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Prevention and control strategies for antibiotic resistance: from species to community level

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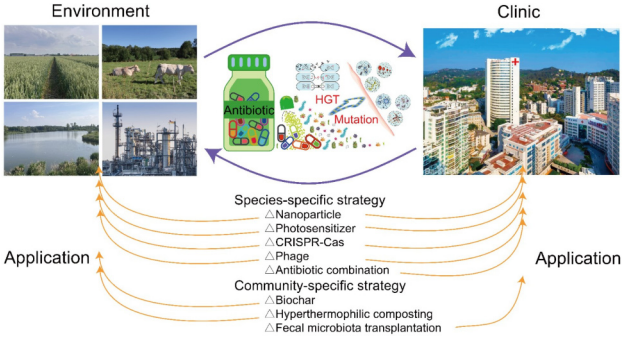
ABSTRACT

- ARGs and ARB in typical environments which exposed to antibiotics are prevalent.
- Nanoparticle- and photosensitizer-related technology can clear specific ARGs or ARB.
- CRISPR-Cas- and phage-related technology can eliminate particular ARGs or ARB.
- Antibiotic combination can be used to eliminate microbial resistance.
- Microbiome-specific technology can eradicate most types of ARGs or ARB in one shot.



Antibiotic resistance genes (ARGs) and antibiotic resistant bacteria (ARB) in the environment pose serious threats to environmental security and public health. There is an urgent need for methods to specifically and effectively control environmental pollution or pathogen infection associated with ARGs and ARB. This review aims to provide an overview of methods abating the prevalence and spread of ARGs and ARB from species to community level. At the species level, species-specific technologies, such as nanoparticle-, photosensitizer-, CRISPR-Cas-, and phage-related technology can be utilized to clear a particular class of ARGs or ARB, and in combination with low-dose antibiotics, a higher removal efficiency can be achieved. Moreover, the combination of antibiotics can be used to reverse microbial resistance and treat recurrent antibiotic resistant pathogen infections. At the community level, community-specific strategies, such as biochar, hyperthermophilic compost, and fecal microbiota transplantation can eradicate most types of ARGs or ARB in one shot, reducing the probability of resistance development. Though some progress has been made to eliminate ARGs and ARB in disease treatment or decontamination scenarios, further research is still needed to elucidate their mechanisms of action and scopes of application, and efforts should be made to explore novel strategies to counter the prevalence of antibiotic resistance.

Keywords antibiotic resistance genes, antibiotic resistant bacteria, treatment strategy, disinfection

1 Introduction

Over the years, antibiotics have saved countless lives but caused the prevalence of antibiotic resistance due to their accumulation in the environment (Pruden et al., 2013; Liu et al., 2018). Terrestrial agriculture (e.g., swine farms and greenhouse vegetable production bases), aquaculture, pharmaceutical manufacturing, and hospitals are four critically important sources of environmental exposure to antibiotics (Pruden et al., 2013; Ouyang et al., 2015; Zhu et al., 2017; Chen et al., 2019; Pu et al., 2020; Larsson and Flach, 2022), promoting the proliferation of antibiotic resistance bacteria (ARB). There were an estimated 4.95 million deaths associated with bacterial antimicrobial resistance (AMR) in 2019, including 1.27 million deaths attributed directly to bacterial AMR (Antimicrobial Resistance, 2022). Infections with ARB can lead to inadequate, delayed, or even failed patient outcomes. Especially, nosocomial infections associated with the highest morbidity and mortality globally are frequently caused by ARB infection (Tacconelli, 2006; Blair et al., 2015). The escalating incidence of hospital-acquired pneu-

monia resulting from ARB infection has led to a rise in inappropriate empirical antibiotic therapy, thereby increasing the risk of hospital mortality (Kollef et al., 2008; Shorr et al., 2008; Diaz et al., 2013).

Mechanisms of antibiotic resistance include decreasing drug influx, increasing drug efflux, modifying or protecting drug target sites, and inactivating or degrading antibiotics (Ruddaraju et al., 2020). The acquisition of antibiotic resistance in microbiomes is not accidental, but rather an inevitable result of biological evolution. Microorganisms gain antibiotic resistance features in two ways, i.e., mutation and horizontal gene transfer (HGT). Microbes with mutation in single nucleotide, single loci, or even entire gene on chromosome or plasmid may survive under antibiotic stress (Martinez and Baquero, 2000; Martínez et al., 2014). Horizontal gene transfer induced by plasmids, integrons, transposons, and phages can recruit and spread antibiotic resistance genes (ARGs) between different organisms (Thomas and Nielsen, 2005). For instance, the plasmid-mediated *mcr-1* gene, often detected in *Klebsiella pneumoniae* and *Pseudomonas aeruginosa,* would be transferred into *Escherichia coli* with high conjugation efficiency (Liu et al., 2016b). Our previous research also revealed the transfer of RP4-mediated ARGs from *Pseudomonas putida* to over 15 bacterial phyla in the soil after 75 days of incubation (Fan et al., 2019).

In addition to being widespread, ARGs and ARB are persistent and difficult to be removed from various environments. Numerous approaches such as advanced oxidation, filtration, chlorination, and UV-irradiation, have been reported to eliminate ARGs and ARB from contaminated area (Sanganyado and Gwenzi, 2019). But abundant ARGs and ARB could still be detected in the effluent of wastewater treatment plants (Wang et al., 2015; Hrenovic et al., 2017) and drinking water (Zhang et al., 2019b; Huang et al., 2021), which have been treated through different disinfection approaches. These results suggest the imperative need for novel strategies with high ARGs and ARB removal efficiency, then some technologies have emerged and can be categorized as species-specific and community-specific techniques, which have not been systematically elaborated before. In this paper, we summarize the characteristics of technologies currently used for the removal of ARGs and ARB at species and community levels (Table 1) and further discuss their effectiveness and corresponding mechanisms. We aim to find out some methods with high efficiency in removing ARGs and ARB or controlling ARB-induced infection for specific environment.

2 Strategies abating ARGs and ARB at the species level

The devastating and pervasive characteristics of antibiotic resistance would threaten the healthcare system, thus technologies with high specificity for abating ARGs and ARB at the population level or even single-cell level have become global concerns. Technologies such as nanotechnology, photodynamic therapy, clustered regularly interspaced short palindromic repeats and associated Cas proteins (CRISPR-Cas) technology, phage therapy, and antibiotic combination

Table 1 Advantages and disadvantages of the existing strategies to control and prevent the prevalence of antibiotic resistance.

Category	Technology	Advantages	Disadvantages
Species-specific	Nanoparticle	Control and modify molecular structures at the nanoscale to achieve intelligent, targeted, and controlled delivery.	Neurotoxicity, genotoxicity, and cytotoxicity of nanomaterials are still unresolved.
	Photosensitizer	Cause both plasma membrane and DNA damage of specific bacteria.	The specific wavelengths of light to excite many types of photosensitizers are needed.
	CRISPR-Cas	Selectively remove AMR-encoding plasmids or ARGs.	Some microbes have evolved anti-CRISPR systems, which may aid HGT; side effects (e.g., target missing and gene toxicity) may occur.
	Phage	Specifically lyse the host bacteria and does not affect non-host bacteria.	Co-evolution of bacteria and phages may happen; ARGs or toxin genes may be carried by phages; endotoxin exit.
	Antibiotic combination	Reverse the selective advantage of ARB in competing with sensitive bacteria and may reduce the antibiotic resistance evolution rate.	The superposition between drugs is complex; the absorption and osmotic efficiency of different drugs in the body are not consistent.
	Fecal microbiota transplantation	Modify community structure at ecological niches, without antibiotic usage.	The donor's sample should be carefully examined, or superinfection may arise.
Community-specific	Biochar	Remove most ARGs by the sorption and electrostatic repulsion of some biochar.	Different kinds of biochar have different effects; some kinds may result in an undesired outcome; certain types of biochar are less efficient.
	Hyperthermophilic composting	Remove ARGs effectively and cut down their half-lives as well.	The mineralization and humification mechanisms of organic matter, and the migration and transformation mechanisms of pollutants during the process of hyperthermophilic composting remain unclear.

therapy could be designed to treat ARB infections specifically without negatively impacting the endogenous microbiota. Moreover, nanoparticles, photosensitizers, and phages have a wide perspective application in the environment, in addition to being used as source reduction methods in the clinic.

2.1 Nanoparticle

Nanomaterials are normally used as antimicrobial agents or used to carry and transport antimicrobial agents, enzymes, and photosensitizers (Fig. 1A) due to their nano-size-related properties, such as small volume, large surface area, quantum size effect, and excellent mechanical property (Ojemaye et al., 2020). Nanoparticles have the capacity to induce alterations and damage to the membrane of ARB, influencing the transport of electrons, oxidization of protein, and metabolic activity within the cells (Fatima et al., 2020). Raffi et al. (2010) have demonstrated that copper-based nanoparticles would lead to cell death via disrupting DNA helical structure after interaction with carboxyl and amine groups on the cell surface. The synthesis of various nanosized molecules has facilitated the development of nanotechnology with potential applications in medicine, therapy, and diagnostics (Thabit et al., 2015). Thus, nanoparticles (e.g., silver, mesoporous silica, chitosan, titanium dioxide, carbon, clay) (Ojemaye et al., 2020) used in nanotechnology should be biocompatible, biodegradable, non-immunogenic, and non-intrinsically toxic to ensure their biosafety (Weldrick et al., 2019). Nanotechnology maintains three main antibacterial mechanisms, i.e., oxidative stress response, dissolved metal ion release, and non-oxidative mechanisms (electrostatic, van der Waals force, hydrophobic, and receptor-ligand interactions) (Ruddaraju et al., 2020).

In addition to acting as antimicrobial agents, nanoparticles have been used as antibiotic carriers to enhance the efficiency of antibiotic penetration to the target microbial infection sites (Ranghar et al., 2014; Ruddaraju et al., 2020). Using the interaction between cationic groups carried by nanoparticles, the negatively charged in bacteria membrane, and some specific recognitions of bacteria can help to enhance the delivery of antibiotics (Patwardhan et al., 2012; Angsantikul et al., 2018). The nanostructured lipid carriers have high entrapment efficiency and stability. When combined with these carriers, the penetration and retention of entrapped antimicrobial peptides nisin Z were enhanced, yielding prominent therapeutic effects (Lewies et al., 2017). The enhanced biofilm penetration and accumulation of antibiotics carried by the sensitive nanoparticles also help in the improvement of antibiotic antimicrobial activity in choppy environments (such as biofilm microenvironments). The mixed-shell-polymeric-micelles, consisting of a hydrophilic poly-shell (ethylene glycol) and pH-response poly (β-amino ester), can selectively accumulate in biofilms. After accumulation, the particles penetrate the cell membrane and transport antimicrobials such as triclosan to their target sites (lipid synthesis) (McMurry et al., 1998; Liu et al., 2016a), bypassing biofilm recalcitrance to antimicrobial penetration. Nevertheless, coupling the photothermal capacity and optimal biocompatibility of polydopamine nanoparticles with the membrane targeting and lytic activity of antimicrobials enables the specific targeting of ARB's membrane and disruption of their integrity (Fekrazad et al., 2017; Andoy et al., 2020). Andoy et al. (2020) reported that laser irradiation of polydopamine nanoparticle-CWR11 (an engineered-tryptophan-rich antimicrobial peptide) nanosystem could not only specifically target and destabilize the outer membrane of *E. coli* but also mitigate collateral damages to healthy cells surrounding sites of infection. Aided by polydopamine nanoparticles, CWR11 could inactivate bacteria and reduce their hemolytic activity at low temperatures.

Although some nanomaterials have shown their performance in prolonged antimicrobial efficacy as well as insignificant toxicity in *in vitro* experiments and experimental animal models, evidence from *in vivo* tests and clinical trials remains insufficient (Fatima et al., 2020). Additionally, the release of metallic irons from metal oxide nanoparticles could potentially impact non-targeted cells, posing a risk to human health if the therapeutic dose exceeds (Cameron et al., 2022). Another hazard of nanomaterials is the excessive production of reactive oxygen species (ROS) trigged by nanoparticles. ROS can inhibit the growth of microorganisms by interfering with DNA replication, limiting amino acid synthesis, and affecting lipid peroxidation, ultimately killing the ARB (Wang et al., 2017). However, excessive ROS may also trigger the body's defense mechanism, causing irreparable damage to normal cells, and even leading to cell necrosis or apoptosis (Cho et al., 2022). The neurotoxicity, genotoxicity, and cytotoxicity of nanomaterials remain unresolved, so long-term *in vivo* and clinical trials are needed to comprehensively assess their hazards, improve the stability of nanomaterials, and achieve targeted drug delivery. Nanoparticles contribute to the development of efficacious antibacterial agents as well as acting as immunomodulatory carriers in the clinic, either alone or in conjunction with therapeutic agents (e.g., antibiotics, photosensitizers, and vaccines), and they can also be used to address the dilemma of antibiotic resistance in water/wastewater.

2.2 Photosensitizer

Photosensitizers are endogenous or exogenous compounds that generate toxic molecules upon optical irradiation and can be employed to inactivate specific proteins or for light-induced cell killing (Castano et al., 2006). A previous study revealed that the conjugative transfer frequency of RP4 would be inhibited when UV light reached the intensity

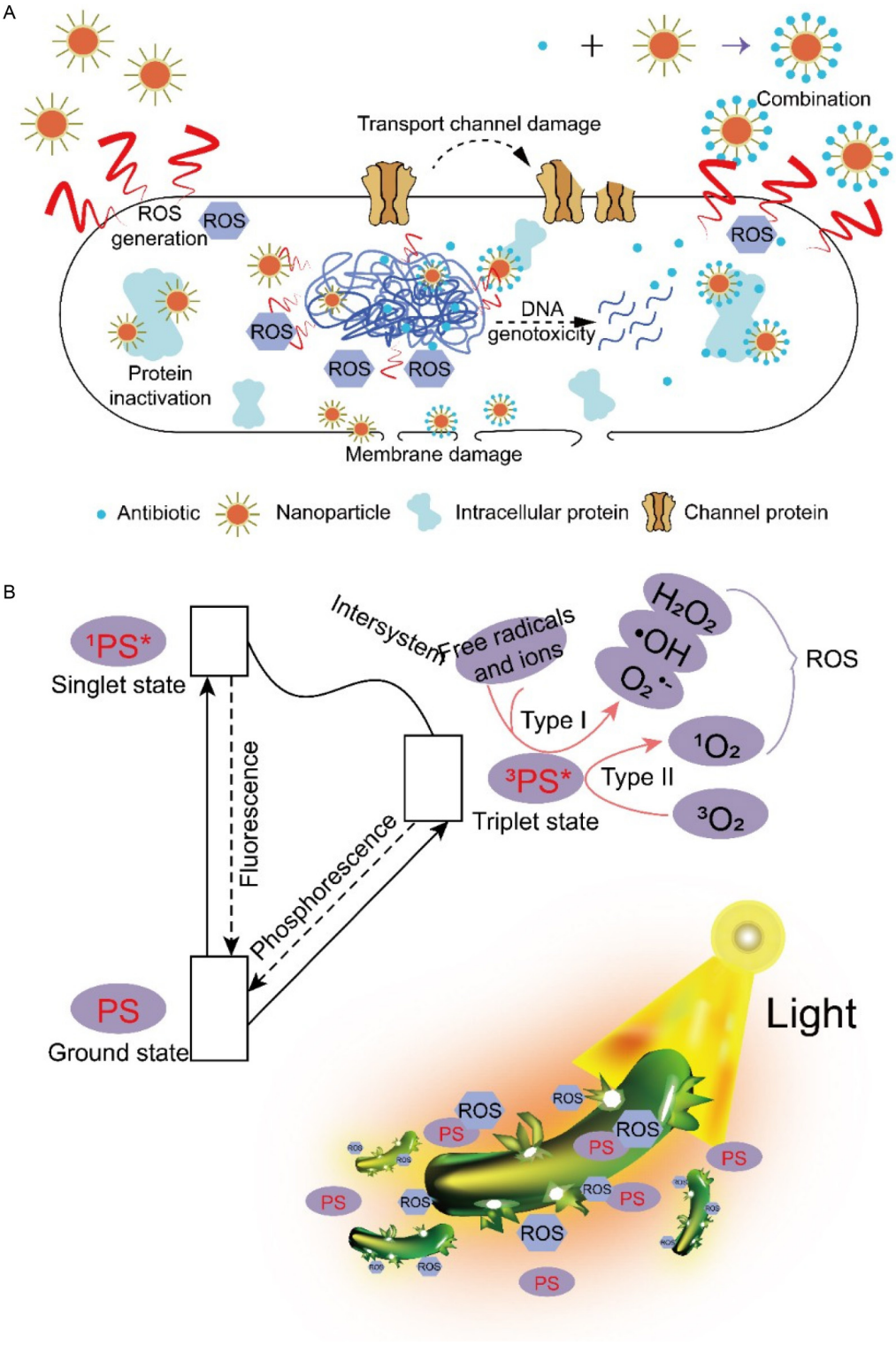


Fig. 1 Antibacterial mechanisms of nanoparticles and nanoparticles in combination with antibiotics (A) (Adapted from (Fatima et al., 2020; Ruddaraju et al., 2020)). Photochemical mechanisms in PDT (B). When a photosensitizer (PS) in the ground state is irradiated by light, it will be converted into the singlet state ($^1PS^*$), then loses energy by fluorescence or changes into a triplet state ($^3PS^*$) by intersystem crossing, following loss energy by phosphorescence or photochemistry from long-lived triplet state to the ground state. This photochemistry produces rich ROS (superoxide (Type I) and singlet oxygen (Type II)), which are cytotoxic to bacteria (Adapted from (Kharkwal et al., 2011; Zhang et al., 2018)).

above 10 mJ cm^{-2} (Guo et al., 2015) and photosensitizers addition during the conjugation process will reinforce the photocleavage of plasmid DNA (Chatterjee et al., 1998), affecting the expression of plasmid-carried ARGs. Photosensitizers absorb photons and release phototoxic products at the appropriate wavelength of light and can even selectively eliminate pathogenic bacteria in a short time without generating drug resistance (Zeina et al., 2002; Al-Mutairi et al., 2018; Anas et al., 2021) through numerous ROS generation (Fig. 1B) (Anas et al., 2021). It has been reported that the photoelectrocatalytic process could inactivate *E. coli* S1-23 in 10 h and damage its ARGs (extracellular and intracellular) within 16 h, indicating the high efficiency of photosensitizers in eliminating ARGs and ARB (Jiang et al., 2017). Photosensitizer-involved photodynamic antimicrobial chemotherapy (PACT) affects ARB in two basic ways. The first one is that photosensitizers damage the plasma membrane and lead to the leakage of cell content (Jori et al., 2006) or inactivation of transport systems and enzymes in the cell membrane (Soncin et al., 2002). The other one is that photosensitizers would directly cause DNA damage by destroying both single-stranded and double-stranded DNA (Nitzan et al., 2004; Wang et al., 2024), resulting in the partial disappearance of the superhelix structure of plasmid (Bertoloni et al., 2000). Salmon-Divon et al. reported that tetra-meso (N-methylpyridyl) porphine (TMPyP)-dependent would photodynamically inactivate *E. coli* JM109, resistant to ampicillin, primarily depending on the photodamage of genomic DNA.

Photosensitizers can be modified to enhance their specificity to target ARGs or ARB. Qing et al. (2019) described a smart triple-functional nanostructure (Thermo-Responsive-Inspired Drug-Delivery Nano-Transporter) that could effectively kill ARB including multidrug resistant bacteria (MDR) with low-dose antibiotics usage by achieving the integrated fluorescence monitoring and synergistic chemo-photothermal killing. Besides, Zhao et al. (2018) developed a boron-dipyrromethene-based glycosylated photosensitizer pGEMA-1 to abate *P. aeruginosa* pollution. Biofilm formation mediated in part by galactose-specific lectin LecA endows galactose as the pathogen recognition of pGEMA-1. Thus, the engineered pGEMA-1 could not cause detectable toxicity to human cells in the dark but selectively attach to *P. aeruginosa* over normal cells, resulting in effective pathogen ablation. In the realm of the photodynamic process, polymer-based nanoparticles can also improve the delivery and release of photosensitizers at the target sites. Zhang et al. (2018) reported a promising clinical antimicrobial therapy featuring an efficient near-infrared triggered β-carboxyphthalocyanine zinc (CPZ) carried by lanthanide-doped upconversion nanoparticles (LiYF4:Yb/Er) and polyvinylpyrrolidone, which avoided the aggregation of CPZ and showed high anti-infection activity against multidrug resistant bacteria (*Staphylococcus aureus* by 4.7 $\log_{10}$ and *E. coli* by 2.1 $\log_{10}$).

Although photosensitizers can produce phototoxicity under visible or UV excitation and have been widely used for blood disinfection and sterilization, most photosensitizers can usually kill pathogenic bacteria only under excitation at specific wavelengths, and the absorption wavelengths of natural pathogenic bacteria often do not meet the needs (Baptista et al., 2021; Wang et al., 2024). For example, psoralens must be activated by UV light in wavelengths ranging from 320 to 400 nm with high energy, and while killing pathogenic bacteria, there is a high risk of damage to healthy cells due to the photodamaging effects (Laskin, 1994). Thus, new photosensitizers excited by visible light irradiation are warranted. Furthermore, many photosensitizers are hydrophobic and insoluble in water, limiting their therapeutic efficiency, whereas used in conjunction with nanoparticles, the aqueous solubility, bioavailability, stability, and delivery of photosensitizers to their target will be improved (Manoto et al., 2017). Moreover, *in vivo* experiments are still required to confirm the universal applicability of photosensitizers in clinical practice. Photosensitizers with high photodynamic antimicrobial efficiency are developing rapidly in clinical applications, and have good application prospects for disinfection in indoor and sunlight environments, especially through modification, where their specificity and bactericidal efficacy will be improved.

2.3 CRISPR-Cas

The clustered regularly interspaced short palindromic repeats and associated Cas proteins (CRISPRs-Cas) protect bacteria against foreign DNA like virus-carried ARGs and plasmids (Fig. 2A). Bacteria and archaea acquire immunity by integrating short fragments of foreign genetic material into CRISPR loci, which provides a molecular genomic memory of previous encounters with that foreign DNA (Carter et al., 2017). Immunity can be obtained by processing CRISPR transcripts encoding the molecular memory, into short CRISPR RNAs (crRNAs) that specifically guide CRISPR-associated proteins (Cas) and act as protective nucleases toward the foreign DNA targets (Carter et al., 2017). According to the structure and function of the Cas protein, the CRISPR-Cas system can be divided into two classes (class I and class II) or six types (type I-VI) (Makarova et al., 2015). Smart tailoring of the CRISPR-Cas system has been proposed as a technology to abate specific bacterial strains including ARB and bacteria carrying ARGs, phages and plasmids can be powerful vectors for the engineered CRISPR-Cas delivery as well (Gomaa et al., 2014; Pursey et al., 2018), providing a new approach to effectively manipulate the composition of environment and human microbial communities.

To achieve this, the CRISPR-Cas system is redirected to

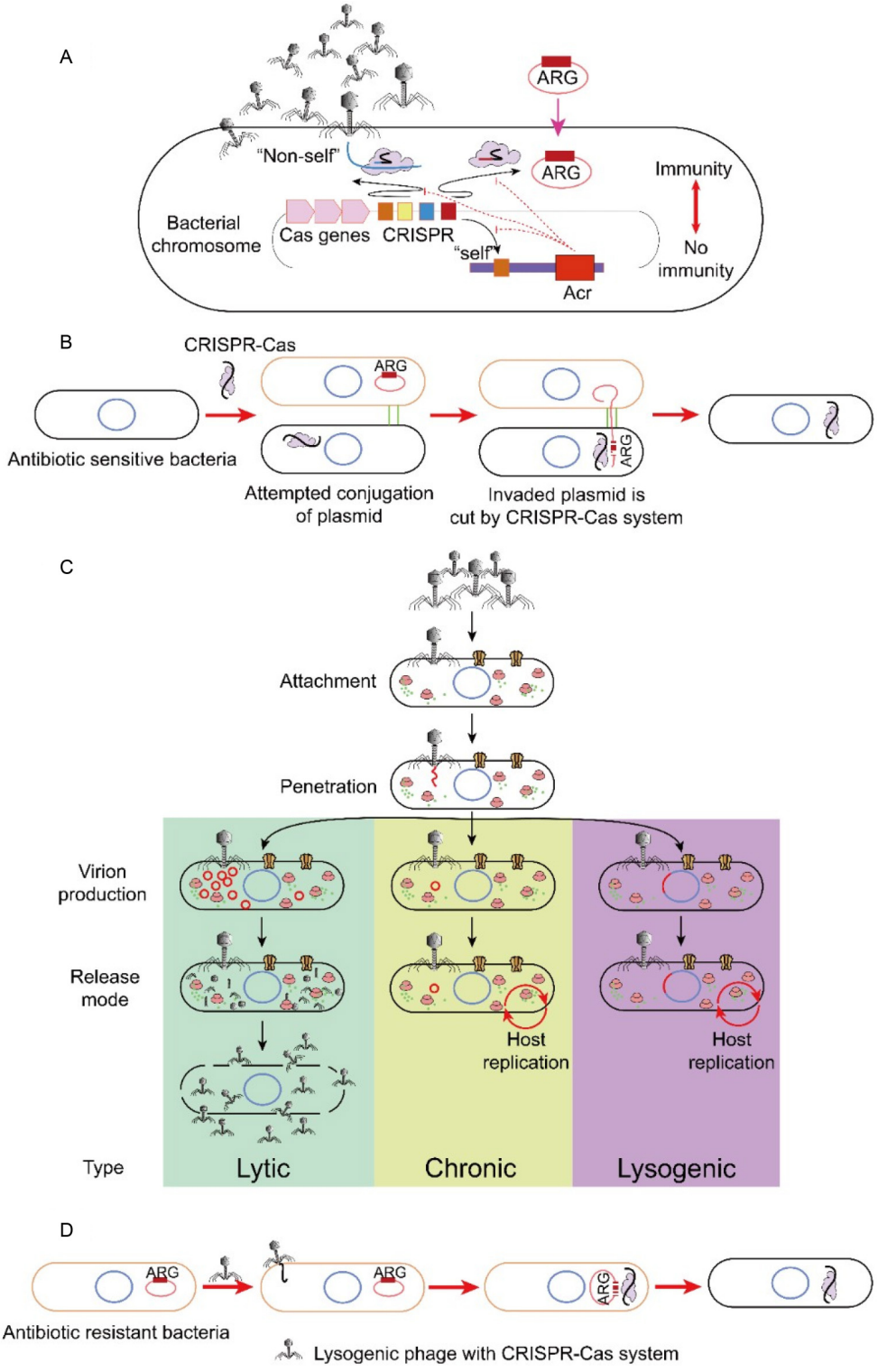


Fig. 2 CRISPR-Cas system-mediated survival model (A). The cell with a chromosome encoding: CRISPR-Cas, anti-CRISPR (Acr). If the CRISPR locus has spacers complementary to targets in the viral genome, plasmid, or genome, this may elicit viral immunity, plasmid immunity, or even autoimmunity. But if the bacterial genome encodes Acr proteins that block Cas9 cleavage, preventing CRISPR-induced immunity, will make the cell more susceptible to subsequent virus or plasmid infection. The CRISPR-Cas system prevents the uptake of plasmid DNA (B). The engineered CRISPR-Cas encoding genes can be added into cells through plasmid or phage. Phage infection models (C). Phage may enter either a productive cycle (lytic infection and chronic infection) or a non-productive cycle (lysogenic infection) after invasion of the host cell. The CRISPR-Cas system combined with phages is used for antimicrobial sensitive population selection by killing targeted ARB or re-sensitizing ARB (D) (Adapted from (Buckner et al., 2018; Chevallereau et al., 2021)).

the combination with the crRNA-guided nuclease Cas9 (CRISPR-associated protein 9), which belongs to type II and can directly kill the antibiotic resistant bacteria by targeting virulence genes or re-sensitize bacteria to antibiotics by selectively removing ARG-encoding plasmids. Cas9 is one of the crRNA-guided nucleases and has been widely used as programmable molecular scalpel in precise genome surgery (Barrangou and Doudna, 2016). Bikard et al. (2014) developed a programmable and sequence-specific antimicrobial agent using plasmid pDB121 which carried *Streptococcus pyogenes cas9*, tracrRNA (trans-activating crRNA), and a programmable CRISPR array sequence (e.g., *aph-3* kanamycin resistance gene, *mecA* methicillin resistance gene). The CRISPR with target ARG insertion endows pDB121 with the memory of the target ARG, also the *cas9* ensures pDB121 the ability to cleavage the target ARG precisely. Moreover, the engineered antimicrobial agents can be delivered by bacteriophages to eradicate targeted bacteria from complex bacterial populations. Additionally, the CRISPR-Cas system often functions as an attractive strategy, and can be used to prevent plasmid transmission by 'vaccination' (Buckner et al., 2018) (Fig. 2B). Upon a CRISPR-Cas system targeting plasmid resistance genes inserted into bacteria harboring plasmids encoded with ARGs, the number and expression of ARGs in bacteria will decrease but not extinct, and a full reversal to antibiotics sensitive phenotype will be achieved under the plasmid maintenance (Tagliaferri et al., 2020). Bikard et al. (2014) also reported that reprograming the CRISPR sequence to target ARGs harbored by staphylococcal plasmids could immunize avirulent staphylococci and prevent the spread of plasmid-borne resistance genes. Apart from the CRISPR-Cas9, many other CRISPR-Cas systems (e.g., type V Cas12a system, type I and III CRISPR-Cas system) have been discovered and used for genome editing (Gomaa et al., 2014; Liu et al., 2020). These systems could potentially be employed to selectively and quantitatively remove individual bacterial strains from complex communities.

CRISPR-mediated adaptive immune system represents formidable barrier to viral predation, whereas viruses have evolved 'anti-CRISPR' proteins that suppress the immune system. In several clinical bacterial species, the presence of CRISPR-Cas system was inversely correlated with ARGs, and a positive association between anti-CRISPR genes (*acr* genes) and acquired antibiotic resistance in some species was found (Shehreen et al., 2019). The *acr* genes gained from MGEs will block or reduce the CRISPR-Cas activity and facilitate the uptake of ARGs, thus aiding in the HGT. Furthermore, gene-editing technology still has side effects, such as target missing and gene toxicity (Anzalone et al., 2020; Liu et al., 2022), then before its application in natural microbial communities, the precision of the CRISPR-Cas strategy needs to be further optimized, to achieve higher efficiency and prevent the formation of undesired byproducts. Moreover, given that clinical pathogenetic bacteria frequently harbor different resistance genes in chromosomes or plasmids, multiple guide RNA for potentially targeting and removing genes should be utilized to reverse bacterial susceptibility. Despite these admonitions, CRISPR-Cas system offers numerous potential advantages over traditional antibiotics, and the programmed system can be exploited to target different bacterial species or bacterium with several ARGs recorded at the same time. This system can drastically eliminate targeted bacteria from complex populations or resistance genes from mobile genetic elements, refraining from the rise of resistant mutants. Accordingly, the programmable DNA cleavage using CRISPR-Cas technology as a source reduction method has a multitude of applications in biomedicine, as well as for engineering novel antimicrobial drugs, and controlling the dispersion of diseases-carrying insects.

2.4 Phage

Since ARGs are rarely encoded in phages (Enault et al., 2017), phage therapy appears to be an appropriate method for treating bacterial infections, including those caused by MDR pathogens (Wittebole et al., 2014) (Fig. 2C). Phages can specifically lyse susceptible bacteria without affecting non-host bacteria, and after the inactivation of host pathogenetic bacteria, the phages diminish as well, maintaining microbial stability and diversity (Ye et al., 2019). Furthermore, phages in combination with the engineered CRISPR-Cas system aiming at ARGs can kill pathogens or re-sensitize them to antibiotics (Bikard et al., 2014; Fig. 2D). Yosef et al. (2015) used temperate phages (λ) to deliver a programmable DNA nuclease, CRISPR-Cas. The engineered CRISPR-Cas was designed to target and devastate plasmids coding resistance genes *ndm-1* and *ctx-M-15*. The specialized CRISPR-Cas harbored by λ phages was transferable to bacteria by lysogenization, and it could reverse antibiotic resistance and eliminate the transference of ARGs between bacteria, reducing the prevalence of ARB on treated surface and the skin of medical personnel.

Currently, formats of phage therapy include cocktail therapy, phage-antibiotic combination, phage-phage-related enzyme combination. These approaches are frequently employed in addressing bacterial infections across plants, animals, and humans (Pires et al., 2016; Kim et al., 2020; Guo et al., 2021; Mahler et al., 2023). Phage therapy, an environmentally friendly technique has been applied in food security to control pathogenic bacteria in plant and soil systems. Zhao et al. (2019) found that the application of polyvalent bacteriophages in the soil would significantly decrease the pathogenetic bacteria and corresponding resistance genes in the soil-carrot system. Besides,

research showed that the addition of phages reduced pathogen density, enriched bacterial species, and decreased disease incidence in tomatoes by 80% (Wang et al., 2019). Notably, using a phage cocktail instead of a single phage exhibited higher efficacy in reducing disease incidence and lowering disease symptom level (Mousa et al., 2022). Also, the effectiveness of phage therapy in the treatment of animal infections caused by infectious antibiotic resistant pathogens has been proven. Phage SH-Ab15519 administered intranasally could effectively rescue mice from lethal *Acinetobacter baumannii* lung infection without generating deleterious side effects (Hua et al., 2017). Moreover, bacteriophages have been proposed as natural antimicrobial agents to deal with ARB associated with human infections. Phages were screened from *Mycobacterium* isolated from patients with symptomatic disease, and then they were administrated intravenously, or by aerosolization, or both, to 20 patients, finally favorable clinical or microbiological responses were observed in 11 patients (Dedrick et al., 2023).

However, there are still many problems with the preparation of phage and its application in phage therapy. First, due to the co-evolution of bacteria and phages, bacteria evolve resistance to phages through defense mechanisms such as receptor adaptation and expansion of the CRISPR-Cas system (Barrangou et al., 2007; Labrie et al., 2010; Marraffini, 2013). Second, bacteriophages can be carriers of bacterial toxin genes or ARGs which might become part of the bacterial genome in case of lysogenic conversion, bringing risks to the disease treatment (Colavecchio et al., 2017; Fillol-Salom et al., 2019; Gomez-Gomez et al., 2019). Third, interactions exist between phages and the human body, and the lysis of pathogenic bacteria may lead to the accumulation of endotoxins and antigens, resulting in inflammations in the body (Clarke et al., 2020; Luong et al., 2020). Hence, before the application of phages in clinical therapy, sequencing of the phage genome is mandatory to confirm the absence of genetic determinants conferring lysogeny, virulence, and antibiotic resistance to ensure the safety of bacteriophages. Owing to the distinctive features of high efficiency, specificity, and environment friendly, phage technology can be applied in medicine, food industry, agriculture, aquaculture, etc. to fight pathogenic bacteria during the antibiotic resistance era.

2.5 Antibiotic combination

ARB develop antibiotic resistance mainly through drug efflux pumps, tight outer membranes, and antibiotic-degraded enzymes; accordingly, some antimicrobial agents could be used to restore antibiotic sensitivity by restraining these resistance mechanisms (Fig. 3A, 3B, and 3C). The usage of antibiotic alone may be inclined to increase the resistance, while the combination of antibiotics and modulation of the interactions between antibiotics can restore or increase microbial sensitivity to antibiotics (Baym et al., 2016). Antibiotic combination therapy can be divided into three categories based on the pathway of antibiotic action: (1) inhibition of antibiotic resistance targets in different pathways; (2) inhibition of different antibiotic resistance targets in the same pathway; (3) inhibition of the same antibiotic resistance target in different ways (Fig. 3A and 3B) (Fischbach, 2011; Worthington and Melander, 2013). The combination of isoniazid, rifampicin, pyrazinamide, and ethambutol currently implemented for pulmonary human tuberculosis and most forms of extrapulmonary, which would block at least three pathways (e.g., inhibit mycolic acid synthesis, inhibit transcription, inhibit translation, and inhibit arabinogalactan biosynthesis) in acquiring antibiotic resistance of *Mycobacterium tuberculosis* (Ginsberg and Spigelman, 2007).

The combined action of antibiotics has three superimposed effects in controlling antibiotic resistance, considering the physiological and evolutionary interactions between drugs (Fig. 3C) (Palmer and Kishony, 2013). Firstly, when one drug inhibits another, the bacteria that develop resistance to the first drug would lose its protection and turn more sensitive to the second one. Secondly, the mutation that confers resistance to one drug also increases the synergy between the two drugs. Thirdly, an evolutionary trade-off of bacteria, the resistance to one drug generates sensitivity to the other (Baym et al., 2016). These interactions of antibiotics illustrated above use the characteristic of ARB in competing with sensitive bacteria and can be applied to increase the sensitivity of bacteria to antibiotics. Besides, the combination of antibiotics and inhibitors of antibiotic resistance is another successful strategy in controlling antibiotic resistance (Gonzalez-Bello et al., 2020). Antibiotic resistance inhibitors include inhibitor adjuvant (β-lactamase inhibitors; efflux pump inhibitors), natural and biological addenda (phenolics; terpenoids), and outer membrane penetrant (cationic; amphiphilic), which have been successfully used in clinical therapy (Jacobs et al., 1997; Sandanayaka and Prashad, 2002; Buynak, 2013). Most of these inhibitors are yielded from the same bacterial species, which produce corresponding antibiotics, showing their advantage in combination (Baym et al., 2016). However, the toxicity of inhibitors, the difference in pharmacokinetics between inhibitors and antibiotics, and the specificity of inhibitors have limited their applications in clinical treatment.

The absorption and permeation efficiency of different types of drugs in the body is not uniform, which should be characterized clearly before application. Moreover, the drug concentration should be adjusted precisely to achieve dose control of drugs in the human body. The misuse of antibiotic combination may in turn contribute to the generation of ARGs and ARB when tackling the affection induced by specific ARB. The complexity of the acting environments

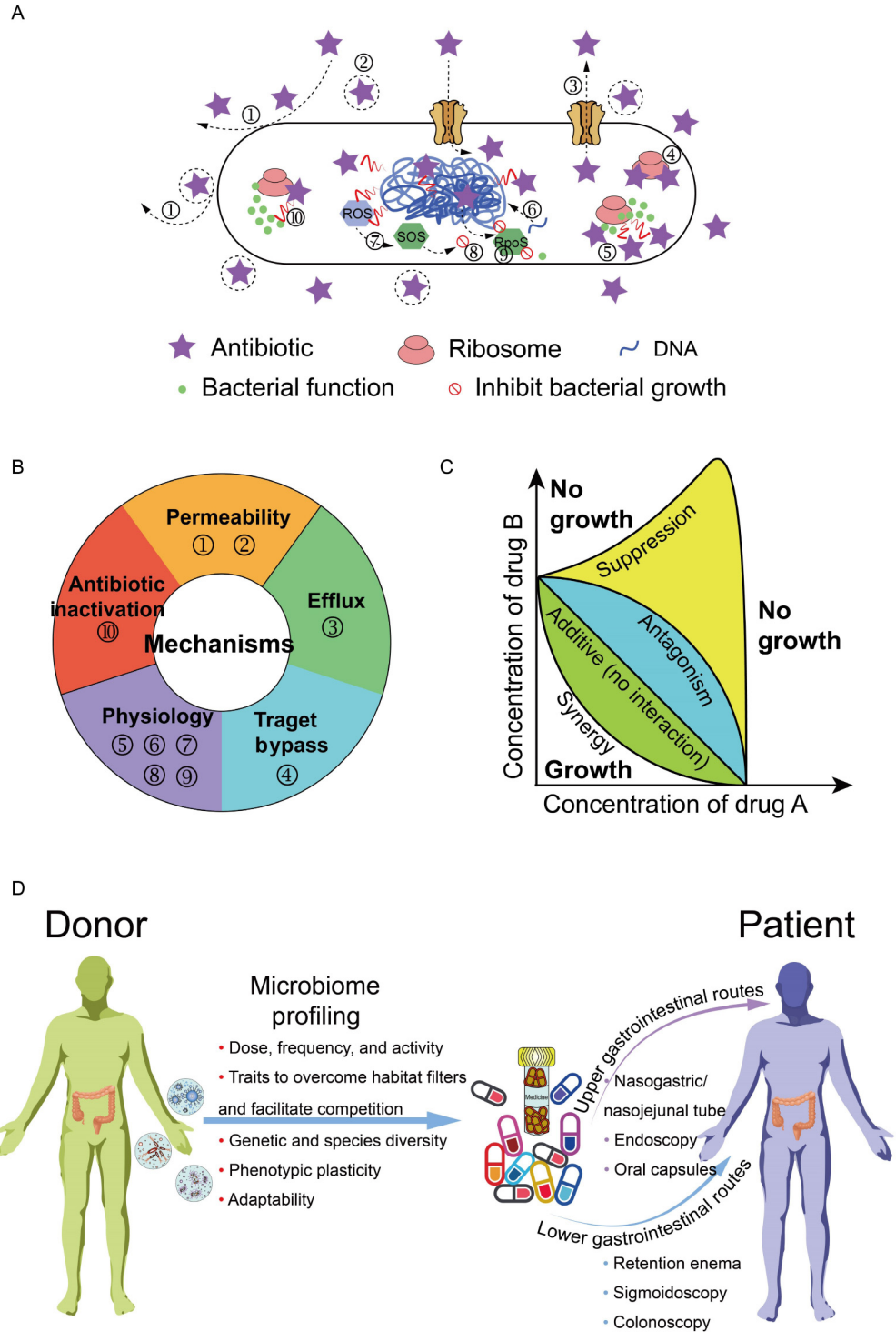


Fig. 3 Factors influence the activity of antibiotics in a susceptible bacterial cell (A, B). These include changes in drug permeability (barrier to prevent drug uptake ①; free drug combined with protein ②), efflux pump ③, alteration or bypass of drug target ④, changes in physiological states (the target function is increased to compensate for inhibition ⑤; the cell repair ⑥; different ROS and SOS response rates ⑦; cell do not replicate or replicate slowly ⑧; stationary phase ⑨), and antibiotic-deactivating mechanisms ⑩. These responses of bacteria can be overcome by the combination of antibiotic usage (same pathway, different pathways, same target, and different targets). The physiological interactions of antibiotic combination (two antibiotics combination for an example) (C). The MIC of a drug appears where the isoline intersects the axes. When there is no drug interaction, the MIC line is linear; when the drugs have synergistic effects, it corresponds to a concave MIC line; when the drugs have antagonistic effects, it corresponds to a convex MIC line; when the using effect of the drug combination is less than that of a single drug used alone, it corresponds to a nonmonotonic MIC line (Adapted from (Baquero and Levin, 2021; Baym et al., 2016; Wright, 2016)). The procedure of fecal microbiota transplantation in clinical therapeutics (D), including rigorous microbial profiling and administration modes (Upper gastrointestinal routes and lower gastrointestinal routes) (Adapted from (Walter et al., 2018)).

makes the application of antibiotic combination unique, which calls for a range of strategies to increase the popularity of antibiotic combination therapy. Considering the advantages of antibiotic interactions and the difficulty of developing new antibiotics, antibiotic combination therapy can be used to reverse microbial resistance and thereby improve the outcome of recurrent infectious diseases with drug-resistant pathogens in hospital.

3 Strategies abating ARGs and ARB at the community level

Except for technologies that specifically target and remove ARGs and ARB at the species level, conventional disinfectants (chlorine and ozone), advanced oxidation processes (UV and electron beam), and physical and chemical combination technologies that universally target the whole community have been applied to remove ARGs and ARB at the community level. Chlorine disinfection, ozone disinfection, UV disinfection, and a combination of chemical and physical methods of disinfection have achieved good results in the removal of ARGs and ARB in water treatment (Oh et al., 2014; Sharma et al., 2016; Yoon et al., 2017; Hu et al., 2019), while in other areas, such as sewage and sludge treatment plants, chemical and ozone methods have obtained relatively good effects (Zheng et al., 2017; Iakovides et al., 2019; Zheng et al., 2019). The effectiveness of other community-specific techniques like fecal microbiota transplantation technology, biochar, and hyperthermophilic composting as the terminal control methods for the removal of antibiotic resistance contamination, have also been investigated.

3.1 Fecal microbiota transplantation

In recent years, the discovery rate of new antibiotics has steadily declined, and most current antibiotics could not effectively kill the ARB but instead increase their antibiotic resistance (Agrawal, 2013), whereas fecal microbiota transplantation (FMT) is effective in curing immune-compromised patients without antibiotic usage (Romo and Quiros, 2019). FMT helps diseased individuals re-establish healthy intestinal flora (Fig. 3D) by replacing the sick recipient's gut microbiota with secured fecal material from a healthy donor. The secured fecal microbiota of the healthy donor, the suitable dosage of FMT, and the optimal route of administration (by upper gastrointestinal routes or lower gastrointestinal routes) are the key factors of the success of FMT (El-Salhy et al., 2021). Indeed, FMT has been demonstrated to durably alter the gut microbiota of recipients and efficiently cure patients with recurrent clinical infections by *Clostridium difficile* (Kassam et al., 2013). Beyond the treatment of *C. difficile* infection, FMT has shown its advantages in the treatment of diseases associated with alterations in gut microbiota, such as ARB infection (Laffin et al., 2017), inflammatory bowel disease (Benech and Sokol, 2020), irritable bowel syndrome (Camilleri and Dilmaghani, 2022), and metabolic syndrome (Proenca et al., 2020), thus FMT is usually considered as a source control (Kelly et al., 2015). Abigail Freedman and Stephen Eppes (2014) have successfully eradicated drug-resistant *K. pneumoniae* colonization from a patient with recurrent clinical infection caused by highly resistant *K. pneumoniae*. Through rigorous donor screening, 48 h bowel cleanse of the patient with polyethylene glycol, infusion of prepared fresh donor stool by nasoduodenal tube, followed by the uptake of probiotics for 6 months, the patient recovered from the recurrent severe *K. pneumoniae* infection.

Accordingly, FMT should be safe overall as it can avoid the use of antibiotics and thus reduce the incidence of allergies, antibiotic resistance, and adverse reactions (Rineh et al., 2014). Dai et al. (2019) applied FMT in a series of critically ill patients with antibiotic-associated diarrhea through the nasojejunal tube, or gastroscopy, or enema, then good clinical outcomes without infectious complications were observed, probably owing to the restoration and significant interactions on the immunity of gut microbiota (Limketkai et al., 2019; Chu et al., 2021). Furthermore, fecal microbiota transplantation therapy can help patients receive a higher recovery rate than antibiotic treatment, showing better therapeutic effects in the long run. The recurrence rate of *C. difficile* infection in patients is 30%−65% following antibiotics treatment, nevertheless, FMT increases the cure rate to upwards of 90% (Brandt et al., 2012). Moreover, accurate computational models can enable optimal donor selection and optimal colonization resistance of transplanted microbiota, thereby improving the efficiency of FMT. Jones and Carlson (2018) derived data from *C. difficile* infected mouse model experiment and considered *C. difficile* sporulation and antibiotic-resistant mutation to synthesize a generalized Lotka-Volterra model, revealing that both fecal transplant timing and transplant donor were important to increase the efficacy of FMT.

Since fecal microbiota used in FMT is a complex mixture of living organisms, which must then interact with the microbiota and the immune system of the recipient (Chu et al., 2021), the strict criteria for donor screening and rigorous assessments of the status of recipients including their age, immune function, and nutritional status are important (Zhang et al., 2019a). In addition, the reasonable fecal microbiota preparation method and suitable administration route are both vital. Restoring the normal microbial community structure of the gut through fecal microbiota transplantation may be an effective way to protect the human body from recurrent ARB infection, which occurs frequently in antibiotic therapy.

3.2 Biochar

Biochar could remove ARGs and ARB mainly via sorption and electrostatic repulsion (Barancheshme and Munir, 2017) attributed to its abundant mineral elements and large surface area. As shown in Fig. 4A, biochar with a porous structure offers habitats for bacterial colonization and provides labile carbon nutrients for their growth. Thus, it is commonly used in soil remediation, especially combined with manure compost, which has been demonstrated as an important method to improve soil fertility and control the spread of ARGs among different soil ecosystems (Chen et al., 2019). The maize biochar has been confirmed to effectively decrease the abundance of ARGs and ARB in the edible parts of plants through sorption (Ye et al., 2016; Duan et al., 2017; Jiao et al., 2018). In contrast to pristine biochar, the physical or chemical modification of biochar enhances its ability in absorbing ARGs based on the physical and chemical adsorption mechanisms, such as hydrogen bonding, π-π interactions, and electrostatic interactions (Du et al., 2023). The magnetic biochar modified by quaternary phosphonium salt could also adsorb more extracellular DNA than those without modification, and the modified biochar could remove over 92.7% of resistance genes in the water (Fu et al., 2021b). Additionally, the combination of biochar with phage is an environment-friendly and efficacious measure in controlling antibiotic resistance prevalence in vertical soil column systems (Ye et al., 2018; Sun et al., 2019).

Abundant studies showed that biochar addition significantly decreased the abundance of ARGs and ARB in the environment (Ye et al., 2016; Chen et al., 2018; Fu et al., 2021a; Du et al., 2023), whereas researches also indicated that the effi-

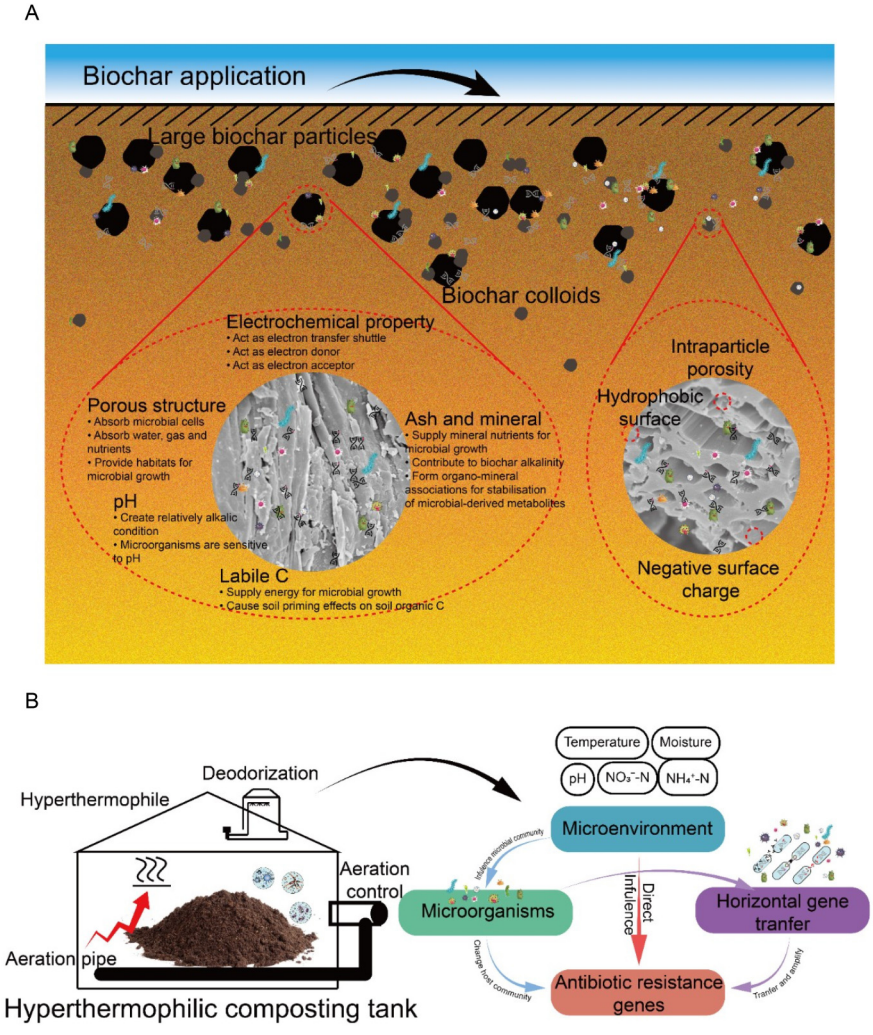


Fig. 4 The special physicochemical properties of biochar (A). Biochar contains parent biochar materials (electrochemical property, porous structure, pH, labile C, ash, and mineral) and pristine biochar colloids (intraparticle porosity, hydrophobic surface, and negative surface charge), which play important roles in altering the activity, diversity and community structure of microorganisms (Adapted from (Dai et al., 2021; Yang et al., 2020)). The main technological process of hyperthermophilic composting, and three main ARGs response pathways in compost, including microenvironment-ARGs, microenvironment-microorganisms-ARGs, and microorganisms-HGT-ARGs (B) (Adapted from (Huang et al., 2021; Wang et al., 2021)).

ciency of biochar for ARG removal depends on the types and pyrolysis temperature of them. Cui et al. (2016) reported a lower removal rate of ARGs and ARB in compost with rice straw biochar addition compared with those without biochar addition. Besides, the heavy metals carried by biochar maybe facilitate the propagation of ARGs. Ding et al. (2019) indicated that a high dose of heavy metals in biochar could increase ARG abundance in collembolan guts after its application in soil, and subsequently enhanced the spread of ARGs through collembolan movement. Moreover, our previous study showed that the rice straw biochar and rice husk biochar had limited effects on the soil-lettuce resistome in the short term (Wang et al., 2022). Future research should focus on comprehensive environmental risk assessment of biochar, including metal content, absorption efficiency, and long-term benefit. Collectively, biochar is an extremely green and cheap adsorbent that can be applied on a large scale, and its effective absorption and remediation in controlling antibiotic resistance contamination makes it suitable for the remediation of environments with low-level ARG contamination (such as soils and water bodies) in the long term.

3.3 Hyperthermophilic composting

Both conventional aerobic composting and anaerobic digestion proved to be insufficient in effectively controlling the proliferation and diffusion of ARGs from sludge or solid waste (Liao et al., 2019), nevertheless, the hyperthermophilic aerobic composting technology developed recently exhibits a remarkable ARG elimination (Oshima and Moriya, 2008). The temperature of hyperthermophilic composting is extremely high (up to 90°C), even without exogenous heating during the fermentation process of the compost (which was 20−30°C higher than the temperature in conventional compost) (Oshima and Moriya, 2008), demonstrating the low energy consumption of hyperthermophilic composting (Fig. 4B). In addition to the excellent treatment efficiency in pollutant digestion, hyperthermophilic composting can effectively eliminate ARGs and ARB by killing most bacteria during composting. Liao et al. (2018) evaluated the efficacy of hyperthermophilic composting in ARG removal and revealed that the half-lives of ARGs were cut down, as well as bacterial abundance and diversity of potential ARG hosts were decreased.

Enhancement with additives can help to improve the removal efficiency of ARGs and ARB during hyperthermophilic composting. Lu et al. (2018) demonstrated that 10% coal gasification slag addition during composting would effectively reduce ARG's potential host bacteria and restrain HGT by reducing MGE abundance. Hyperthermophilic composting not only significantly cuts down the abundance of ARGs and reduces the risk of ARGs spreading in agricultural environments, but also produces organic fertilizers with higher nitrogen content (Cui et al., 2019). However, under the extreme thermophilic condition of hyperthermophilic composting, how microorganisms drive the mineralization and humification of organic matter, and the migration and transformation mechanisms of pollutants mediated by microorganisms are two unexplored facets of this technology. Moreover, due to the limitation of culture conditions and research methods, whether extreme thermophilic microorganisms have effects on the diffusion of ARGs in the hyperthermophilic composting system remains unsolved. Therefore, future research should focus on dynamic monitoring of organic matter mineralization, pollutant transportation and transformation, microbial community dynamic, and ARG dissipation during hyperthermophilic composting to figure out the contribution of each factor to the controlling of ARGs. The characteristics of efficient reduction of pollutants and high ARG removal efficiency make hyperthermophilic composting technology suitable for treating sludge, garbage, and other sites contaminated with serious antibiotic resistance pollution.

4 Challenges and outlook

The occurrence of ARGs and ARB is inevitable, human activities as well as natural physical and biological forces have effects on the propagation of ARGs and ARB. The selection pressure largely promotes the evolution of ARGs in the environment, so it is an urge to deal with the problems caused by antibiotic resistance. In summary, the prevention and control strategies (nanotechnology, photodynamic therapy, CRISPR-Cas technology, phage therapy, antibiotic combination, fecal microbiota transplantation, biochar, and hyperthermophilic composting) have been increasingly applied to address environmental antibiotic resistance contamination or infection with antibiotic resistant pathogens in humans (Table 1).

Precise and efficient ARGs and ARB control and prevention technologies and a profound understanding of antibiotic resistance dissemination pathways are highly required. Supervision of ARGs and ARB in pollutant areas, optimization of ARGs or ARB detection and quantification technology are needed as well. The following suggestions for controlling the spread and combating the menace of antibiotic resistance can be taken into consideration: (1) in addition to the well-known mechanisms, there still exist remarkable diversity mechanisms that need to be discovered, thus deepening research in genomics, systems biology, and structural biology, may contribute to the discovery of other mechanisms and new agents; (2) look for the combination usage of antibiotics with nanotechnology or biotechnology to achieve effective bactericidal effect at low-dose of antibiotic usage; (3) utilize the interaction of different types of antibiotics

to strengthen the bactericidal effect of antibiotics; (4) accelerate the development of antibiotics and antibiotic resistance inhibitors, by taking the antibiotic producers may as fruitful sources of resistance mechanism inhibitors into consideration; (5) ensure the biosafety of ARGs and ARB removal technology before application.

Overall, only with a comprehensive investigation of the antibiotic resistance affected area, pointing out the occurrence mechanisms of antibiotic resistance, then adopting appropriate strategies at species or community level can we better address the problem of antibiotic treatment failure and antibiotic resistance contamination.

Conflict of interest

The authors declare there is no conflict of interest.

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