnO$_2$), since it could effectively catalyze H$_2$O$_2$ conversion into H$_2$O and O$_2$ [176, 177] to prepare a photosensitizer (Ce6)-carrying MnO$_2$ nanometre system (Ce6@MnO$_2$-PEG NPs). Owing to the ability of MnO$_2$ to convert H$_2$O$_2$ into O$_2$, Ce6@MnO$_2$-PEG NPs could greatly enhance the photodynamic treatment-induced antibacterial efficacy within the oxygen-deficient/H$_2$O$_2$-enriched environment compared to free Ce6.

**Combination with gas therapy**

Recently, due to the therapeutic efficiency, mild side effect, and rare chance to induce bacterial MDR, gas therapy has attracted enormous attention in antibacterial applications [178]. Among the gases used, NO is the one that has been most
extensively explored due to its multi-antibacterial mechanisms [179, 180], including inhibiting bacterial growth by reacting with bacterial DNA and blocking the repair of damaged DNA, and reacting with ROS to generate reactive peroxynitrite (ONOO–) molecules with enhanced bactericidal activity. However, a high concentration of gas can inevitably damage in vivo normal tissues [181, 182]. Therefore, photothermal treatment combined with gas therapy formed another kind of strategy for antimicrobial therapy. For example, Gao et al. [183] reported a new near-infrared 808 nm laser-mediated NO-releasing nanovehicle (MoS2-BNN6), that could not only exhibit photothermal treatment efficacy but also precisely control NO release to generate oxidative/nitrosative stress under NIR irradiation (λ=808 nm). In vivo results showed that MoS2-BNN6 with enhanced photothermal treatment/NO synergetic antibacterial function achieves >97.2% inactivation of bacteria within 10 min of NIR irradiation, and could also effectively repair wounds through the formation of collagen fibres and elimination of inflammation during tissue reconstruction. Similarly, Cai et al. [28] presented an all-in-one phototherapeutic nanoplatform AI-MPDA, which includes L-arginine (L-Arg), ICG and mesoporous polydopamine (MPDA) (Figure 13A). AI-MPDA not only generated heat but also produced ROS and catalyzed L-Arg to release NO under NIR irradiation, furthermore, the released NO significantly enhanced the therapeutic effects of photodynamic treatment and low-temperature photothermal treatment (≤45 °C), contributing to the elimination of bacterial biofilm. Different from NO gas, hydrogen (H2) can selectively scavenge intracellular ROS without inducing any toxic effect on normal cells even at high concentrations [184, 185], which has been recognized as a green, safe and excellent antioxidant combined photothermal treatment in antibacterial and wound-healing therapies. For example, Xue et al. [186] reported a NIR-mediated hydrogen release photothermal agent, PdH nanohydride, which combined both merits of bioactive hydrogen and the photothermal effect of Pd, exhibiting excellent antibacterial activities in vitro and in vivo due to its synergistic hydrogen-photothermal antibacterial process occurring through oxidative stress and membrane damage pathway.
Additionally, carbon monoxide (CO) has been considered a potent antibacterial agent against diverse microorganisms [187] via the p38-mediated surface expression of toll-like receptor 4 (TLR-4), activation of host immune responses [188], and inhibition of cellular respiration [189]. Furthermore, it even exhibits a high eradication effect on bacterial biofilms [190]. Therefore, CO therapy has been also combined with phototherapy for antibacterial treatment. Cai et al. developed a photodynamic treatment-driven CO-controlled delivery system (Ce6&CO@FADP) by the chemical conjugation of Ce6 and physical encapsulation of CORM-401 into peptide dendrimer nanogels [191]. The schematic illustration of the preparation of Ce6&CO@FADP can be found in Figure 13B. The *In vitro* antibacterial effect shows that the survival rate of the Ce6&CO@FADP-treated *E. coli* was only 0.5%, which is significantly lower than that achieved by other treatment groups. Therefore, the combination of CO and photodynamic treatment has a good prospect in bacterial infection treatment.

**Multiple combination therapy**

Because multi-channel antibacterial therapy has good antibacterial effects with the continuous development of nanomedicine, multiple combination therapy strategies have been developed and used in bacterial infection treatment in recent years. The heat induced by photothermal treatment can not only increase the ambient temperature of tissue to achieve antimicrobial efficacy but also increase blood flow and oxygen supply to enhance the $^1\text{O}_2$ generation of photodynamic treatment, and so the multiple treatment strategy combined with photodynamic and photothermal therapy achieves a better antibacterial effect than that achieved by the individual therapies alone. For example, Zhang et al. [135] utilized the intrinsic antibacterial action of chitosan oligosaccharide (COS) and the photodynamic and photothermal properties of graphene quantum dots (GQDs) to prepare COS functionalized GQDs (GQDs-COS) that exhibit multiple synergetic antibacterial activities, and could interact with negatively charged bacterial surfaces via electrostatic attraction. Additionally, under 450 nm light irradiation, GQDs-COS could simultaneously kill
Gram-positive and Gram-negative bacteria via three types of antibacterial activity (photodynamic, photothermal and chemical therapy). In addition, as wound repair is very important in local bacterial infection treatment, Zhou et al. [192] reported hybrid hollow core–shell heterostructured AuAgCu$_2$O NSs, including a hollow gold–silver (AuAg) core and Cu$_2$O shell. The AuAgCu$_2$O NSs have been used as a photothermal therapeutic agent for cutaneous chronic wound and nonhealing keratitis with drug resistant bacterial infection. As shown in Figure 14, under NIR irradiation, the silver ion could be released from the hollow AuAg core and cooperate with the photothermal treatment of Au to eradicate MDR bacteria, including extended-spectrum β-lactamase *Escherichia coli* and MRSA. In addition, wound-healing effects could be boosted because of the rapid endothelial cell angiogenesis and fibroblast cell migration achieved by the copper ion released from the Cu$_2$O shell.

**Conclusions and perspectives**

Intensive efforts have been devoted to the development of phototherapy-based antibacterial nanomaterials to deal with bacterial infections. In this review, we first summarized recent commonly used phototherapy agents, including organic phototherapy agents (e.g., small molecule photosensitizers and loaded-photosensitizer nanoparticles) and inorganic phototherapy agents (metal nanomaterial, upconversion nanoparticles and quantum dots). Then the advantages and disadvantages of single mode photothermal treatment were analyzed by introducing their specific situations. Moreover, to address the limitations of photothermal therapy in bacterial infection treatment, many combination therapy strategies have emerged, such as combination with chemotherapy, combination with chemodynamic therapy, combination with gas therapy and multiple combination therapy. In particular, combination with chemodynamic therapy and gas therapy can solve the problem of MDR resistance very well due to the lack of antibiotics used in the combination therapy system.

In the future, only very biocompatible antibacterial nanomaterials are promising for potential clinical application. Therefore, although these combined strategies have
shown promising results in the treatment of infectious diseases, many important 
fundamental issues of nanomaterials must be studied in depth and fully elaborated, 
including the synergistic action mechanisms, accumulation of lesions, metabolic 
pathways and toxicities toward vital organs. More importantly, before designing 
nanomedicine, it is necessary to consider how to use them in patients (e.g., 
intravenous injection, oral, subcutaneous injection or spray). Additionally, for deep 
tissue infection, phototherapy cannot be used unless the site of infection has been 
identified, which severely limits its clinical use in antibacterial infections treatment. 
Moreover, a consensus has been reached among researchers worldwide that the 
patient survival rate can be greatly increased if the disease is effectively diagnosed 
and treated at the early stage [193, 194]. Based on this investigation, Wang et al. 
reported a magnetic nanosystem combined with photodynamic treatment, which could 
identify bacterial species for early sepsis diagnosis and extracorporeal photodynamic 
blood disinfection [29]. Therefore, designing a phototherapy-based nanoplatfrom with 
integrated diagnosis and treatment abilities is a very promising strategy to address 
bacterial infections and should have good imaging capabilities (e.g., magnetic 
resonance imaging, fluorescence imaging, ultrasound, etc.) at the infected site to 
accurately guide light to the site, to prevent toxicity to normal tissues during the 
phototherapy process.

Acknowledgements

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(Grant NO. 2682019CX76).

Competing Interests

The authors have declared that no competing interest exists.

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**Figures and tables**

![Diagram](image_url)

**Figure 1.** (A) The mechanism of photodynamic treatment or photothermal treatment activity by phototherapy agent. (B) Combination of different therapies with phototherapy (photodynamic treatment and photothermal treatment), including combination with chemotherapy, combination with chemodynamic therapy, combination with gas therapy and multiple combination therapy.
Figure 2. (A) Constituent elements of Ppa-PLGVRG-Van. Ppa: pyropheophorbide-α, signal molecule; PLGVRG: Pro-Leu-Gly-Val-Arg-Gly, an enzyme-responsive peptide linker; Van: vancomycin, a targeting ligand. (B) Illustration of bacterial infection imaging based on an in vivo aggregation strategy[18]. Copyright 2016, Wiley-VCH.
Figure 3. (A) Schematic illustration of preparation of the nanovehicle (gadofullerene nanoparticles, GFNPs) and (B) killing *P. aeruginosa* at infected alveoli by photothermal treatment [22]. Copyright 2019, ACS Publications.
Figure 4. (A) The building process of the vancomycin-resistant staphylococcal infection in a murine model and the photodynamic treatment procedure. (B) Bioluminescence images after the treatments with different strategies. (C) Relative bioluminescence intensities and relative bioluminescence areas after each treatment[23]. Copyright 2017, Wiley-VCH.
Figure 5. Schematic illustration of the main synthetic procedure and coordinated antimicrobial strategy of photodynamic treatment and photothermal treatment [36]. Copyright 2020, ACS Publications.

Figure 6. Schematic illustration of the antibacterial mechanism of glycol chitosan conjugated carboxyl graphene (GCS-CG) [54]. Copyright 2018, Elsevier.
Figure 7. Schematic representation of the photothermal conversion of light to heat and the subsequent antimicrobial mechanism taking place. Top right are scanning electron micrographs of E. coli cells before (left) and after (right) treatment with photothermal nanomaterials [69]. Copyright 2018, Wiley-VCH.
Figure 8. Schematic illustration of antibody-conjugated oval-shaped gold nanoparticles to selectively target and destroy pathogenic bacteria [109]. Copyright 2010, Wiley-VCH.
Figure 9. Schematic illustration of 2D reduced graphene oxide supported Au nanostar nanocomposite (rGO/AuNS) triggered antibacterial photothermal lysis [111]. Copyright 2019, ACS publication.

Figure 10. (A) Synthesis roadmap of carbon quantum dots (CQDs) and their appearance as an aqueous suspension under visible and UV light illumination. (B) Concentration and illumination time dependent photodynamic inactivation studies employing CQDs against S. aureus ATCC-6538 and E. coli 8099 [137]. Copyright 2020, Elsevier.
Figure 12. (A) Synthetic route of polyethylene glycol functionalized molybdenum disulfide nanoflowers (PEG-MoS$_2$ NFs). (B) Relative bacteria viabilities of *E. coli* and *B. subtilis* after incubation with different conditions without or with NIR irradiation [101]. Copyright 2016, ACS Publications.

Figure 13. (A) Synthetic route of ICG-loaded L-arginine conjugate mesoporous polydopamine nanoparticles (AI-MPDA) [28]. Copyright 2018, Wiley-VCH. (B) The schematic illustration for the preparation of Ce6&CO@FADP, FADP: fluorinated amphipilic dendritic peptide [191]. Copyright 2020, ACS publication.
Figure 14. (A) Synthetic route of AuAgCu$_2$O NSs (a hollow gold−silver (AuAg) core and Cu$_2$O shell). (B) Cumulative release amounts of Ag and Cu ions from AuAgCu$_2$O NS hydrogel suspension. (C) Representative macroscopic appearance of MRSA-infected full-thickness dorsal cutaneous incisions on BALB/c mice disposed by diverse treatments[192]. Copyright 2020, ACS publications.

<table>
<thead>
<tr>
<th>Type</th>
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<th>Phototherapy type</th>
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<td>S. aureus</td>
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<td>Photodynamic</td>
<td>MRSA</td>
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<td>[20]</td>
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<td>Ce6</td>
<td>Encapsulation</td>
<td>Photodynamic treatment and photothermal treatment</td>
<td>MRSA [21]</td>
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<td>------------------------</td>
<td>-----</td>
<td>---------------</td>
<td>-----------------------------------------------</td>
<td>-----------</td>
<td></td>
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<td>ICG</td>
<td>Encapsulation</td>
<td>Photodynamic treatment</td>
<td>P. aeruginosa</td>
<td>[22]</td>
<td></td>
</tr>
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<td>PpIX</td>
<td>Encapsulation</td>
<td>Photodynamic treatment</td>
<td>S. aureus</td>
<td>[23]</td>
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<td>MRSA [24-26]</td>
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<td>Encapsulation</td>
<td>Photodynamic treatment</td>
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<td>Mesoporous Polydopamine nanoparticles</td>
<td>ICG</td>
<td>Encapsulation</td>
<td>Photodynamic treatment and photothermal treatment</td>
<td>S. aureus [28]</td>
<td></td>
</tr>
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<td>F&lt;sub&gt;3&lt;/sub&gt;O&lt;sub&gt;4&lt;/sub&gt; nanoparticles</td>
<td>Ce6</td>
<td>Conjugate</td>
<td>Photodynamic treatment</td>
<td>S. aureus [29]</td>
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<td>S. aureus</td>
<td>[30]</td>
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<td>S. aureus</td>
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<td>S. aureus</td>
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<td>E. coli</td>
<td>[33]</td>
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<td>E. coli</td>
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<td>E. coli</td>
<td>[35]</td>
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<td>Photodynamic treatment and photothermal treatment</td>
<td>MRSA [36]</td>
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<td>MRSA [37]</td>
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### Table 2. Comparison of photothermal carbon nanomaterials for antibacterial activities

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<td><em>E. coli</em> and <em>S. aureus</em></td>
<td>[56]</td>
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<td><em>E. coli</em> and <em>S. aureus</em></td>
<td>[57]</td>
</tr>
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<td>AA@GS@HA–MNPs</td>
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<td><em>E. coli</em> and <em>S. aureus</em></td>
<td>[58]</td>
</tr>
<tr>
<td>GO–IO–CS</td>
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<td><em>E. coli</em> and <em>S. aureus</em></td>
<td>[59]</td>
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<td>Van-rGO</td>
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<td><em>E. coli</em></td>
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<td>[61]</td>
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<td>GAS-Ab-MWNT</td>
<td>Tube</td>
<td>800 nm</td>
<td><em>Planktonic</em> and GAS</td>
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<td>IgG-MWCNT</td>
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<td>MRSA</td>
<td>[63]</td>
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### Table 3. Comparison of photothermal metal nanomaterials for antibacterial activities

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<th>Ref.</th>
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<td>Au</td>
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<td>525 nm</td>
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<tr>
<td>Au@SiO₂</td>
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<td>810 nm</td>
<td><em>E. faecalis</em></td>
<td>[71]</td>
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<tr>
<td>AuNSs</td>
<td>Star</td>
<td>808 nm</td>
<td><em>S. aureus</em></td>
<td>[72]</td>
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<tr>
<td>AuNRs–PVCL gel</td>
<td>Rod</td>
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<td>AMR <em>E. coli</em></td>
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<tr>
<td>AuPd</td>
<td>Sheet</td>
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<td><em>S. aureus</em> and <em>E. coli</em></td>
<td>[74]</td>
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<td>Au@Ag NPs</td>
<td>Sphere</td>
<td>800 nm</td>
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<td>Au–Ag–Au NRs</td>
<td>Rod</td>
<td>785 nm</td>
<td><em>E. coli</em></td>
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<td>Au@PtAg NRs</td>
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<td><em>E. coli</em> and <em>S. aureus</em></td>
<td>[77]</td>
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<td>PEG–Au@Ag NPs</td>
<td>Triangle</td>
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<td>AuNP–N–C</td>
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<td>MRSA</td>
<td>[79]</td>
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<td>Apt@AuNRs</td>
<td>Sphere and rod</td>
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<td><em>E. coli</em></td>
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<td>MRSA</td>
<td>[82]</td>
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<tr>
<td>Tetra@AuNR@TiO₂</td>
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<td>830 nm</td>
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<td>Fe₃O₄–Au</td>
<td>Eggs</td>
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<td><em>A. baumannii</em></td>
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<tr>
<td>Material</td>
<td>Shape</td>
<td>Size</td>
<td>Target Bacteria</td>
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<td>Fe$_3$O$_4$–alumina</td>
<td>Necklace</td>
<td>785 nm</td>
<td>E. coli, S. pyogenes, S. saprophyticus, E. faecalis and E. faecium</td>
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<tr>
<td></td>
<td>Sphere</td>
<td>808 nm</td>
<td>E. coli and S. typhimurium</td>
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<tr>
<td>Fe$_3$C$_2$</td>
<td>Spheroid</td>
<td>808 nm</td>
<td>A. baumannii, E. coli, E. faecalis and S. pyogenes</td>
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<tr>
<td>In$_2$Se$_3$</td>
<td>Sheets</td>
<td>808 nm</td>
<td>S. aureus and E. coli</td>
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<td>CuS</td>
<td>Plate-like</td>
<td>980 nm</td>
<td>S. aureus and E. coli</td>
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<td>CuS–PVP</td>
<td>hexagonal nanoparticles</td>
<td>808 nm</td>
<td>S. aureus</td>
<td></td>
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<tr>
<td>BSA–CuS</td>
<td>Platelike or sphere</td>
<td>980 nm</td>
<td>S. aureus</td>
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<td>Ce6-labeled BSA–CuS</td>
<td>Sphere</td>
<td>1064 nm</td>
<td>S. aureus and E. coli</td>
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<td>LuVO$_4$:Nd$_3$+/Yb$_3$+/Er$_3$+@SiO$_2$@Cu$_3$S</td>
<td>Olivelike</td>
<td>808 nm</td>
<td>S. aureus and E. coli</td>
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<td>PEG–MoS$_2$</td>
<td>Flower-like</td>
<td>808 nm</td>
<td>Ampr E. coli and B. subtilis</td>
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<tr>
<td>CS–Fe$_3$O$_4$–MoS$_2$</td>
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<td>S. aureus and E. coli</td>
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<td>MoS$_2$–BNN6</td>
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<td>S. aureus</td>
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<td>MoS$_2$–penicillin</td>
<td>Sheet</td>
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<tr>
<td>MoO$_3$–x/Ag</td>
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<td>E. faecalis</td>
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<td>Van–LaB$_6$@SiO$_2$/Fe$_3$O$_4$</td>
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<td>S. aureus and E. coli</td>
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[90] E. coli and S. typhimurium
[91] A. baumannii, E. coli, E. faecalis and S. pyogenes
[92] S. aureus and E. coli
[93] S. aureus and E. coli
[94] S. aureus and E. coli
[95] S. aureus
[96-98] E. coli
[99] S. aureus and E. coli
[100] S. aureus and E. coli
[101] Ampr E. coli and B. subtilis
[102] S. aureus and E. coli
[103] S. aureus
[104] S. aureus and E. coli
[105] S. aureus and E. coli
[106] S. aureus and E. coli
[107] E. coli
[108] S. aureus and E. coli
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### Table 4. Comparison of photothermal composite nanomaterials for antibacterial activities

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<th>Ref.</th>
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<td><em>MRSA</em></td>
<td>[114]</td>
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<td><em>E. coli</em>, <em>P. aeruginosa</em> and <em>B. subtilis</em></td>
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<td>GO–Tob@CuS</td>
<td>980 nm</td>
<td><em>E. coli</em> and <em>P. aeruginosa</em></td>
<td>[119]</td>
</tr>
<tr>
<td>Fe₃O₄@GO–QCS</td>
<td>808 nm</td>
<td><em>E. coli</em> and <em>S. aureus</em></td>
<td>[120]</td>
</tr>
<tr>
<td>rGO/AuNS</td>
<td>808 nm</td>
<td><em>E. coli</em> and <em>S. aureus</em></td>
<td>[111]</td>
</tr>
<tr>
<td>rGO/MSN/Ag</td>
<td>808 nm</td>
<td><em>E. coli</em>, <em>P. putida</em> and <em>Rhodococcus</em></td>
<td>[121]</td>
</tr>
<tr>
<td>Ag@rGO–Fe₃O₄–PEI</td>
<td>785 nm</td>
<td><em>E. coli</em></td>
<td>[122]</td>
</tr>
<tr>
<td>rGO–Fe₃O₄–Au–Ag–Au</td>
<td>785 nm</td>
<td><em>E. coli</em></td>
<td>[123]</td>
</tr>
<tr>
<td>Ag/ZnO/rGO</td>
<td>808 nm</td>
<td><em>E. coli</em></td>
<td>[124]</td>
</tr>
<tr>
<td>Fe₃O₄–CNT–PNIPAM</td>
<td>808 nm</td>
<td><em>E. coli</em> and <em>S. aureus</em></td>
<td>[125]</td>
</tr>
<tr>
<td>BP/Au</td>
<td>808 nm</td>
<td><em>E. faecalis</em></td>
<td>[129]</td>
</tr>
</tbody>
</table>

### Table 5. The common toxic and side effects of each type of antibiotics

<table>
<thead>
<tr>
<th>Type</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillins</td>
<td>Pain and allergic reactions</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>Allergic reactions</td>
</tr>
<tr>
<td>Macrolides</td>
<td>Gastrointestinal side effects, temporary auditory impairment and cardiotoxicity</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>Gastrointestinal side effects and nephrotoxicity</td>
</tr>
<tr>
<td>Polymyxins</td>
<td>Nephrotoxicity, allergic reactions and neurotoxicity</td>
</tr>
</tbody>
</table>