Developments in Antibacterial Therapy: Focus on Physical Stimuli Approaches

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At present, various antibacterial therapeutic modalities are available in the clinic. However, due to the rampant abuse of antibiotics over the past few decades and the consequent emergence of innumerable drug-resistant strains of bacteria, it is imperative to develop new and effective antibacterial therapeutic strategies. In recent years, the physical stimuli–based approach to antibacterial therapy has aroused much interest as an alternative to antibiotics and has become a major focus of antibacterial research. In this review, the application of different physical stimuli, including electricity, magnetism, light, ultrasound and thermal stimulation, in antibacterial research is critically examined in order to provide new ideas and directions for the further development of antibacterial therapy in clinical dentistry.

Key words: *acoustics, electricity, magnetism, photodynamics, physical stimulation, research progress, thermal*
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As one of the greatest inventions in the history of human medicine, antibiotics have undoubtedly saved hundreds of millions of lives. However, due to the widespread abuse of antibiotics seen over the past few decades, the increasing emergence of drug-resistant strains of bacteria now poses a serious challenge to human health and the ecological environment[1,2]. In the fields of dentistry and oral health, microbial infection also poses a formidable challenge to both clinicians and patients. The oral environment is a very complex microenvironment in which a variety of microorganisms coexist. In the context of a dental implant repair or orthodontic treatment alike, the therapeutic efficacy is largely dependent on the antibacterial properties of the biomaterials utilised. In oral implantology, bacterial infection is one of the main causes of implant failure and resulting periodontitis. A survey found that 28% to 56% of patients will develop peri-implant inflammation after having their dental implant repaired[3,4], and the initial cause of peri-implant inflammation is usually bacterial infection. Severe periodontitis is one of the most common oral diseases and eventually leads to tooth loss, alveolar bone resorption and even diabetes and other systemic diseases. If not treated in due time, this will undoubtedly affect the patient's quality of life. The initial trigger for periodontitis is often bacterial infection; thus, research

into antibacterial agents is usually the key focus of periodontitis prevention and treatment[5-7]. In recent years, a large number of studies have focused on enhancing the antimicrobial capacity of implant materials through surface modifications such as antibacterial coatings, but very often the long-term antimicrobial effect is poor and unable to meet clinical requirements due to the short half-life of drugs and weak combination of coatings[8,9]. In prosthodontics, commonly used materials for removable dentures include methyl methacrylate, which is conducive to the adhesion and reproduction of bacteria and fungus due to its high hydrocarbon content and thus results in oral infection[10]. Adhesives and filling materials often lead to secondary caries lesions due to microleakage, causing repair failure[11]. Postoperative infection is also the main causative factor of treatment failure in the covering of bone defects. If the antibacterial property of the materials can be effectively improved without changing their structure, the therapeutic effects will be greatly improved[12]. In orthodontic treatment, due to the use of bracket steel wire, plaque is more likely to accumulate in the oral cavity, leading to caries lesions, periodontitis and other diseases. The occurrence of such complications has also posed a major problem to orthodontists. Researchers proposed the idea of designing antibacterial brackets, and successfully validated the effectiveness of some nanomaterials used in such brackets[13,14]. In other oral diseases such as oral cancer, patients are prone to infection due to their poor postoperative immunity. Surgical wounds in the oral environment usually have an infection rate of 18.8% to 100.0%[15]. However, toxic and allergic reactions to antibacterial materials and bacterial tolerance caused by rampant abuse of antibiotics are major clinical challenges[16-18]. Therefore, there is an urgent and dire need for effective and stable antibacterial therapeutic strategies to enable dental clinics to deal with infectious oral pathogens.

At present, antibiotics and antimicrobial agents are the main clinical antibacterial treatment modalities, but these have several disadvantages[19]: abuse or continuous use of antibiotics or bactericidal agents will eventually lead to drug resistance[20-23]; drug diffusion is often limited due to the formation of microbial biofilms, and the concentration of antibiotics or bactericidal agents on the surface cannot be properly controlled[24]; and microbial sediments can react with antimicrobial agents and prevent their diffusion[25,26]. It must be noted that there are currently no effective treatment modalities for typical antibiotic-resistant bacteria such as methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecalis*[27].

In order to reduce drug dependence and achieve effective antibacterial action, minimally invasive treatment modalities with alternative antimicrobial agents and antibiotics have emerged in recent years, each with their own merits. Unlike antimicrobial drugs that need to act and react with a specific target, physical stimuli–based approaches instead generally act on multiple targets by interfering with microbial metabolism and respiration and by destroying microbial structure, lowering the probability of emergence of microbial resistance[28].

The common physical stimuli–based antibacterial therapeutic modalities are mainly classified into five distinct categories: electrical, magnetic, photodynamic, ultrasonic and heat treatments. Among these, photodynamic therapy and electrostimulation are the most utilised techniques and have achieved promising results in antibacterial efficacy, demonstrating great potential to replace conventional antibacterial agents and antibiotics in the future[29,30].

Common physical stimulation techniques and their current research status

Electrical stimulation: introduction and classification of techniques

It is common knowledge that electrons are transmitted through proteins of the respiratory chain, which generates energy to maintain the metabolism and physiological activities of cells. The respiratory chain proteins of eukaryotes are located in the mitochondria, which generate energy, whereas the respiratory chain proteins of prokaryotes such as bacteria are located on the cell membrane surface. Therefore, microorganisms are much more sensitive to external electrical disturbances.

Charged polymer surfaces have been reported to be bactericidal[31]. In tissue engineering applications, based on the characteristics of the electric signal, these can be categorised into direct current stimulation, capacitive stimulation, electromagnetic stimulation and inductive coupling stimulation. Additionally, depending on whether there is an external power supply, they can simply be classified as wired and wireless power. The most basic method of electrical stimulation is direct current and simple direct current can be generated by batteries[32], whereas more complex stimulation can be in the form of unidirectional direct current or bidirectional alternating current[33]. By applying electric fields to generate direct current and alternating current, reactive oxygen species (ROS) such as OH, $^1O_2$ and H_2O_2 can be generated, which kill microorganisms and inhibit

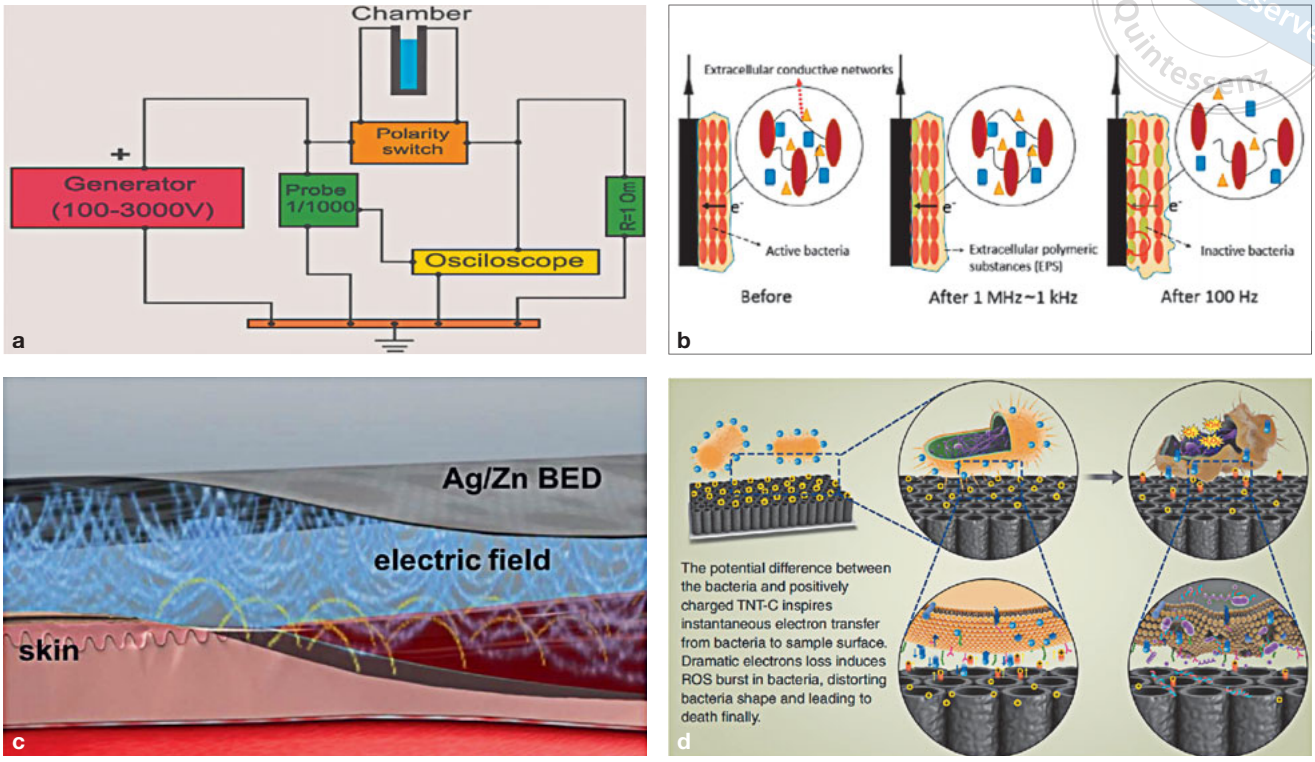

Fig 1 Common types of electrical stimulation to achieve antibacterial effects. **(a)** Different types of external power supply of direct current electric field. Reprinted from Emanuel et al[35] with permission. **(b)** Different types of external power supply of alternating current. Reprinted from Wang et al[36] with permission. (c and d) Different types of electrical stimulation without external power supply after implantation: **(c)** The materials generate spontaneous current. Reprinted from Banerjee et al[38] with permission; **(d)** Piezoelectric materials that can store electricity. Reprinted from Wang et al[41] with permission.

bacterial growth[34]. Emanuel et al[35] changed the density of direct current and found that an increase in current density led to an increase in permeability and volume of P. putida F1, and the bacterial kill rate increased when the current density ranged from 0.02 ± 0.01 to 5.2 ± 0.5 A cm^{-2}. The schematic diagram of the experimental setup is given in Fig 1a[35]. During the process of direct current electrolysis, corrosion on the surface of the metal is usually accelerated, and toxic chemicals may be introduced to the reaction surface. By contrast, with an alternating current, there are periodic changes to the direction of the current that minimise the chemical reaction, particularly under high frequency, which effectively limits the corrosion reaction on the surface of the object and the oxidation–reduction reaction in solution. Wang et al found that high frequency alternating currents ranging from 1 MHz to 1 kHz can only temporarily inhibit the activity of biofilms[36]. However, lower frequency (100 Hz) alternating current treatment resulted in a more persistent decrease in biofilm activity due to current-induced damage to the biofilm and loss of the intercellular electron transport network. A schematic illustration of the underlying mechanisms is presented in Fig 1b[36]. Another method is to build an electroactive material system and apply an electric field or electrochemical reaction on the material itself to generate spontaneous current so that the material exhibits electroactivity[37]. This weak electrical stimulation is biocompatible and usually does not inflict any harm on the human body, but can promote the wound healing process and inhibit the formation of bacterial biofilms. There is no need for an external power supply to achieve the antibacterial effect; therefore, it is known as wireless electroceutical dressing (WED)[38,39]. This type of implant material can attain certain antibacterial properties through physical or chemical modification of its surface to better meet the clinical needs of implantation. The mechanism of these modifications can eventually be applied to confer electroactive properties on selected materials. A schematic illustration of the weak electric field produced by Ag/Zn dressing after contacting the skin is presented in Fig 1c; this physiological electric stimulation could inhibit bioflim formation[38,40]. Figure 1d is a schematic illustration of the antibacterial mech-

anisms of carbon doped TiO_2 nanotubes after charging or discharging; by changing the carbon content, the capacitance of the material could also be changed. The researchers found that the antibacterial efficacy increased as capacitance increased[41].

Applications of electrical stimulation

Food disinfection and sterilisation

The application of electrostimulation is evident everywhere in daily life. Chemical agents such as sodium hypochlorite, chlorine dioxide, hydrogen peroxide, organic acid and ozone are commonly-used disinfectants in the food industry. However, these may be harmful to human health as they can have phototoxic side effects and cause pollution. A new antibacterial method utilising slightly acidic electroylsed water (SAEW) (pH 5.0–6.5; available chlorine concentration 10–30 mg/l) was introduced in Japan several years ago, which is highly acclaimed and has been used up to the present day. The production of electrolytic water is achieved by the electrochemical reaction of a battery with two electrodes. The anode is separated from the cathode and when a current is applied, the ion movement exerts an antibacterial effect[42]. The application of SAEW has minimised the harm and toxicity of Cl_2 and hypochlorite to human health[43]. New electrical stimulation methods such as pulsed high electric field, with short duration, less harmful byproducts and high efficiency, have been widely used to achieve rapid disinfection[44]. Khan found that under the condition of 121 ± 14 V/mm, 300 pulses, 80% to 100% of the bacteria in an area of 50.5 ± 9.9 mm^2 can be eliminated[45]. Also, under the condition of 235 ± 6.1 V/mm, 150 pulses, 80% to 100% of the bacteria in an area of 13.4 ± 0.65 mm^2 can be eliminated, indicating that the efficacy of sterilisation treatment is enhanced with an increase in pulses. Emanuel et al found that when the number of pulses was 200, 2000, 5000 and 10000, at a frequency of 100 Hz and pulse duration of 10 μs or 20 μs, respectively, the current density ranged from 0.02 ± 0.01 Acm^{-2} to 5.2 ± 0.5 Acm^{-2}, and the bacterial mortality increased as current density increased[35].

Water pollution treatment

Water pollution is one of the key problems affecting people's quality of life. Water polluted by pathogens is one of the main transmission routes of diarrhoea and other infectious diseases. However, water treated with ozone, chlorine and other oxidative chemicals may form carcinogenic byproducts and cause health problems[46]. Self-powered nanogenerators have been demonstrated to be low-cost and highly efficient for sterilisation of raw river water without production of any harmful byproducts. The Ag/ZnO nanogenerator prepared by Tian et al, which produced 50 V voltage and 107 V/m nanobrush, can reduce the count of Gram-negative bacteria from 106 colony-forming units (CFU)/ml to 0 within 30 seconds, and could still exert an effective antibacterial effect 20 minutes after the generator was stopped[47].

Biological dressing

A weak electric field is often present in biological tissues, and piezoelectric materials have been utilised to fabricate piezoelectric composite material systems, which can produce a weak electric field by polarisation or deformation. Electrical stimulation in the physiological range can exert not only antibacterial effects but also pro-osteogenic effects, and is therefore widely used in biomaterials[48,49]. Piezoelectric materials have been used as an electroactive dressing for skin wounds that inhibits biofilm formation and promotes wound healing, and can also be used to fabricate scaffolds or implant materials in tissue engineering. They are widely used for the prevention or treatment of infection in tissue defects, which may delay wound healing during the process of repair surgery and material implantation[40,50]. It is reported that the WED fabricated with Ag and Zn could produce a 1-V weak electric field when in contact with the wound, which could prevent bacteria from accumulating in the contacted wound within 2 hours and destroy the formed biofilm 7 days after the wound appeared. However, this weak electric field cannot damage normal cells, but can increase the migration of keratinocytes and promote wound healing[38,40]. Generally speaking, electrical stimulation is widely utilised in food safety, water sterilisation and bioengineering applications. With further advancements in material technology, increasing attention will be placed on biological dressing.

Research status

At present, there is some understanding of the antibacterial effects of electrical stimuli. Dehghani et al stimulated microrganisms with low-frequency alternating current and found that the antibacterial effects correlated with the current parameters[51]. Electrical stimulation can affect the adenosine triphosphate (ATP) activity and bacterial morphology, and modulate the metabolic activity of bacteria. A real-time monitoring and processing platform for biofilm formation on the surface of 3D biomed-

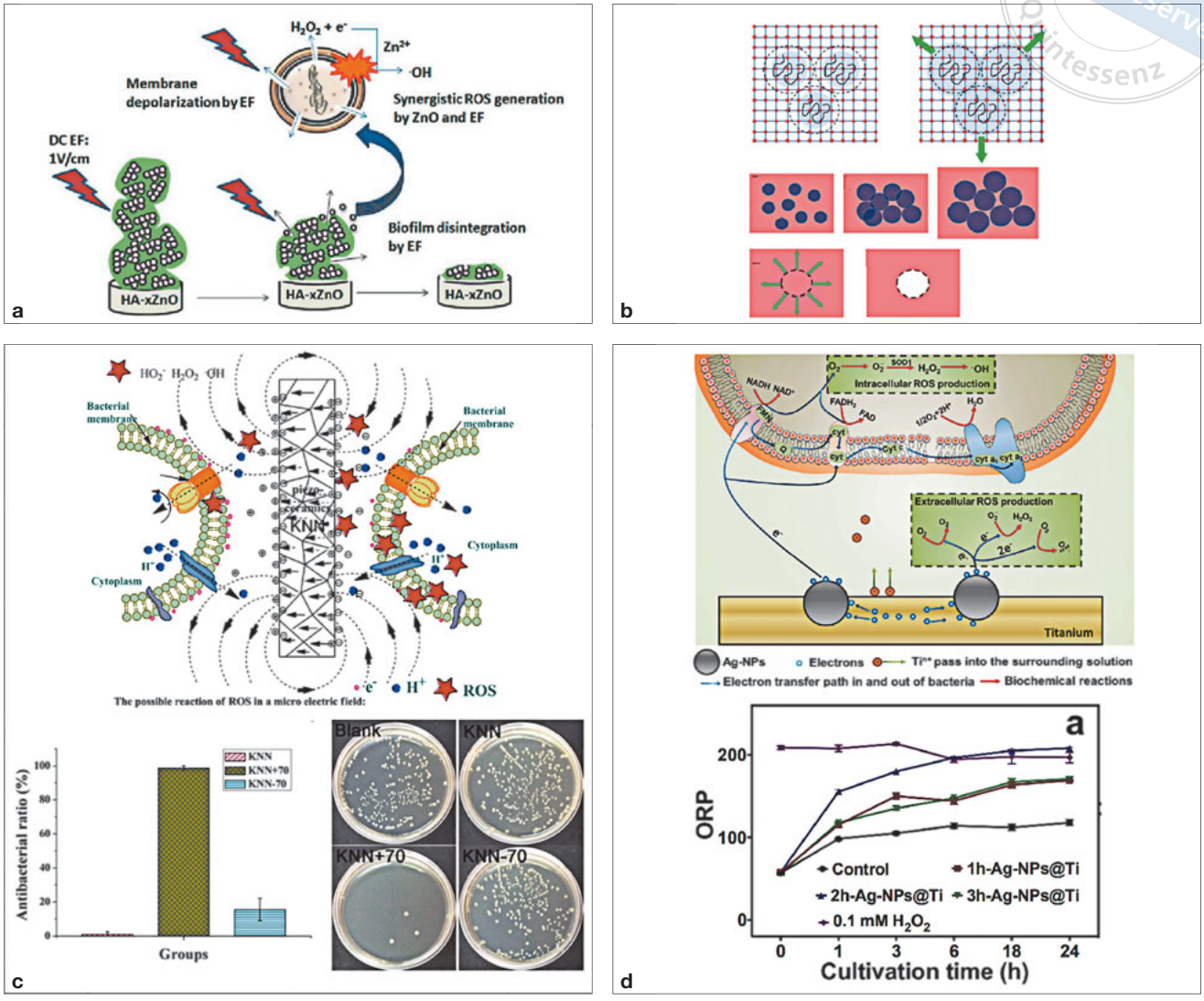

Fig 2 Mechanisms of the antibacterial effects of electrical stimulation. **(a)** The antibiofilm effect of direct current electric field. Reprinted from Boda et al[50] with permission. **(b)** Rupture of the peptidoglycan matrix of bacteria. Reprinted from Rauch and Leigh[53] with permission. **(c)** Mechanisms of the antibacterial effects of one type of piezoelectric material. Reprinted from Tan et al[48] with permission. **(d)** Mechanism by which the piezoelectric material exerts antibacterial effects through generation of spontaneous current. Reprinted from Wang et al[54] with permission.

ical devices was established by Huiszoon et al[52]. Biofilm growth was evaluated by impedance monitoring at 100 Hz alternating current and 50 mV signal amplitude. The results showed that the impedance decreased by 30% in 24 hours, indicating that the biofilm of *Escherichia coli* (*E. coli*) was formed on the surface. The biofilm could be removed by applying a bioelectric effect, resulting in a 12% increase of impedance. Barki et al established a pig chronic wound infection model with multiple bacterial biofilms[40]. They provided electrical stimulation through an electrified dressing and found that a weak electric field could inhibit the formation of biofilms due to the increased expression of multiple virulence factor regulators (MvfR), rhlR and lasR genes, and the silencing of miR-9 and E-cadherin of Pseudomonas aeruginosa. This could also mitigate inflammation caused by the biofilm. In summary, a strong electric field can cause bacterial membrane perforation or produce reactive oxygen, directly destroying the structure of bacteria, resulting in leakage of the intracellular contents of the bacteria and direct destruction or removal of the biofilm. Boda et al[50] used a low-intensity direct current electric field (1 V/cm) to inhibit *Staphylococcus aureus* infection. They found that the live bacteria rate decreased by 60% in 12 hours, and the level of ROS saw a 3.5-fold increase in 18 hours. Under the synergistic effects of electric field and

ZnO, the bacteria were killed by the production of ROS (Fig 2a)[50]. As illustrated in Fig 2b, Rauch et al found that when the electric field was applied to bacteria, stress was generated between teichoic acids, which constitute the bacterial cell wall[53]. When it reached the critical value, the stress broke the wall and led to the formation of pores. However, the mechanisms of weak electric field stimulation are still unclear, and there are few in-depth studies in this field. Electrical stimulation of piezoelectric ceramics can inhibit the formation of bacterial biofilms, generate ROS through energy production from electron transfer, trigger the bacterial oxidative stress response and destroy bacterial morphology and structure[48], as shown in Fig 2c. It has been reported that electron transfer between Ag nanoparticles and Ti substrate could disrupt the respiratory chain on the bacterial cell membrane and interfere with bacterial metabolism[54], as shown in Fig 2d. However, the specific in-depth mechanisms of expression are unclear, but it is obvious that electrical stimulation has antibacterial effects; this has been confirmed by many studies[38,41,48,49,54]. At present, pulse electroporation is a popular research direction because of its high efficiency and absence of harmful byproducts. However, the energy cost of pulse power is rather high, which limits its application. The self-cycle generator does not need an external power source and has the potential to achieve highly efficient and sustainable antibacterial effects by relying on its own electrical energy storage cycle system. In bioengineering, multifunctional WED is a promising direction for future development.

Significance

With regard to scientific significance, the behaviour of bacteria can be modified according to the surface charge and electrical properties of materials, with different types of bacterial response being elicited on different materials[55]. This is helpful for further studies of bacterial activity in inhibition or proliferation, as well as providing cues for the development of new biomaterials and therapeutic modalities. From an application perspective, electrical stimulation has been widely used in the food and water pollution treatment industries. The modulation of the physiological electrical microenvironment has provided a new direction for the prevention and treatment of infection, which has important clinical significance in the prevention of postimplant infection within the oral cavity, repair of bone defects, treatment of chronic skin wounds and prevention of infection after various major surgeries.

Magnetic sterilisation: introduction and classification of techniques

Magnetic sterilisation involves sterilisation by magnetic field and is widely utilised in food processing. Under the application of certain magnetic field strengths, food can be sterilised at room temperature. This type of sterilisation method does not require heating and has broad-spectrum antimicrobial effects. After treatment, the flavour and quality of food are usually unaffected, so it is widely used in the food industry. In recent years, magnetic field sterilisation has attracted much attention because it negates the requirement for heating[56]. Compared with other sterilisation methods, magnetic field sterilisation has many advantages, such as controllable operation, low costs and strong, broad sterilisation effects. At present, this research field can be broadly divided into static magnetic fields (SMFs) and pulsed magnetic fields (PMFs). An SMF is a constant magnetic field applied on bacteria that does not change with time. PMF sterilisation, which is inspired by pulsed electric field (PEF) sterilisation, is a new sterilisation technology without thermal effects, that involves the application of an intermittent magnetic field on bacteria with changing frequency[57]. The crest and trough of the PMF can be adjusted according to different needs.

Applications of magnetic sterilisation

SMFs

The application of SMFs in sewage treatment and sludge management has been reported, and its biological effects in water treatment have also been investigated[58]. Bacteria are affected by induced current within a magnetic field. When the magnetic field strength increases to a certain extent, it produces a certain intensity of induced current that can denature bacterial proteins and cause structural damage that achieves the sterilisation effect. Another mechanism of the sterilisation effect is that the magnetic field affects the adhesion of bacteria. Mhandi et al exposed *E. coli* adhering to indium tin oxide (ITO) and glass plate to horizontal and vertical magnetic fields with an intensity of 0.5 T[59]. It was found that the direction of bacteria adhering to the magnetic field was related to the direction of the magnetic field and the type of material surface. A horizontal magnetic field could inhibit the directional adhesion of *E. coli*. Bajpai et al placed Gram-positive bacteria (*Staphylococcus epidermidis*) and Gram-negative bacteria in a medium static magnetic field (100 mt) to study the adhesion and growth behav-

iour of bacteria[60], as shown in Fig 3a, and to investigate the antibacterial properties with an external magnetic field. It was found that an electromagnetic field can inhibit the growth of bacteria, increase the permeability of the bacterial inner membrane and damage the bacterial exterior membrane. In addition, the antibacterial effect on *Staphylococcus epidermidis* is not as good as that on *E. coli*. Ktiri et al reported that exposure to SMFs can lead to changes in microbial metabolism[61]. Under SMFs (250 mt)[61], the growth and viability of *Saccharomyces cerevisiae* decreased after 6 hours of treatment, and the number of CFU also significantly decreased. In addition, the antioxidant enzyme activity increased. The results showed that application of a certain magnetic field strength can induce oxidative stress in microorganisms. Currently, there are few research studies on the mechanisms of the antibacterial effects of magnetic fields. A popular hypothesis is that charged or magnetic particles in microorganisms are affected by the Lorentz magnetic force, which directly affects microorganisms' normal physiological activities. For example, applied magnetic fields can perturb some enzymes with metal groups, which can lead to macromolecular denaturation and inactivation.

PMFs

The sterilisation effect of PMFs is similar to that of PEFs, except that direct contact between the electrode and sterilisation material is avoided and the operation is relatively simpler. A schematic diagram of bacteria being exposed to a PMF is shown as Fig 3b[62]. Lin et al[62] found that PMFs could increase cell membrane permeability, decrease ATP activity and inhibit bacterial DNA synthesis. PMF sterilisation can reduce the number of bacteria by two orders of magnitude in 1 μs. Due to its short duration and thorough sterilisation, PMF is widely used in water treatment, as well as in the food and beverage industries. Moore et al found that *E. coli* at a titre of 100/ml was inactivated when exposed to an oscillating magnetic field with intensity of 0.15 T and frequency of 0.05 Hz[63]. When they used a PMF with intensity of 12 T and frequency of 6000 Hz to treat *Streptococcus thermophilus* in milk, the number of *Streptococcus thermophilus* was significantly reduced. Khokhlova et al investigated the effects of SMFs and alternating PMFs on the activity of microbial amylase[64]. The results showed that PMFs can directly or indirectly affect the activity of microbial amylase, but the mechanism is unclear, and the antibacterial effects of magnetic fields are influenced by various factors such as microbial species, types of magnetic field and direction. The mechanisms of PMF sterilisation are complex for various reasons including induced current effect of the magnetic field, Lorentz magnetic force, oscillation effect, ionisation effect and free radical effects of microorganisms under a magnetic field. Further research is required to explore the mechanisms of magnetic field sterilisation.

Magnetite nanoparticles

Utilising magnetic nanoparticles is another strategy in the field of antibacterial research. The most common artificial magnetic nanoparticles are based on Fe_3O_4 (magnetite). Pure magnetic nanoparticles do not have antibacterial properties, but are often used as a carrier of antibacterial materials or drugs due to their superparamagnetism, which can achieve high-efficiency sterilisation of targeted bacteria. In recent years, however, much research interest has been focused on magnetosomes, which are magnetic particles wrapped by membranes, with a length of 35 to 120 nm. The chemical composition is mainly magnetite (Fe_3O_4), with high chemical purity, and they are usually in the form of fine and uniform particles, which is far better than artificial nanoparticles. These unique advantages make magnetosomes of special interest for their application in drug delivery and anti-infection treatment[65,66]. Tao et al found that use of directional magnetic nanocrystals can kill *Staphylococcus aureus*[67] (Fig 3c). Magnetotactic bacteria can synthesise magnetic nanocrystals in vivo, which can generate heat when placed in a variable magnetic field. Tao et al[67] utilised magnetic fields to guide magnetotactic bacteria into the depths of infected tissues, which can then exert a therapeutic effect by killing bacteria through heat. In another study, Chen et al prepared a device to generate a low thermal oscillating magnetic field and evaluated the killing effects of magnetotactic bacteria MO-1 on *Staphylococcus aureus*[68]. They found that *Staphylococcus aureus* could be killed when it adhered to MO-1 under the effect of an applied magnetic field. When the adhesion rate increased, so too did the sterilisation rate. Further analysis showed that MO-1 produced a mechanical force of around 8 KPa under an applied magnetic field, which acted on *Staphylococcus aureus* and caused bacterial death. This research shows that the magnetic particle targeting treatment of infected tissues can significantly improve the curative effects of magnetic hyperthermia and effectively reduce unacceptable heating of healthy tissue. It is a novel treatment strategy to kill pathogens which has shown much promise.

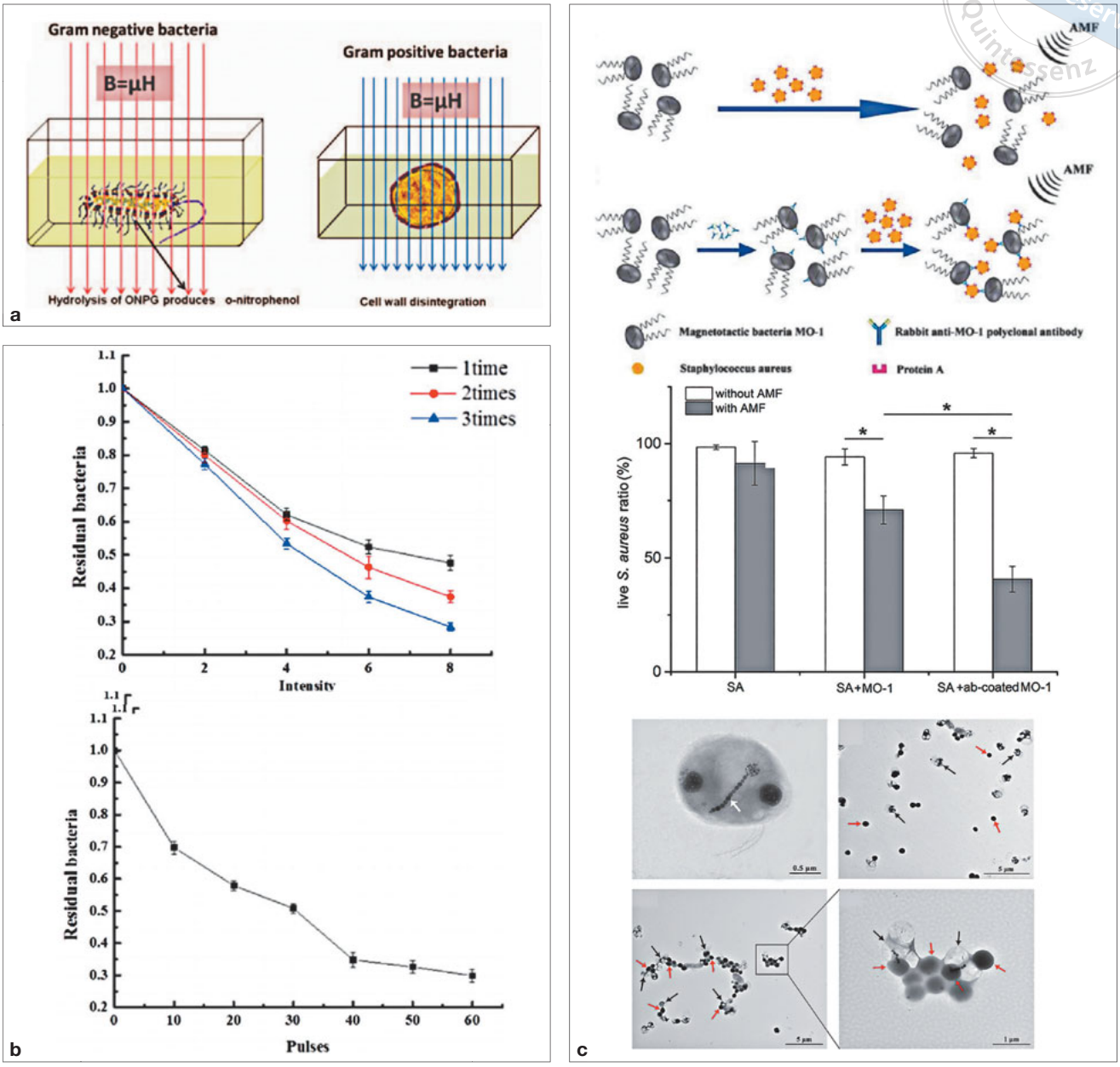

Fig 3 Three common types of bacteria exposed to magnetic field. **(a)** Schematic illustration of bacterial cell membrane disintegration upon exposure to SMF. Reprinted from Bajpai et al[60] with permission. **(b)** Schematic illustration of the disintegration of *E. coli* exposed to PMF. Reprinted from Lin et al[62] with permission. **(c)** Schematic diagram of magnetic thermotherapy against *Staphylococcus aureus* mediated by magnetotactic bacteria. Reprinted from Chen et al[67] with permission.

Light stimulation: introduction and classification of techniques

The most widely used forms of light stimulation are ultraviolet (UV) sterilisation and antibacterial photodynamic therapy (APDT). UV light is a broad term that encompasses electromagnetic radiation with wavelengths ranging from 10 to 400 nm, with those between 250 and 260 nm having the strongest germicidal effect and being commonly used for medical disinfection. UV light can directly inhibit DNA replication and growth of microorganisms, resulting in the destruction of growing or regenerating cells, thereby achieving the effects of sterilisation and disinfection. However, long-term UV radiation can also penetrate host cells, causing irreversible effects on the human body and even resulting in con-

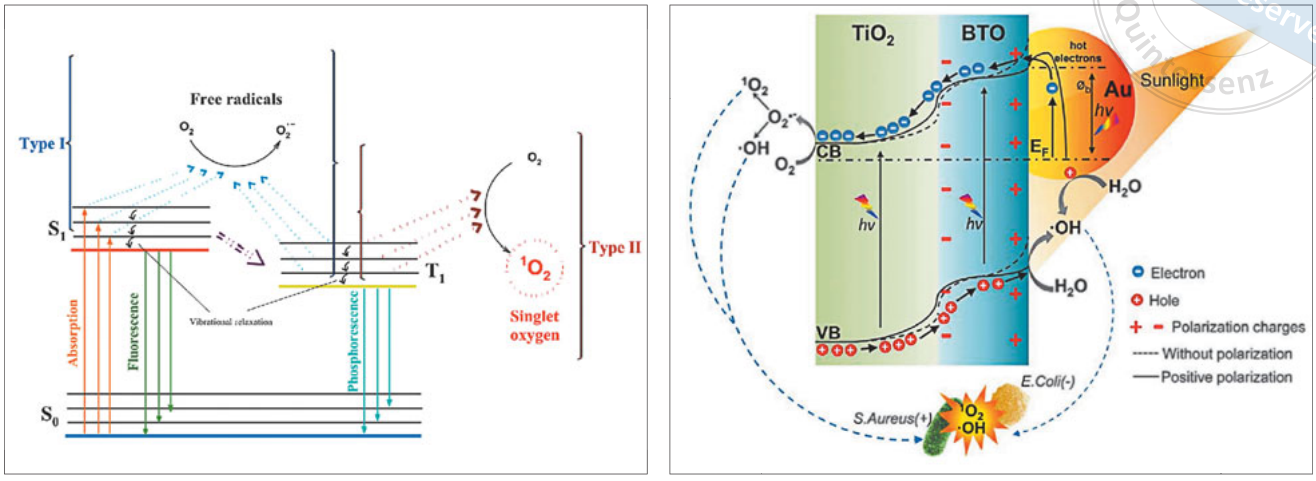

Fig 4 Antibacterial mechanisms of photodynamic therapy. **(a)** Schematic illustration of a typical photodynamic reaction. Reprinted from Sobotta et al[71] with permission. **(b)** Photodynamic antibacterial mechanism. Reprinted from Yu et al[2] with permission.

junctivitis, keratitis and skin cancer. Thus, UV irradiation is rarely used directly on the human body. Photodynamic therapy is composed of light stimulation, photosensitiser (or nontoxic excimer) and oxygen. Under light stimulation, photosensitiser transfers energy and then changes from the ground state to the excited state. This is followed by a series of physical and chemical reactions that produces singlet oxygen or superoxide and changes the morphology of microorganisms, eventually leading to cell damage and necrosis[69]. Phototherapy originated in ancient Greece, Egypt and India, but has not been well developed. In the 20th century, Danish physicist Niels Finsen successfully proved that phototherapy can treat lupus vulgaris[70], which gradually led to the application of phototherapy in clinical practice.

Mechanisms of APDT to kill bacteria

The mechanism of APDT involves converting light energy into chemical energy. Photosensitiser is the intermediate platform of energy conversion. It absorbs a quantum dot of light that changes its structure from the S0 to S1 state. The S1 state is an excited state, active but short-lived. This state can be further reconstituted into the trilinear state T1 through electronic dislocation. The T1 state then reacts with the substrate directly to generate free radicals. Free radicals and oxygen electron transfer generate free radical ions, which are in turn converted into hydroxyl radicals; this is called the type I process. The T1 state reacts with the ground state oxygen to form singlet oxygen, which exerts harmful effects on microorganisms. It can destroy the microbial cell membrane and increase membrane permeability. This is the type II process of the mechanism of APDT[71-73], as shown in Fig 4a. Yu et al found that when TiO_2/$BaTiO_3$/Au nanomaterials were exposed to light, the electrons of gold nanoparticles transferred to $BaTiO_3$, then to TiO_2, which improved the conversion rate of light energy and produced active oxygen species and free radicals, thus killing bacteria, as shown in Fig 4b[2].

Classification and current research status of common photosensitisers

First-generation photosensitisers: haematoporphyrin derivatives

Porphyrins are a type of aromatic heterocyclic compound that widely occur in nature. Haematoporphyrin derivatives (HPD), the first-generation photosensitisers, have achieved remarkable therapeutic effects in the clinic and have been successfully used in the treatment of acne and fungal infections[74]. It was reported that 10 μm haematoporphyrin monomethyl ether (HMME) decreased the titre of live *Candida albicans* by a magnitude of ≈ 107 upon exposure to light, as shown in Fig 5a[75]. However, haematoporphyrins have some obvious disadvantages, such as short absorption wavelength, poor tissue permeability and slow metabolism, which can easily induce phototoxic side effects and require avoidance of light for a long duration after treatment. This is highly inconvenient to patients and also limits their scope of usage; thus, new types of photosensitisers need to be developed.

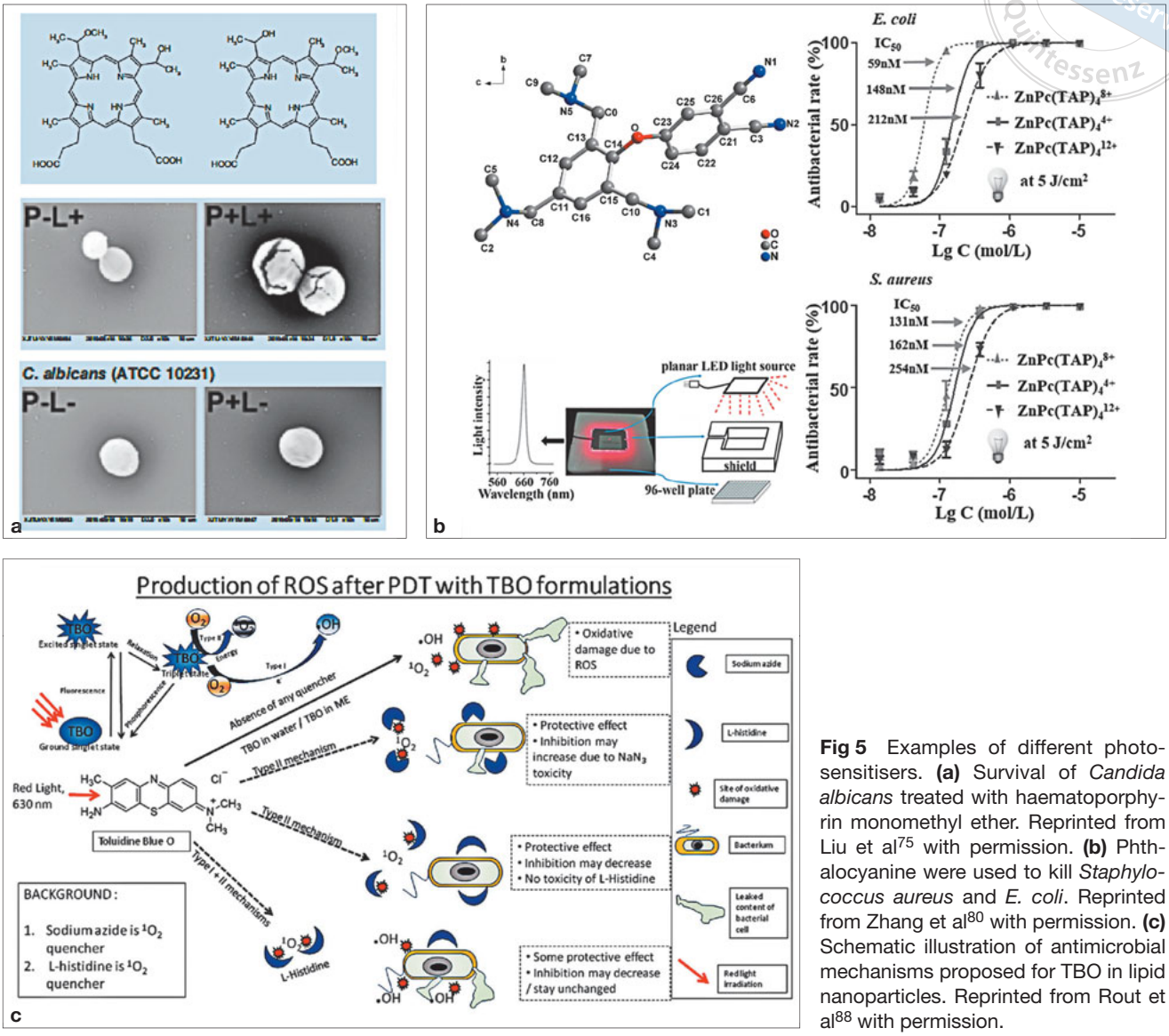

Fig 5 Examples of different photosensitisers. **(a)** Survival of *Candida albicans* treated with haematoporphyrin monomethyl ether. Reprinted from Liu et al[75] with permission. **(b)** Phthalocyanine were used to kill *Staphylococcus aureus* and *E. coli*. Reprinted from Zhang et al[80] with permission. **(c)** Schematic illustration of antimicrobial mechanisms proposed for TBO in lipid nanoparticles. Reprinted from Rout et al[88] with permission.

Second-generation photosensitisers: porphyrin derivatives, phthalocyanine derivatives and porphine derivatives

1. Porphyrin derivatives

The parent structure of porphyrin and its derivatives is porphine. Battistia et al used *Helicobacter pylori* as the target and found that the bacteria that can accumulate endogenous porphyrin were inactivated under light[76]. Liu et al reported that HMME under light stimulation can significantly inhibit the growth activity of *Candida albicans*[77], destroy its DNA and inactivate it. Generally speaking, second-generation porphyrins are optimised on the basis of the first generation and have a wider absorption spectrum, better applicability, clearer structure and, most importantly, stronger targeting.

2. Phthalocyanine derivatives

Phthalocyanine is a chemical compound with very stable chemical properties. It can sensitise some oxidation reactions after being excited by photons of appropriate wavelengths. Its structure is similar to that of haematoporphyrins. Compared with porphyrins, phthalocyanine displays a red shift of the maximum absorption wavelength and has a wider range of applications. It has a single structure that is easy to modify into many variable structures. It can form complexes with metals, which have good photocatalytic properties. Zinc phthalocyanine and aluminium phthalocyanine are chemical compounds of great interest[78], which are highly effective on Gram-negative and Gram-positive bacteria[79]. Cation-modified metal phthalocyanine compounds have good applicability, biocompatibility and strong penetration

and can increase hydrophilicity, which has attracted much research interest[80], as shown in Fig 5b. However, there are still some shortcomings to the clinical applications of phthalocyanine. One of the main research directions is to design a type of phthalocyanine that can be used for precise targeting of photodynamic therapy and reduce damage to healthy host tissues. Huang et al synthesised layered double hydroxides (LDH)–zinc phthalocyanine nanocomposites by introducing pH targeting factors[81], while Liu et al combined the targeting group polypeptides with photosensitisers, greatly improving their specificity and efficacy[75].

3. Porphyrin derivatives

Porphine is the parent structure of porphyrins. Phytochlorine, bacterial porphine and chlorophyll are the most common derivatives. In recent years, porphines have become a major research focus due to their high singlet oxygen output and ideal spectrum. Dihydroporphyrins synthesised from chlorophyll-a are one of the most promising photosensitisers[82]. The chlorophyll-a alkyl derivatives synthesised by Pandey et al have shown good activity; on this basis, Pandey et al expanded the absorption spectrum and improved the light utilisation rate[83]. Moreover, due to the introduction of ethoxy, they increased the lipophilicity of photosensitisers and made adjustments to obtain moderate amphiphilicity. Chlorin E6 (CE6) is a degradation product of chlorophyll that is refined and modified from natural chlorophyll. It is a new type of photosensitiser with excellent performance. It has many advantages such as clear molecular structure, large absorption coefficient within the infrared region, good photodynamic reaction and negligible side effects, and is therefore one of the ideal materials to be a photosensitiser.

Third-generation photosensitisers: nanoparticles

Although the properties of second-generation photosensitisers are already rather good, there are still disadvantages such as the lack of specific targeting in clinical application. Thus, researchers have introduced targeting groups to the second generation of photosensitisers to form the third generation. The most common targeting groups are nanoparticles, peptides, monoclonal antibodies, pH targeting factors, polysaccharide targeting factors and subcellular organ targeting factors[84-87]. Rout et al utilised lipid nanoparticle–encapsulated toluidine blue O (TBO) and found that the added nanoparticles greatly increased the production of free radicals during APDT, which destroyed the structure of bacteria and resulted in exudation of cellular contents and DNA damage (Fig 5c)[88]. However, nanoparticles have been given the most attention by researchers due to their capacity for increasing ROS production, enhancing targeted therapy and increasing water solubility and multifunctional therapy[89]. Nanomaterials commonly used in APDT include fullerene, graphene, carbon nanotubes, titanium dioxide and gold and silver nanoparticles. Fortner et al pointed out that nanofullerenes at concentrations as low as 0.4 mg/l can inhibit the growth of *Bacillus subtilis* and *E. coli*[90]. Wang et al utilised titanium dioxide plates as substrate, added barium titanate and gold nanoparticles[2] and exposed these to light stimulation, and observed effective inhibition of *E. coli* and *Staphylococcus aureus* growth, which in turn promoted wound healing in infected tissues. Ristic et al synthesised graphene electronic quantity points by an electrochemical synthesis method[91], which can produce ROS under stimulation with 470 nm light. It was demonstrated to be effective against methicillin-resistant *Staphylococcus aureus* and *E. coli*, thus indicating the potential of graphene nanomaterials in APDT. The diameter and surface charge of nanoparticles are the two key parameters that influence their antibacterial effects. On one hand, nanoparticles are small in scale and can easily pass through the membrane, which can increase the uptake of photosensitisers by microorganisms and promote the bactericidal effect of photosensitisers. On the other hand, through their surface modification, nanoparticles exhibit more specific targeting in bacterial recognition and reduce phototoxicity to the human body. At present, however, research in this field is still superficial and the mechanisms of the antibacterial effects of nanomaterials are unclear and still under investigation, but the potential of nanotechnology in APDT cannot be ignored.

Prospects

Compared with surgery or radiotherapy, APDT has the advantages of reducing long-term reinfection rates, having minimal side effects and not aggravating other conditions. Extensive research on phototherapy has led to an accumulated database for the development of new technologies. Phototherapy is highly effective for the treatment of tumours and lesions in the oral cavity and other parts of the body, and is also an increasingly popular treatment for bacterial and fungal infections[92-94]. Generally speaking, APDT is an effective antibacterial technique and although it has not been widely used in the clinic, it will be given more attention with the development of photosensitisers. Nanomaterials can effectively solve the problem of poor targeting by photosensitisers, which is expected to be a major research trajectory

for the development of an ideal photosensitiser in the future. The clinical applications of APDT will gradually become more mature with time[95,96].

Acoustic stimulation: introduction and classification of techniques

Therapeutic ultrasound (TU) can be classified into two categories according to spatial-peak and time-average intensity (ISPTA): low intensity (< 3 W/cm^2) and high intensity (> 5 W/cm^2). The objective of low-intensity treatment is to stimulate biological and physiological responses to injury or to accelerate some reaction processes, whereas the purpose of high-intensity treatment is to selectively destroy tissues. The definition of ultrasonic frequency is very broad. A range between 500 kHz to a few mHz is defined as high frequency, whereas a frequency below several hundred kHz is usually defined as low frequency.

As early as 1928, Harvey et al[97] found that the light of luminescent bacteria exposed to ultrasound was rapidly diminished upon exposure to high-power high-frequency sound waves, excluding other possible influencing factors. When bacteria were exposed to 400000 Hz ultrasound for 30 minutes, it was found that the light of the bacteria disappeared and all of them were killed[97]. This led to an increased amount of research into ultrasound as a sterilisation method. Currently, ultrasonic sterilisation is mainly classified into ultrasonic treatment sterilisation and sonodynamic therapy. O'Leary et al studied the bactericidal effects of dental ultrasonic scaler on the main periodontal pathogens, actinobacteria and *Porphyromonas gingivalis*[98]. They found that ultrasonic debridement and ultrasonic cleaning (frequency < 25 kHz) could effectively remove plaque biofilm. Matteo et al reported that ultrasound can inhibit the formation of biofilms[99]. The combination of antibiotics and ultrasound with an intensity of 0.3 W/cm at 67 kHz significantly enhanced the antibacterial effect, as compared to antibiotics alone. Antanas et al used a high-intensity ultrasonic system to treat bacterial suspension, with ultrasonic power of 300 to 600 W, and at a frequency of 28 kHz[100]. The schematic illustration of this setup is shown in Fig 6. It was found that 600 W had better decontamination effects than 300 W with both Gram-negative and Gram-positive bacteria, as well as viruses.

Mechanisms of ultrasonic antibacterial effects

Many studies have investigated the mechanisms of ultrasonic antibacterial effects. It was reported that ultrasonic antibacterial effects can be attributed mainly to cavitation effects; this refers to the continous expansion and contraction of microbubbles that are forced to oscillate and break under ultrasonic stimulation[101]. This phenomenon in turn generates shear forces, which destroys the structure of bacteria. Furthermore, the energy of microbubbles breaking reacts with water to generate free radicals, which can kill the bacteria[101]. As shown in Fig 7, free radical intermediates are formed inside collapsed cavitation bubbles or in the heated gas–liquid interface, upon ultrasonic treatment in the presence of sonosensitisers. These intermediates can react with dissolved oxygen and form peroxyl radicals, which damage the integral structures of microorganisms[102]. Based on this hypothetical basis of antibacterial mechanism, a number of studies have investigated the use of ultrasonic cavitation. Williams et al found that the combination of gentamicin with ultrasound at a frequency of 70 kHz and intensity of 4.5 W/cm^2 can enhance the bactericidal effect of gentamicin[103] because ultrasound can produce microbubbles and increase the permeability of the bacterial cell membrane, which in turn facilitates the entry of gentamicin into the bacterial cell to exert its bactericidal effects. However, Davison et al proposed that low-frequency low-intensity ultrasound has a positive impact on bacterial adhesion and metabolism[22], because while low-frequency low-intensity ultrasound is insufficient for destroying the structure of bacteria, it can increase the entry of nutrients into the bacteria, thereby enhancing bacterial metabolism. Dong et al subjected methicillin-resistant *Staphylococcus aureus* that formed biofilms to treatment with low-frequency ultrasound and vancomycin[104]. They found that much vaporisation and cavitation gradually occurred after ultrasonic and 37°C heat treatment, which can directly destroy the biofilm. It was confirmed that the combination of ultrasound and vancomycin can significantly reduce the metabolic activity of *Staphylococcus aureus* bacteria within biofilms. Therefore, the combination of ultrasound and antibiotic drugs is a popular topic in current research. High-frequency ultrasound can induce the formation of microbubbles that produce shear force and ROS, resulting in direct destruction of the bacterial membrane wall and promoting the absorption of drugs by bacteria. Low-frequency ultrasound can also destroy biofilms, improve the permeability of the bacterial cell membrane and increase the endocytosis of drugs, so as to exert therapeutic effects.

Sonodynamic antibacterial therapy

Based on ultrasonic stimulation, sonodynamic antibacterial therapy (ASDT) was inspired by APDT. ASDT

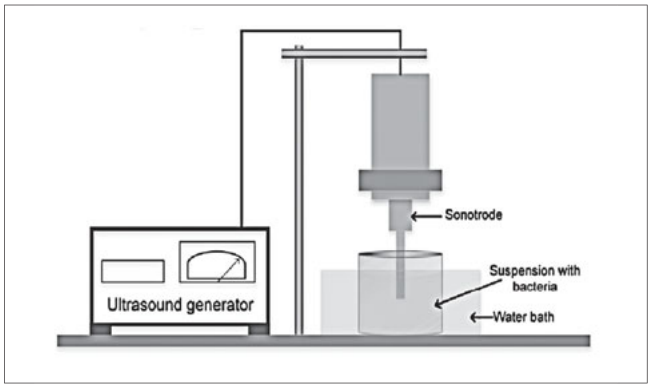

Fig 6 Schematic illustration of microorganism suspension sonication setup. Reprinted from Sarkinas et al[100] with permission.

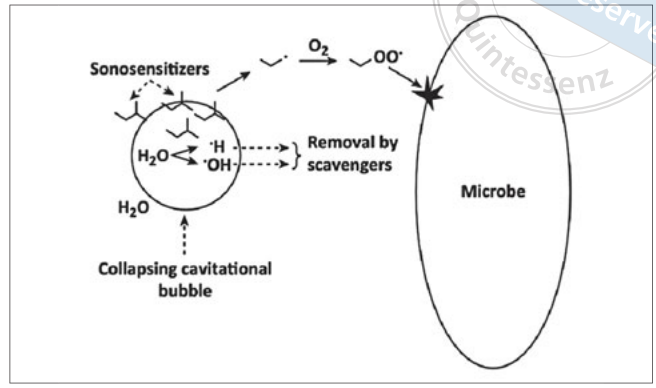

Fig 7 Schematic illustration of the mechanism of sonodynamic antimicrobial chemotherapy. Reprinted from Harris et al[102] with permission.

uses ultrasound to excite the acoustic sensitiser and generate electron transfer. It can produce ROS and kill bacteria upon reacting with water and oxygen. Its principle is similar to that of APDT. The sonosensitisers are also mostly derived from photosensitisers. Compared with light stimulation, ultrasound has better tissue penetrating and targeting capacities, which can reduce damage to healthy host tissues. Zhuang et al found that 50 μg/ml of haematoporphyrin monomethyl ether could kill over 95% of *Staphylococcus aureus* bacteria with ultrasound stimulation[105]. Wang et al found that curcumin is sensitive to acoustic stimulation[106]. Low-intensity ultrasound can activate curcumin, induce the production of ROS and trigger cell death. They combined curcumin with ultrasound stimulation and evaluated antibacterial activity and bacterial unit counts. The results showed that curcumin exhibited obvious inactivation effects on foodborne bacteria, *E. coli* and *Bacillus cereus*. However, like photosensitisers, sonosensitisers also suffer from poor hydrophilicity and stability, aggregation and a lower capacity to produce ROS, which pose a major challenge in the clinic. Figs 8a and 8b show the antibacterial effects of upconversion nanoparticles@Rhodamine B–modified silica layer (UCNP@SiO2-RB)[107] and chlorin e6 respectively[108]. The present authors found that nanomaterials can reduce the cavitation threshold of ultrasound, increase the solubility of acoustic sensors and enhance ROS production. The application of nanomaterials in ASDT involves two major strategies. The first is using the acoustic sensitivity of some nanoparticles. For example, TiO_2 is a type of nanomaterial with good photo activity and sound sensitivity. Rahmat et al showed that ultrasound can activate TiO_2 and greatly increase the production of hydroxyl radicals[109], which amplifies the bactericidal effects. Other nanoparticles such as silicon nanoparticles, zinc oxide nanoparticles and fullerenes also exhibit similiar properties. Second, the combination of nanomaterials and traditional sonosensitisers can effectively improve the physical and chemical properties as well as the targeting capacity of traditional sonosensitisers, thereby enhancing the efficacy of ASDT. Nanoliposomes are commonly utilised as a carrier of acoustic sensitisers. Pang et al developed a novel multidrug resistant (MDR) bacterial theranostic strategy by encapsulating P18 into nanoliposomes (MLP18) and by modifying cholesterol with bacterial targeted maltose, and this was demonstrated to increase ROS production with significantly superior antibacterial activity (Fig 8c)[110].

Future directions and significance

With the widespread and rampant abuse of antibiotics and the increasing emergence of various types of drug-resistant bacteria, ASDT is a new treatment modality based on APDT. However, its clinical application is still relatively narrow. The acoustic sensitiser must be optimised further and the antibacterial mechanisms characterised. The introduction of nanomaterials is a great advancement in the field of APDT and ASDT that can dramatically improve the physical and chemical properties of photosensitisers and sonosensitisers, increase the production of ROS and greatly enhance bactericidal effects. Thus, ASDT has broad prospects for clinical applications, but the field is still in its infancy and needs further research. Additionally, it was found that in clinical settings, neither ASDT nor APDT alone can achieve an ideal effect, but when combined, the antibacterial effects will be far better than with either technique alone[107]. As such, multifunctional nanomaterials and multimodal antibacterial therapy need to be studied further.

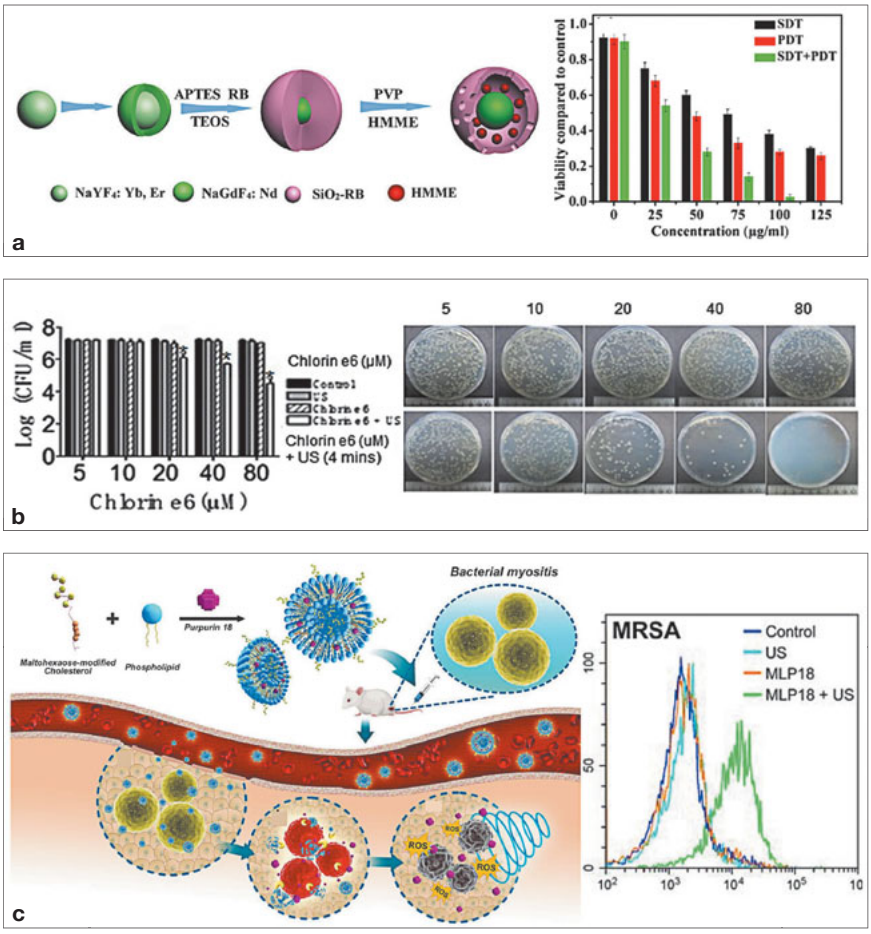

Fig 8 Antibacterial effects of sonodynamic therapy. **(a)** UCNP@SiO2-RB combine photodynamic and sonodynamic therapy for effective killing of bacteria. Reprinted from Xu et al[107] with permission. **(b)** Antibacterial activity of chlorin e6 as a sound sensitive agent. Reprinted from Xu et al[108] with permission. **(c)** Schematic illustration of nanoliposomes for sonodynamic antibacterial therapy. Reprinted from Pang et al[110] with permission.

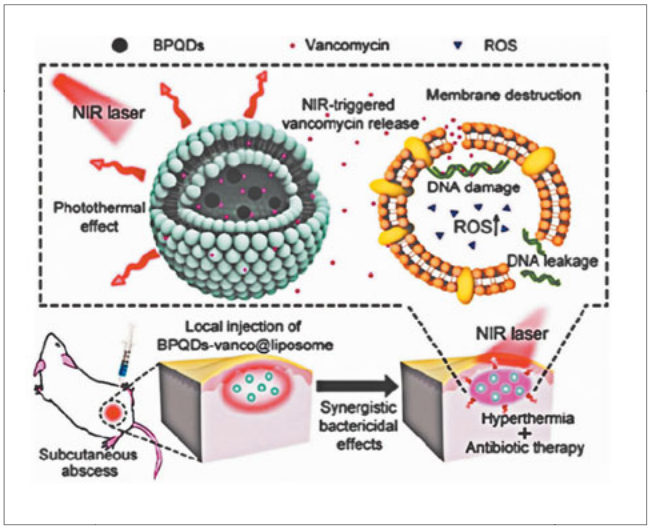

Fig 9 Schematic illustration of the BPQDs and thermal-sensitive liposome for sterilisation. Modified from Zhang et al[111] with permission.

Thermal antibacterial therapy: introduction and classification of techniques

The common heat-based sterilisation techniques include high temperature sterilisation, pasteurisation and ultra-high temperature (UHT) sterilisation. High temperature sterilisation is commonly encountered in daily life, such as in boiling water, cooking food in a saucepan and disinfection. High temperature kills bacteria through the denaturation of bacterial proteins. The pasteurisation method involves continuous heating to 61°C to 63°C for 30 minutes. Although the sterilisation capacity is limited, it can reduce damage to nutrients; thus, the pasteurisation method is mainly used in milk sterilisation. UHT refers to rapid sterilisation when the temperature of food is raised to 135°C to 140°C for a few seconds. High temperature sterilisation is widely used in the medical devices and food industries. At present, however, thermodynamic therapy is one of the most widely studied antibacterial techniques in the medical industry. Thermodynamic antibacterial therapy usually uses radiowaves, microwaves or ultrasound to increase the temperature of lesions, but it also has the disadvantages

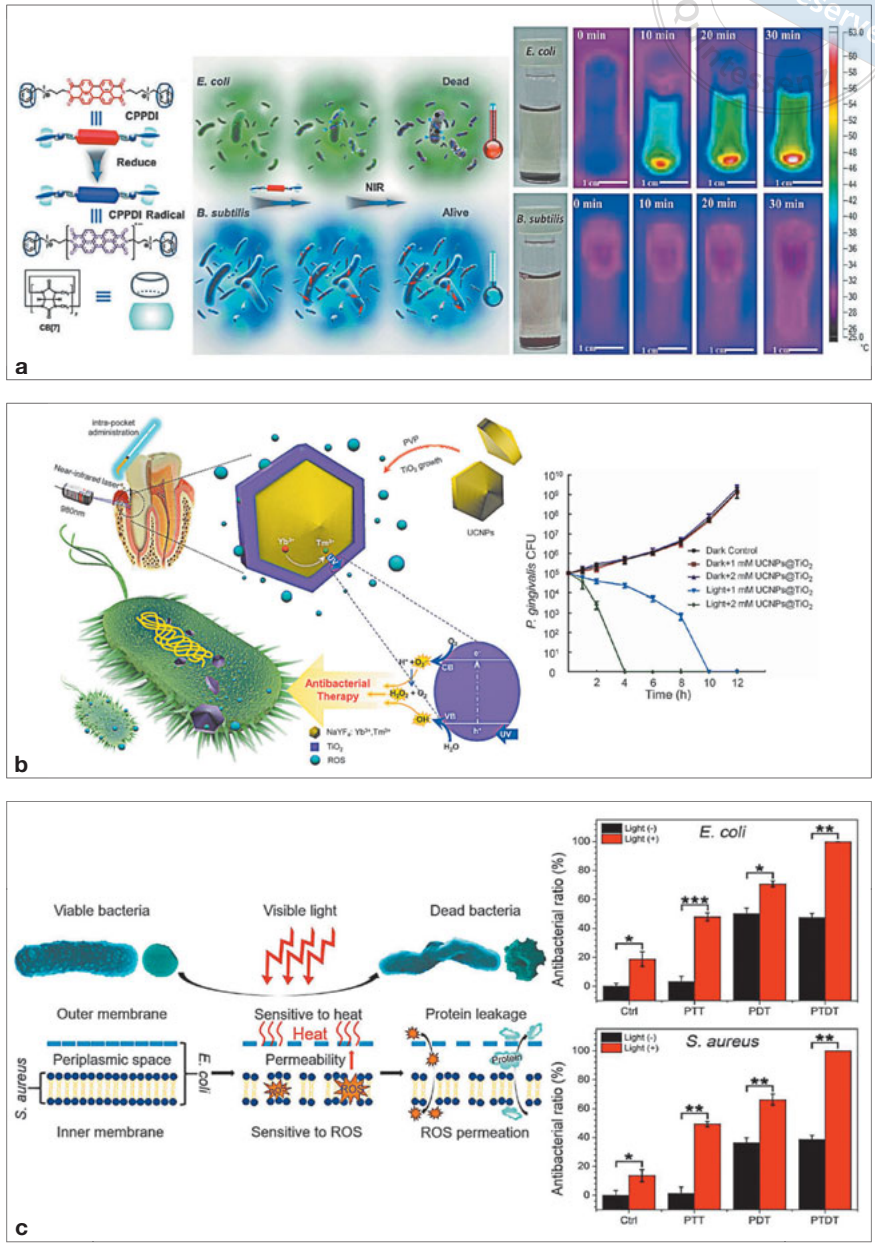

Fig 10 Schematic illustration of PTT research. **(a)** Diagram of PTT for CPPDI against *E. coli*. Reprinted from Yang et al[112] with permission. **(b)** Antibacterial activity of UCNPs@TiO2 under NIR irradiation. Reprinted from Qi et al[113] with permission. **(c)** PAM-PDA/Ag@AgCl hydrogels combining PTT and APDT improved the antibacterial ability. Reprinted from Mao et al[114] with permission.

of high temperature and poor targeting. Therefore, current research is focused mainly on combining thermodynamic therapy with APDT.

Introduction of photothermal antibacterial therapy

Photothermal therapy (PTT) is another form of APDT. By utilising materials that are near-infrared light absorbing, with a high photothermal conversion rate, light energy can be converted into heat energy, which causes the surface of the bacterial cell to heat up, denaturing the bacterial protein and killing it. PTT can prevent the development of drug resistance. Because it only acts on the target tissue and hardly harms the adjacent normal tissues, it is an effective method to kill resistant bacterial strains. The photothermal effects can be combined with drugs, and thermal sensitisers can be utilised as the carrier of the antibiotic to reduce the drug dosage, transfer the drug to the infection site more specifically and improve the antibacterial effects. This mechanism is illustrated in Fig 9; the black phosphorus quantum dots (BPQDs) and vancomycin were encapsulated in thermal liposomes[111] and, when under near-infrared radiation, the photothermal effects of BPQDs destroyed the structure of thermal liposomes, resulting in the release of encapsulated drugs to kill bacteria. At the same time,

the local temperature rise caused by the thermosensitive liposomes also effectively ablated bacteria.

PTT research status

Yang et al fabricated a supramolecular complex of perylene diimide derivative (PPDI) and cucurbit urea (CB) through host–guest interaction[112]. Utilising the chemical response of the supramolecular complex to bacteria, supramolecular free radicals were generated in situ, which can convert light energy into heat energy, thus raising the surface temperature of facultative anaerobes. Hence, this new type of supramolecular photothermal material can kill bacteria in a highly selective and efficient way (Fig 10a)[112]. Qi et al prepared nanoparticles by thermal decomposition, followed by upconversion of nanoparticle@TiO_2 near-infrared light core-shell nanostructure by hydrothermal TiO_2 modification[113]. Three periodontitis-related pathogens, *S. sanguinis*, *P. gingivalis* and *F. nucleatum*, were studied. The treatment-positive group displayed a significant antibacterial effect (Fig 10b). Mao et al fabricated a photocatalytic polyamide (PAM)-polydopamine(PDA)/Ag@AgCl hydrogel system that can overcome the disadvantages of photodynamic antibacterial therapy and thermal treatment alone[114], increase ROS generation, reduce the working temperature to around 50°C and enhance the antibacterial effects while reducing damage to healthy tissues. Temperature can increase the outer membrane permeability of gram-negative bacteria, which in turn enhances the bactericidal effects of ROS (Fig 10c). Due to the endomembrane of Gram-positive and Gram-negative bacteria, this system has a wider scope of action.

Significance

PTT is a new type of noninvasive antibacterial therapy that can convert light energy into heat energy. It has the advantages of good biocompatibility, high performance and simple and environmentally-friendly preparation[115], and can effectively kill bacteria and remove biofilm, thereby providing a new avenue for noninvasive treatment. It is of great significance to the clinical treatment of bacterial infection, and exerts minimal damage on normal tissues.

Research direction

Single antibacterial treatment modalities are often no longer adequate to meet clinical needs. Researchers have recently begun to combine many different types of treatment modalities. This multimodal antibacterial therapeutic strategy is currently a major focus of research, and is still in the initial stages of development. Finding new multifunctional composite materials and combining the advantages of various new materials is a key direction in future research.

Progress of research into antibacterial mechanisms of physical stimulation

The application of physical stimuli in the antibacterial field has a long history, but research on antibacterial therapy through physical stimulation remains inadequate. In particular, the mechanisms of the antibacterial effects of physical stimulation are still unclear. Generally, there are two types of mechanisms of antibacterial effects through physical stimulation. First, physical stimulation can produce ROS such as singlet oxygen and superoxide anion free radicals through energy transfer, which have strong oxidative effects. ROS can destroy the ion channel of bacteria, increase the permeability of the cell membrane, reduce enzyme activity, disrupt protein synthesis and finally lead to bacterial mutation, ageing or death. Secondly, the mechanical force from physical stimulations, such as electric field force or magnetic field force, can disrupt metabolic and physiological processes by perturbing the movement of various types of electrons and ions located within the integral structure of the bacterial phospholipid bimolecular layer and cytoplasm. Additionally, the directional movement of electrons and ions induced by an electric field force or magnetic field force can cause conformational or morphological changes of bacteria, which may lead to bacterial cell death.

Conclusion and future outlook

In conclusion, physical stimulation has been widely used in food sterilisation and domestic water treatment, but its application in the medical field has not been fully developed, particularly in clinical treatment. Considering the inaccessibility of the biofilm growth environment and the increase in its tolerance to antibiotics, physical stimulation may be a promising alternative to antibiotic sterilisation in the future because it can inhibit biofilm formation and even remove formed biofilms, as well as act on multiple targets and destroy the structure of bacteria. Representative research systems, advantages and application scenarios of physical stimuli–based antibacterial treatment modalities are summarised in Table 1[2,29,40,41,67,68,92,94,111,114,116-143].

The mouth is one of the four major reservoirs of bacteria in the human body. When the oral environment changes, the balance of microbial flora in the oral cav-

Table 1 Summary of antimicrobial therapeutic modalities.

Therapy	Advantages	Typical material system	Applications	References
Electrical stimulation	Almost no drug resistance; easier to control	Piezoelectric ceramics	Antibacterial dressing; antibacterial platform	Barki et al[40], Kadam et al[116], Maijer et al[117], Zhao et al[118]; Wang et al[41], Negut et al[119], Yao et al[120], Swain et al[121]
Magnetic field	Fewer side effects; targeted specifically	Magnetite nanoparticle Fe_3O_4	Drug carrier; combined with other methods	Chen et al[68], Chen et al[122], Stanton et al[123], Rouhani and Singh[124]
				Chen et al[67], Beretta et al[125], Trang et al[126], Wang et al[127]
Photodynamic therapy	Lower toxicity; wide range of sterilisation	Titanium dioxide, gold, silver nanoparticles	Ulcers and oral infections; combined with other methods	Siddiqui et al[92], Gursoy et al[94], Niazi et al[128], Tartaroti et al[129]; Yu et al[2], Sun et al[29], Mao et al[114], Tong et al[130]
Photothermal therapy	Lower toxicity; high energy conversion efficiency	Nanoliposome	Biological antibacterial materials; combined with other methods	Zhang et al[111], Aksoy et al[131], Zhang et al[132], Zhao et al[133]; Mao et al[114], Zhang et al[134], Yang et al[135], Wang et al[136]
Sonodynamic therapy	Noninvasive; strong tissue penetration	Nanoparticles	Drug carrier; ultrasonic scaling	Pang et al[110], Khames et al[137], El-Housiny et al[138], Seabra et al[139]; Hinchman et al[140], Krishna and De Stefano[141], Mamajiwala et al[142], Wennström et al[143]

ity is disrupted and infection easily occurs. Therefore, it is imperative to develop antibacterial materials that can replace antibiotics and that do not disrupt the delicate balance of the oral environment. For example, traditional removable denture prosthetic materials are often prone to infection caused by bacterial adhesion, but the addition of antimicrobial agents may lead to changes in the physical properties of the materials[10]. The direct contact of impression materials with saliva is an important factor for cross-infection between doctors and patients. However, common means of immersion disinfection can cause impression deformation[144]. In terms of root canal disinfection, the efficacy of hydrogen peroxide in the clinic is limited, and many areas of root canals may not be covered[145]. Patients with oral cancer are often more likely to be infected due to their low immunity and long-term usage of drugs that have many side effects[16]. Therefore, physical stimulation has great potential for oral clinical treatment, particularly in the design of base materials, impression materials and antibacterial dressing with antibacterial physical properties, because this approach will not only change the performance of the material but also achieve long-term, effective antibacterial properties.

Prospectively, the development of multimodal, highly efficient and multifunctional targeted materials is a key objective for the future because the single mode of physical stimulation cannot meet the complex needs of clinical treatment. Photodynamic therapy, sonodynamic therapy and photothermal sterilisation have great potential to replace antibiotics in the future[29,107,114,146-148], and hold much promise for novel applications in clinical anti-infection therapy in the field of dentistry.

Conflicts of interest

The authors declare no conflicts of interest related to this study.

Author contribution

Drs Ting PAN and Yi Ping LI collected the literature and prepared the manuscript; Profs Xu Liang DENG, Xue Hui ZHANG and Boon Chin HENG designed and revised the manuscript.

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