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Biological treatment strategies for antibiotic contamination: mechanisms, applications, and future perspectives

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The persistence of antibiotic residues in aquatic environments poses significant environmental and health risks. Biological treatment technologies, owing to the cost-effectiveness and environmental benefits, represent a crucial strategy for addressing this challenge. This review systematically elucidates the degradation mechanisms centered on microbial cometabolism, which involves a series of biochemical reactions mediated by functional microorganisms, including hydrolysis, oxidation, reduction, and side-chain modification and cleavage. It also provides a comprehensive evaluation of treatment systems ranging from conventional processes to emerging enhanced technologies such as bioaugmentation, immobilization, and biomaterial coupling. Two major challenges in this field are clearly identified: the inhibitory effects of antibiotics on functional microorganisms, and the secondary dissemination risk of antibiotic resistance genes (ARGs) dissemination. In response, the paper further summarizes recent advances in frontier approaches, such as process intensification, novel material coupling, synthetic biology tools, resource recovery, and intelligent model-based control. These strategies collectively aim to synergistically improve treatment efficiency and mitigate environmental risks. This review aims to provide a valuable reference for developing more efficient and safer biological treatment technologies for antibiotic-containing wastewater.

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1 Introduction

Antibiotics, as one of the greatest medical discoveries of the 20th century, have significantly reduced the mortality rate of infectious diseases and have safeguarded global public health security. However, the success has also led to the overuse and misuse of antibiotics on a global scale.¹ Not only in human medicine, but also in livestock farming and aquaculture, antibiotics are widely used as growth promoters and therapeutic agents.² By 2030, the consumption of antibiotics in developing countries is expected to reach 105.5 kt.³ This extensive use has resulted in significant amounts of antibiotics and their metabolites entering water and soil environments through pharmaceutical wastewater, hospital sewage, agricultural runoff, and domestic sewage.^{4,5} It is reported that approximately 53.80 kt of antibiotics or their degradation products are discharged into aquatic environments each year, thereby emerging as a new type of global environmental pollutant.⁶

Residual antibiotics are frequently detected in various water bodies at concentrations ranging from ng L^{-1} to mg L^{-1} , and in soil from $\mu\text{g kg}^{-1}$ to mg kg^{-1} .^{7,8} In the influent and effluent of urban wastewater treatment plants in China, average concentrations can reach $786.2 \mu\text{g L}^{-1}$ to $186.8 \mu\text{g L}^{-1}$.⁹ In aquaculture wastewater, concentrations are approximately $25.2\text{--}267.3 \mu\text{g L}^{-1}$, while pharmaceutical wastewater can contain concentrations as high as $8\text{--}22.4 \text{ mg L}^{-1}$.^{10,11} These residual antibiotics can enter the human body through the accumulation effects of the food chain and pose a potential threat to human health, including triggering allergic reactions and disrupting the balance of intestinal flora.^{12,13} Additionally, it can also damage the microbial community structure within ecosystems.^{12,14} Long-term exposure to these antibiotics can have potential toxic effects on aquatic and terrestrial ecosystems and exert strong selective pressure.¹⁵ This selective pressure is a key driver behind the generation and spread of antibiotic resistance genes (ARGs).¹⁶ Microorganisms in the environment will acquire and disseminate ARGs through mutations or horizontal gene transfer (HGT) to survive, leading to the enrichment of antibiotic-resistant bacteria (ARB).¹⁷ These ARGs and ARB in the environment can eventually re-enter human society through food chains, drinking water, or direct contact, making previously treatable infections difficult to treat and constituting one of the most severe global public health crises of this century.^{18,19} Previously, a report from the United States indicated that in

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2016, 23 000 people died from antibiotic resistance-related treatment failures.²⁰ And projections estimate that by 2050, this issue could cause 10 million deaths worldwide.^{15,21} The World Health Organization (WHO) has classified antibiotic as one of the “Top Ten Global Health Threats.”

Currently, the commonly used methods for removing antibiotics from water include physical, chemical, and biological approaches. Physical methods, including activated carbon adsorption and membrane separation, primarily transfer pollutants from one phase to another and do not achieve degradation. This can result in the production of high-concentration concentrated waste liquid or waste activated carbon, potentially leading to secondary pollution.²² Chemical methods, such as Advanced Oxidation Processes (AOPs), can effectively degrade and even mineralize antibiotics.²³ However, AOPs often face challenges such as high costs, excessive energy consumption, harsh operating conditions, and the potential generation of unknown toxic by-products.²⁴ Plant remediation technology, including artificial wetlands, utilizes plants to absorb pollutants while root-associated microorganisms degrade antibiotics. However, this method has limitations, including long remediation cycles, low efficiency, and the risk of plant toxicity.²⁵ Biological treatment technology leverages the metabolic capabilities of microorganisms to degrade or transform antibiotic pollutants in the environment.²⁶ This approach is often more cost-effective, environmentally friendly, and produces less secondary pollution. Furthermore, biological treatment technology has the potential to completely mineralize contaminants into CO₂ and H₂O. As such, it presents an extremely attractive alternative or supplementary solution for antibiotic removal. Lou *et al.*²⁷ employed a laccase–syringaldehyde mediator system to degrade sulfanilamide in real aquaculture wastewater. Enzyme kinetics analyses indicated that Novozym 51003 laccase exhibited strong catalytic activity toward sulfonamide compounds, achieving an actual degradation efficiency of 94.84%. Mousavi *et al.*²⁸ investigated the degradation of tetracycline (TC) and ciprofloxacin (CIP) during composting using organic waste, rice husk, and returned activated sludge as microbial sources. The results showed that after 92 days, the removal rates of TC reached 85%, 90%, and 92.5%, while those of CIP were 75%, 77.5%, and 82.5%, respectively. These findings demonstrated that the use of microbial sources during composting can effectively degrade antibiotics in contaminated environments. Wang *et al.*²⁹ reported that, in a continuous-flow reactor for TC degradation, biological degradation was the dominant pathway, accounting for 88.9% of total removal. The continuous-flow reactor provided a more favorable environment for the enrichment and proliferation of functional microorganisms. However, antibiotics are originally designed to inhibit or kill microorganisms, and their inherent biological toxicity poses significant challenges to biological treatment technology.³⁰ The degradation efficiency is highly dependent on factors such as antibiotic type and concentration, microbial community structure, and environmental operating parameters.³¹ Moreover, whether biological treatment systems may accelerate the dissemination of ARGs while removing the parent antibiotic compounds remains a critical issue that must

be clarified prior to their widespread environmental application.

Although numerous studies have reported the degradation of antibiotics by strains or the removal efficiencies achieved by particular treatment processes, a systematic framework for biological treatment technologies is still lacking, and critical perspectives on the key challenges and future research directions remain insufficient. Therefore, this review systematically summarizes and critically evaluates recent advances in antibiotic biotreatment. It aims to provide an in-depth analysis of the core mechanisms of antibiotic biodegradation, including cometabolism, hydrolysis, oxidation, reduction, side-chain modification and cleavage (SMC); comprehensively review the performance and application efficiency of various bioremediation processes, ranging from conventional activated sludge systems to emerging biotechnologies; and particular emphasis on the fate and transmission risks of ARGs during bioremediation. Based on the current state of knowledge, this review further identifies the key challenges in this field and indicates future research directions.

2 Mechanism of antibiotic biodegradation

2.1 Cometabolism

Cometabolism is a fundamental biological pathway by which microorganisms degrade refractory organic pollutants, particularly emerging contaminants such as antibiotics. When microorganisms metabolize easily degradable substrates, which induce the production of non-specific enzymes. These enzymes catalyze the metabolism of the primary substrates. At the same time, they can accidentally attack and transform antibiotic molecules that cannot serve as carbon or energy sources for the microorganisms. In the cometabolism process, the enzyme systems produced by microorganisms facilitate the degradation of antibiotics. However, the antibiotics do not provide the carbon or energy necessary to support microbial growth. Cometabolism significantly enhances the degradation efficiency of refractory antibiotics and is considered a key mechanism for breaking down persistent antibiotic. Furthermore, different microbial groups with unique metabolic networks have evolved diverse cometabolic pathways (Fig. 1). These pathways form the functional core for antibiotic degradation within treatment systems.

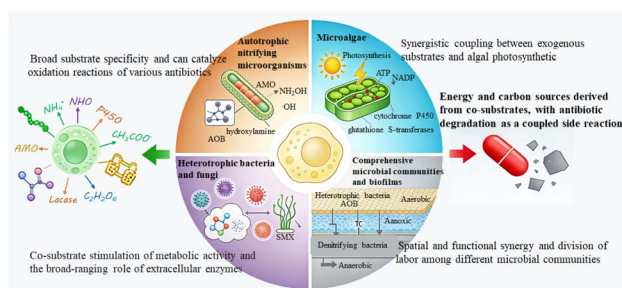


Fig. 1 Cometabolism mechanism of antibiotic biodegradation.



2.1.1 Autotrophic nitrifying microorganisms. Autotrophic nitrifying microorganisms, represented by ammonia-oxidizing bacteria (AOB), are key participants in the wastewater denitrification process and the co-metabolic degradation of antibiotics. The core enzyme of these microorganisms, ammonia monooxygenase (AMO), exhibits broad substrate specificity and can catalyze oxidation reactions of various antibiotics.³² When AOB using ammonia nitrogen as the electron donor and energy source, AMO not only oxidizes ammonia to hydroxylamine but also inserts oxygen atoms into the inert chemical bonds of various antibiotics.³³ For instance, AMO can directly catalyze the cleavage of the piperazine ring in fluoroquinolones (such as CIP) and the deamination reaction of sulfonamide antibiotics.³⁴ Studies have shown that in moving bed biofilm reactors (MBBR) with nitrifying bacteria, AOB-mediated cometabolism plays a dominant role in the removal of CIP, while heterotrophic bacteria contributing only about 9%.³⁵ Moreover, intermediates such as hydroxylamine generated during AOB metabolism can be converted into hydroxyl radicals in subsequent reactions, and further transform antibiotics through an indirect oxidation pathway.

2.1.2 Microalgae. Microalgae, such as *Chlorella* and *Chlamydomonas*, offer an efficient cometabolic pathway for antibiotic degradation. The addition of organic substrates such as acetate and yeast extract to microalgal cultures containing antibiotics significantly enhances the degradation capacity. The underlying mechanism involves a synergistic coupling between the boosted metabolic activity fueled by the exogenous substrates and the algal photosynthetic apparatus.³⁶ On the one hand, the light reaction stage of photosynthesis provides the cell with abundant reducing power (NADPH) and energy (ATP).³⁷ On the other hand, the energy and reducing power markedly upregulate the activities of phase I and phase II metabolic enzymes, including cytochrome P450 and glutathione *S*-transferases.^{38,39} Such a metabolic enzyme–photosynthesis coupling system efficiently drives a series of reactions such as hydroxylation, decarboxylation, and ring-opening of antibiotics. For example, *Chlorella pyrenoidosa* under acetate cometabolism can achieve 100% removal of TC within the concentration range of 1–50 mg L⁻¹. Furthermore, this process effectively reduced the total concentration of 18 antibiotics in actual reclaimed water from 495.54 ng L⁻¹ to 221.80 ng L⁻¹.⁴⁰

However, before intracellular uptake and enzymatic transformation occur, antibiotics may first interact with the extracellular polymeric matrix surrounding microalgal cells. Besides intracellular enzymatic metabolism, microalgal extracellular polymeric substances (EPS) can contribute significantly to antibiotic removal by acting as an extracellular interception layer.⁴¹ Rich in polysaccharides, proteins, and reactive functional groups, EPS can interact with antibiotics through bi-adsorption, electrostatic attraction, hydrogen bonding, hydrophobic interaction, and complexation, thereby reducing their dissolved concentration and buffering direct cellular toxicity.⁴² At the same time, EPS-bound antibiotics may accumulate near the algal surface, facilitating subsequent uptake and intracellular transformation. By restricting the rapid influx

of reactive antibiotic molecules into the cytosol, EPS complexation significantly mitigates intracellular oxidative stress and physiological toxicity, thereby preserving the structural integrity and metabolic vitality required for subsequent intracellular enzymatic degradation.⁴³ Thus, antibiotic removal by microalgae should be viewed as a coupled process of EPS-mediated extracellular retention and intracellular biodegradation.

2.1.3 Heterotrophic bacteria and fungi. Heterotrophic bacteria and fungi can utilize various easily degradable organic substrates, such as methanol, acetate, ethanol, and glucose as growth substrates. During the metabolism of these substrates, microorganisms induce the production of a range of enzymes, including oxidoreductases (such as dehydrogenases), hydrolases (such as esterases, amidases), and peroxidases (such as lignin peroxidase, laccase).⁴⁴ These non-specific enzymes are capable of attacking specific bonds within antibiotic molecules. For example, the cometabolic degradation of sulfamethoxazole by heterotrophic bacteria was significantly enhanced by acetate addition, which can increase the relative oxygen uptake rate by nearly 10-fold.⁴⁵ Extracellular laccases secreted by fungi effectively oxidize pharmaceuticals such as sulfamethoxazole, carbamazepine, ampicillin, and TC.^{46–48} Furthermore, specific functional microorganisms, such as *Arthrobacter* and *Pseudomonas*, drive the transformation of sulfadiazine and sulfamethoxazole through hydroxylation and acetylation reactions under conditions with abundant co-substrates.⁴⁹

2.1.4 Comprehensive microbial communities and biofilms. In practical biological treatment systems, antibiotic degradation is rarely the function of a single microbial species. Instead, it results from the spatial and functional synergy and division of labor among different microbial communities. Within activated sludge flocs, AOB may initiate the preliminary oxidation of antibiotics. This process generates intermediates that are more readily degradable. These intermediates are subsequently mineralized by surrounding heterotrophic bacteria. In biofilms, a unique stratified structure exists. It ranges from aerobic outer layers to anoxic or anaerobic inner layers. The structure provides ideal microenvironments for microorganisms with different metabolic requirements. As a result, complex symbiotic networks are established. AOB and heterotrophic bacteria in the aerobic layer conduct oxidative cometabolism, while denitrifying bacteria and other microbes in the anoxic layers may utilize alternative electron acceptors to further transform the intermediates. The sequential microbial action enables the degradation of various antibiotics, including TC and fluoroquinolones.^{50,51} In photocatalysis coupled with constructed wetland microbial fuel cells (PCW-MFC), *Pseudomonas acidovorans* and *Pseudomonas aeruginosa* work synergistically to convert TC intermediate degradation product acetamide into acetyl groups.⁵²

Although many biological treatment systems can effectively reduce the concentration of parent antibiotics, such removal often results from partial biotransformation rather than complete mineralization. For instance, sulfamethoxazole is frequently converted into N4-acetylsulfamethoxazole, which can be chemically or biologically de-acetylated back to its parent form, acting as a temporary reservoir of toxicity.⁵³ Similarly, the



degradation of CIP often results in the formation of several piperazine-ring-opened products.³⁴ The formation of these intermediate metabolites introduces complex dynamics within the wastewater microbial community. These transformation products may still retain antibacterial activity or exert selective pressure on wastewater functional microbes such as AOB and NOB.⁵⁴ Furthermore, the persistence of these intermediates in the effluent may continue to promote the HGT of ARGs. Therefore, the evaluation of antibiotic removal in biological systems should not be limited to parent-compound disappearance, but should also consider transformation product formation and the residual toxicity of these metabolites.

2.1.5 Kinetic basis and factors influencing enzymatic degradation. Enzyme activity is a key determinant of antibiotic degradation efficiency and is affected by multiple factors, including substrate structure, enzyme specificity, pH, temperature, redox conditions, cofactor availability, and competing substrates. To better reflect this point, we added a kinetic perspective based on the Michaelis–Menten equation, where K_m and V_{max} are used to characterize substrate affinity and catalytic capacity, respectively. For example, the macroscopic degradation rates such as the pseudo-first-order rate constant K_{obs} for TC reaching $3.62 \times 10^{-3} \text{ min}^{-1}$ are fundamentally governed by the enzyme's affinity for the K_m and its overall catalytic efficiency.⁵⁵ While the wild-type enzyme exhibits a substrate affinity (K_m) of $5.34 \pm 1.9 \mu\text{M}$, specific mutations (*T331I*) can increase the overall catalytic efficiency (K_m/K_{cat}) from 6.60 ± 1.7 to $21.37 \pm 0.3 \mu\text{M}^{-1} \text{ h}^{-1}$.⁵⁶ These results underscore that the specificity constant (K_{cat}/K_m), rather than substrate concentration alone, dictates the kinetic limit of antibiotic removal in complex matrices. However, because most published studies on antibiotic removal report reactor-scale or community-level degradation rather than purified enzyme kinetics, directly comparable K_m and V_{max} values for different antibiotic-degrading enzymes remain scarce. We therefore discuss enzyme kinetics as an important mechanistic framework while identifying the lack of harmonized kinetic constants as a current research gap.

2.2 Biochemical reactions

2.2.1 Hydrolysis reaction. The antibiotic biochemical reactions include hydrolysis, oxidation, reduction, and SMC (Fig. 2). Hydrolysis plays a pivotal role in the biodegradation of

antibiotics. Hydrolysis directly cleaves the core chemical bonds of antibiotic molecules through specific enzymes, such as β -lactamases, esterases, and amidases. Consequently, the antibiotics rapidly lose antimicrobial activity. β -Lactamases hydrolyze the β -lactam rings present in drugs like penicillins and cephalosporins.⁵⁷ Esterases and amidases are responsible for breaking the lactone rings of macrolide antibiotics and the amide bonds of sulfonamide antibiotics, respectively. Biological aerated filter can achieve removal efficiencies exceeding 90% for sulfonamides and TCs. The primary removal mechanisms include biodegradation and adsorption. Within the biological component, hydrolytic and photolytic degradation contributed to concentrations of 0.01 – 2.69 mg L^{-1} for sulfonamides and 1.53 – 2.68 mg L^{-1} for TCs.⁵⁸ Similarly, in the anaerobic zone of a hybrid aerated biofilter, hydrolytic enzymes directly attack the piperazine ring of enrofloxacin, cleaving the C–N bond and causing its detachment. The intermediate 1-ethylpiperazine ($\text{C}_6\text{H}_{14}\text{N}_2$, m/z 115) then migrates to the anoxic zone, where it undergoes *N*-dealkylation mediated by hydrolytic enzymes, followed by ring-opening and further degradation in the aerobic zone.⁵⁹

2.2.2 Oxidation reaction. Oxidation reactions involve the loss of electrons and are typically catalyzed by oxidases. It is crucial for attacking the recalcitrant structures of antibiotic and achieving deep transformation. Common oxidases include monooxygenases, dioxygenases, and peroxidases, which generally require cofactors such as NADH and FADH₂.⁶⁰ Cytochrome P450 enzymes and laccases play important roles in microalgae and fungi by catalyzing hydroxylation and dealkylation. For instance, the hydroxylation of the benzene ring in sulfonamide, which introduces a hydroxyl group to alter electron distribution, facilitates subsequent ring-opening reactions.⁶¹ Oxidases are instrumental in directly cleaving aromatic rings of TC intermediates, a critical step toward complete mineralization.⁶² Versatile peroxidase, a type of heme peroxidase, catalyzes two-electron transfers through the formation of unstable compound I and compound II intermediates. The intermediates facilitate the direct oxidation of substrates.⁶³ Notably, under cometabolic conditions, the activity of cytochrome P450 enzymes in microalgae can increase by 20–50%, driving both hydroxylation and ring-opening of TCs.³⁸

2.2.3 Reduction reaction. Reduction reactions is the dominant pathway for antibiotic biotransformation in anoxic or anaerobic environments. Nitroreductases can reduce the nitro groups on antibiotics such as chloramphenicol to amino groups, significantly decreasing toxicity.⁶⁴ Dehalogenases catalyze the removal of fluorine atoms from fluoroquinolone.^{65,66} These reductive transformations are particularly crucial in anaerobic digestion and the anoxic zones of constructed wetlands. The redox processing is exemplified in aerated bi-filters, where enrofloxacin is first converted to an aldehyde intermediate by reductases in the anoxic zone. Subsequently, in the aerobic zone, dioxygenases catalyzed epoxidation of the quinoline ring, resulting in break of the C2–C3 bond and formation of aniline compounds.⁵⁹ Notably, the microalga *Chlamydomonas reinhardtii* demonstrates a distinct mechanism for degrading TC, oxytetracycline, and doxycycline effectively.

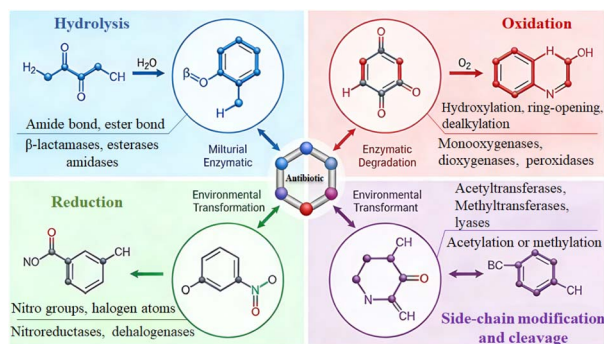


Fig. 2 Biochemical reactions of antibiotic biodegradation.



Interestingly, neither cytochrome P450 enzymes nor primary amine oxidases in *Chlamydomonas reinhardtii* appear to be essential for oxytetracycline degradation. Instead, *Chlamydomonas reinhardtii* utilizes a novel tropinone reductase I (TRI) to mediate oxytetracycline demethylation, resulting in a removal rate of 93.10% within 24 h.⁶⁷ This observation provides an important mechanistic insight into algal antibiotic metabolism. This result suggests that oxytetracycline biotransformation in microalgae can proceed through a distinct cytochrome P450-independent pathway, highlighting the metabolic diversity and specificity of algal responses to antibiotic contaminants.

2.2.4 Side-chain modification and cleavage. The complex side chains of antibiotic often serve as the initial targets for microbial attack. Enzymes such as acetyltransferases and methyltransferases inactivate antibiotics by adding acetyl or methyl groups, simultaneously increasing their water solubility.^{68,69} Concurrently, specific lyases cleave the side chains that connect the aromatic rings to the pharmacophore in antibiotics with complex structures, breaking down large molecules into simpler fragments. This initial cleavage facilitates subsequent oxidative or ring-opening reactions. For instance, sulfamethoxazole is initially degraded by C–N lyase to generate 4-aminobenzenesulfonamide. Then further converted to *p*-aminophenol by oxidases acting on sulfur-containing donors.⁵³ Furthermore, ring-opening reactions represent a hallmark step toward the complete mineralization of antibiotics, typically catalyzed by dioxygenases or monooxygenases. These enzymes directly attack and cleave aromatic structures such as benzene and naphthalene rings, generating linear aliphatic compounds. For example, the ultimate degradation of TC and sulfonamide antibiotics relies on the successful cleavage of their aromatic rings.⁶²

3 Technology of antibiotic biodegradation

3.1 Traditional biological treatment technology

3.1.1 Activated sludge process. The activated sludge process, as a classical wastewater treatment technology, features highly standardized equipment, low operational and maintenance technical requirements, without expensive chemical reagents. It primarily relies on microbial metabolic activity.⁷⁰ Compared to advanced oxidation and membrane separation technologies, it offers lower operational costs and mitigating secondary pollution risks. However, conventional activated sludge exhibits significant limitations in the removal of most antibiotics. The removal efficiencies for TC and quinolone generally less than 80%, while some recalcitrant antibiotics show removal rates below 50% and can even manifest negative removal.^{71,72} For example, Chen *et al.*⁷³ reported negative removal efficiencies of –664.0% and –959.3% observed in the A²/O and AB processes, respectively. Performance declines markedly under complex conditions such as low temperature and high salinity. Low temperatures inhibit the activity of functional microorganisms, while metal ions can form complexes with antibiotics, reducing adsorption and

degradation efficiency.^{74,75} Antibiotic-selective pressure often leads to sludge performance deterioration. High antibiotic concentrations inhibit nitrifier bacteria growth, causing total nitrogen and ammonium nitrogen removal efficiencies to drop below 40%.⁷⁶ Sufficient aeration is essential for biodegradation. However, high dissolved oxygen levels (around 8 mg L⁻¹) induce reactive oxygen species generation, which drives the enrichment of ARGs. Therefore, precise DO control (2–4 mg L⁻¹) is necessary to balance treatment efficacy and resistance risks.⁷⁷ Prolonged antibiotic exposure can also suppress the microbial community, leading to simplified community structures, reduced system resilience, and potential sludge bulking. Currently, parameter optimization and physical enhancement strategies can significantly improve the removal efficiency of antibiotics in activated sludge systems. For instance, the application of a static magnetic field has been shown to enable complete TC removal while reducing treatment time.⁷⁸ In sequencing batch reactor systems, the impact of CIP was found to be highly dependent on the carbon source. Specifically, the addition of glucose stimulated microbial abundance, which subsequently enhanced CIP removal efficiency by 18% to 24%. This improvement was attributed to the positive role of key bacterial genera, such as *Dyella* and *Microbacterium*.⁷⁹

3.1.2 Biofilm process. Biofilm processes exhibit significant advantages in treating antibiotic-contaminated wastewater due to their unique internal stratified structure and diverse microbial ecology. Within the biofilm, a natural gradient of oxygen concentration from aerobic on the outside to anoxic and anaerobic conditions toward the interior. The heterogeneous microenvironment provides ideal niches for microorganisms with varying metabolic requirements, enabling the enrichment of slow-growing yet functionally critical microbial communities. Degradation is achieved through synergistic microbial metabolism and cometabolism. Aerobic microbes in the outer layer initiating the cometabolic oxidation of low-concentration antibiotics.³³ Subsequently, microbes in the anoxic and anaerobic layer complete reduction, ring-opening, and other transformations. This spatially sequential degradation pathway simplifies the molecular structure of final products and markedly reduces their antibacterial activity. For example, the integrated fixed-film activated sludge (IFAS) improves the biotransformation efficiency of trimethoprim by 30% to 50% compared to conventional activated sludge, achieving sulfamethazine removal rates of 69.5% to 90%.^{80,81} In full-scale applications, IFAS attains 50% to 90% removal efficiencies for antibiotics such as amoxicillin and azithromycin.⁸² Mobile bed biofilm reactors (MBBR) treated hospital wastewater achieve approximately 80% removal of antibiotics including roxithromycin and metronidazole.⁸³ Oxygen-based membrane biofilm reactors (MBfR) degraded sulfamethazine and sulfathiazole at rates of 77% and 87%, respectively, while hydrogen-based MBfR synchronously removed 96% of chlor-tetracycline and 99% of nitrate.^{84,85} Furthermore, biological aerated filters (BAF) demonstrate high removal efficiencies of high-strength swine wastewater ranging from 79.6% to 100% for multiple antibiotics, including sulfamonomethoxine and norfloxacin.^{86,87}



3.1.3 Anaerobic biological treatment. Anaerobic biological treatment holds significant potential for treating antibiotic-containing wastewater due to its advantages in handling high organic loads and energy recovery through methane production.⁸⁸ The synergistic metabolism of anaerobic microbial communities under anoxic conditions, enabling the transformation and partial degradation of various antibiotics. The treatment efficacy is significantly influenced by antibiotic type, available electron acceptors, and process configuration. For example, continuous-flow anaerobic digestion systems achieve approximately 45% overall removal of TC. In these systems, biodegradation was identified as the predominant removal mechanism, accounting for 88.9% of this total removal, with the remaining proportion attributed to adsorption.²⁹ In contrast, the degradation pathway of sulfamethoxazole is highly dependent on the presence of coexisting electron acceptors. Under sulfate-reducing conditions, its degradation rate can reach 72.72% within 8 days. It is significantly higher than the 35.65% observed under nitrate-reducing conditions.⁸⁹ Implementing an expanded granular sludge bed (EGSB) reactor for anaerobic co-digestion enhances the removal of amoxicillin and erythromycin from real pharmaceutical wastewater to 78% and 72%, respectively.⁹⁰ Furthermore, coupling anaerobic processes with membrane separation substantially improves treatment efficiency and stability. For instance, anaerobic membrane bioreactors exhibit excellent removal of COD and multiple sulfamethoxazole antibiotics, while anaerobic dynamic membrane bioreactors achieved simultaneous high removal efficiencies for COD, sulfamethoxazole, and heavy metals in swine wastewater, with sulfamethoxazole removal exceeding 94%.^{91,92} Compared to conventional single-stage processes, anaerobic co-digestion system achieved a sulfadiazine removal efficiency of 47.5% at a total solids concentration of 450 mg kg⁻¹.⁹³

3.2 Emerging and coupled biotechnologies

3.2.1 Bioaugmentation. Bioaugmentation involves introducing naturally selected, domesticated, or genetically engineered high-efficiency microbial strains into existing biological treatment systems to enhance the degradation of antibiotics.⁹⁴ For example, the addition of the aerobic denitrifying bacterium *Achromobacter sp. JL9* achieved an 85.16% removal rate of sulfamethoxazole along with a total nitrogen removal efficiency of 91.83%, demonstrating synergistic potential for simultaneous denitrification and pollutant degradation.⁹⁵ Similarly, augmentation with *Pseudomonas* strains resulted in a cefalexin degradation rate of 92.1%.⁹⁶ Strains such as *Glutamicibacter sp. S2* and *Herbaspirillum sp. S8* isolated from activated sludge, achieved over 82% degradation of amoxicillin under optimized conditions, with mechanisms involving β -lactamase production and bio-adsorption.⁹⁷ Additionally, *strain JWJ-09* efficiently degraded quinoline under methanol co-metabolism. When combined with activated sludge to treat actual coking wastewater, the quinolone degradation reached 90.75% total organic carbon removal within 24 h.⁹⁸ However, the practical stability of augmented strains poses a significant challenge, as their

survival and activity are highly dependent on environmental conditions. For instance, isolated *Rhizobium* and *Klebsiella* strains effectively removed cefalexin. In contrast, *Pseudomonas* strains exhibited a strong dependence on multi-substrate mixed cultures. Severe inhibition was observed when exposed to high concentrations or single-substrate conditions of cefalexin.^{96,99} Moreover, the periodic addition of functional sludge, such as anammox sludge, to restore the community structure and functionality of systems stressed by antibiotics is also an effective bioaugmentation strategy.¹⁰⁰

Although engineered bacteria may show high antibiotic degradation efficiency in laboratory studies, their application in wastewater systems is often limited by poor ecological fitness, unstable colonization, and rapid loss of niches. To enhance their persistence, strategies such as carrier-assisted immobilization, biofilm-based retention, pre-acclimation to wastewater conditions, synthetic consortium design, metabolic burden reduction, and microenvironment optimization should be considered.^{101,102} Thus, successful deployment of engineered strains depends not only on degradative capability, but also on their ability to establish stable ecological interactions and persist under complex environmental conditions.

3.2.2 Immobilized microorganism technology. Immobilized microbial technology involves anchoring functional microbial strains or microalgae onto specific carriers and represents a key strategy to overcome challenges in bioaugmentation, such as biomass washout and poor stability. The technology significantly enhances the concentration of functional microbes within reactors, improves its resilience to environmental stress, and enables the recovery and reuse of biocatalysts. For instance, encapsulating *Chlorella* within a semi-permeable, double-network hydrogel created a microalgal gel system that achieved TC removal efficiencies exceeding 99%. The hydrogel effectively shielded the algal cells from direct antibiotic stress and prevented biomass leakage.¹⁰³ Combining *Pseudomonas* spp. with graphene composite hydrogels to create a functionally enhanced system (MC + Pseu-BGH). MC + Pseu-BGH optimized carrier conductivity, modulated microbial communities, and upregulated key enzymes such as nitroreductase, thereby increasing chloramphenicol and sulfamethoxazole removal rates to 99.89% and 94.7%, respectively.¹⁰⁴ Furthermore, immobilizing *Raoultella ornithinolytica CC12* on magnetic biochar derived from corn straw not only enhanced microbial loading but also enhanced the degradation capacity for cyclophosphamide to 305.29 mg g⁻¹ d⁻¹.¹⁰⁵ Moreover, *Bacillus* strains embedded within an active sponge formed a bacterium-microalgae consortium co-immobilized filter (BMCCF) have removed 98.54% of 82 mg L⁻¹ lincomycin within 7 days.¹⁰⁶ Additionally, composite immobilized forms such as algae-bacteria symbiotic granules also demonstrate promising potential for removing antibiotics like TC.¹⁰⁷

3.2.3 Coupling of biology and materials. Coupled bio-material systems, which incorporate functional materials such as modified biochar, graphene, and composite adsorbents into biological treatment processes, represent a promising strategy for enhancing antibiotic removal through the synergy of physicochemical interactions and microbial metabolism.¹⁰⁸ In these



coupled systems, materials transcend their conventional roles as mere adsorbents to concentrate pollutants or simple physical carriers; they actively reconstruct the biological microenvironment through advanced micro-interfacial mechanisms. Specifically, a dynamic adsorption-bioregeneration loop is established, where materials overcome mass-transfer limits by concentrating trace antibiotics, while continuous localized biodegradation naturally regenerates the adsorption sites.¹⁰⁹ Concurrently, high-affinity materials provide critical toxicity buffering by rapidly sequestering toxic parent compounds to safeguard sensitive indigenous microbiota.¹¹⁰ Furthermore, functioning as extracellular electron-transfer mediators, conductive materials facilitate direct interspecies electron transfer, which significantly lowers the activation energy required for the cleavage of recalcitrant antibiotic structures and accelerates the overall transformation kinetics. For instance, the addition of FeCl₃-modified biochar in anaerobic digesters provided a porous refuge for functional microbes such as *Clostridia*, facilitated interspecies electron transfer. And simultaneously enhanced methane production and TC removal efficiency, while effectively reducing the relative abundance of ARGs such as tetA.¹¹¹ Similarly, the fabrication of nitrogen-doped graphene nanosheets anchored with graphene or carbon nanotubes can respectively enhance methane production and antibiotic degradation rates by 20–30%, and achieve 92% TC degradation within 20 minutes.^{112,113} In aerobic or hybrid systems, adsorption-biological coupling reactors constructed with coke or bamboo charcoal was also highly efficient. The removal rates of sulfadiazine and sulfamethoxazole in reactors can reach 88.29% and 96.76%, respectively.⁴⁹ Bamboo charcoal strongly adsorbed TC and sulfamethoxazole through pore retention, π - π interactions, and hydrogen bonding. Its abundant pore structure provided an ideal habitat for functional microorganisms such as nitrifiers, denitrifying bacteria, and *Pseudomonas*.¹¹⁴ In addition, the addition of composite materials such as granular activated carbon and zero-valent iron has also been proven to simultaneously increase the methane production and the antibiotic metabolic activity.¹¹⁵

3.2.4 Combined treatment technologies. Combined treatment technologies, which integrate or couple different treatment units, aim to overcome the limitations of individual methods by achieving synergistic pollutant removal, toxicity reduction, and resource recovery. For high-concentration and highly toxic wastes, the integration of thermal hydrolysis pretreatment and anaerobic digestion process can thoroughly degrade residual antibiotics and produce biogas, thereby realizing harmless treatment and resource recovery.¹¹⁶ For complex antibiotic-containing wastewater, combinations of different biological processes significantly improve removal efficiencies. For example, the “AAO + AAO + MBR” system demonstrated superior and more stable comprehensive antibiotic removal performance compared to the “AB + AAO” system.¹¹⁷ More advanced coupling strategies involve the deep integration of biological treatment with physicochemical or electrochemical processes. For instance, the hybrid system integrating a reticulated polyurethane foam biological trickling filter with vertical-flow constructed wetlands achieved over 94% synchronous

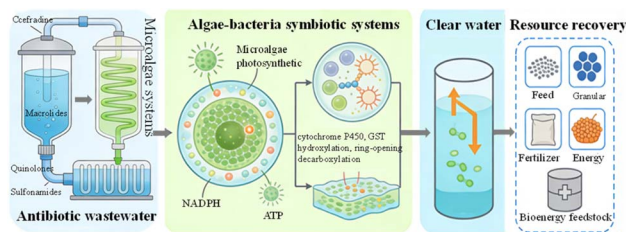


Fig. 3 Process flow of microalgae technology.

removal of antibiotics and heavy metals *via* synergistic adsorption, microbial metabolism, and phytoremediation.^{114,118} The combination of photocatalysis and constructed wetland microbial fuel cells enhanced TC removal to 77.65% through subsequent biological deamination and mineralization of photocatalytic products.⁵² Furthermore, the biogenic manganese oxide-polishing MBBR process substantially increased sulfamethoxazole removal from 24% to 80% through catalytic oxidation by biogenic manganese oxides.¹¹⁹

3.2.5 Microalgae technology. Microalgal technology has attracted increasing attention in antibiotic wastewater treatment due to its environmental friendliness and resource recovery potential (Fig. 3).¹⁶ By leveraging the photosynthetic and metabolic activities of microalgae to efficiently degrade or transform antibiotics, and accumulating high-value biomass.^{120,121} For example, microalgae can achieve a chloramphenicol removal rate of 94.27% in aquaculture wastewater.¹²² *Rhodococcus rhodochrous* exhibited removal efficiencies ranging from 60% to 100% for ten antibiotics including sulfonamides, macrolides, and quinolones within 40 days.¹²³ The underlying mechanisms extend beyond microalgal biosorption and degradation to include synergistic effects generated by constructing algae-bacteria symbiotic systems. For example, an artificial wetland system integrating algae-bacteria consortia with gravel substrate exhibited optimal comprehensive performance in the simultaneous removal of COD, nitrogen, phosphorus, and multiple pollutants such as cefradine.¹²⁴ The harvested microalgal biomass can be further utilized as feed, biofertilizer, or bioenergy feedstock. Thereby enhancing the economic viability and sustainability of the technology. Consequently, microalgae-based technology represents an advanced biological treatment strategy that integrates deep pollutant removal, carbon fixation, and resource recovery.

4 Challenges and innovation

4.1 Challenges and obstacles

A detailed comparison of traditional and emerging antibiotic bioremediation technologies is shown in Table 1. To facilitate comparison among treatment technologies, Table 2 provides a side-by-side summary of the removal efficiencies of major antibiotic classes, including sulfonamides, TCs, and quinolones, under different treatment systems. Although biological treatment technologies show considerable promise for antibiotic removal. The practical application of biological treatment for antibiotic-remediation is primarily bottlenecked by the



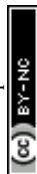


Table 1 Comparative of antibiotic biodegradation technology

| Biodegradation | Technology | Key mechanism | Removal efficiency | Challenges | References |
|---|--|--|---|---|----------------------|
| Traditional biological treatment technology | Activated sludge process | Activated sludge metabolism, lower costs and mitigating secondary pollution | Tetracycline and quinolone generally less than 80%; optimization such as magnetic field, carbon source regulation can be further enhanced | Antibiotics inhibit the functional bacteria; high dissolved oxygen induce the emergence of ARGs; performance is affected by low temperatures, high salinity | 70–79 |
| | Biofilm process | Aerobic/anoxic/anoxic conditions within the biofilm, functional bacteria are enriched, synergistic metabolism | The removal rates of IFAS, MBBR, MBfR, and BAF are usually between 70% and 100% | Parameters (HRT, DO) need to be optimized; high concentrations may damage the biofilm | 33, and 80–87 |
| Emerging and coupled biotechnologies | Anaerobic biological treatment | Synergistic metabolism of anaerobic, converting organic substances into methane, energy recovery | Degradation rate of tetracycline is approximately 45% (mainly through biodegradation); SMX is significantly affected by the electron acceptor | High concentrations inhibit methane production; competition for electron acceptors affects the degradation pathway | 29, and 88–93 |
| | Bioaugmentation | Introduce high-efficiency microbial strains, enhance degradation capacity | SMX and cephalixin have a degradation rate of over 80% to 90% | Difficulty in establishing colonies and compete with the indigenous bacteria; strong substrate dependence; ecological safety risk | 94–100 |
| | Immobilized microorganism technology | Anchoring functional microbial strains onto carriers, enhance stability and recoverability | <i>Bacillus</i> strains embedded within an active sponge resulted in a 7 days removal rate of 98.54% for lincomycin | Carriers have high costs; mass transfer limitations; long-term operational stability | 103–107 |
| | Coupling of biology and materials | The material serves as an adsorbent, carrier and electronic medium, synergy between physicochemical and microbial metabolism | Coke or bamboo – biological coupling achieved the removal rates of sulfadiazine and sulfamethoxazole reach 88.29% and 96.76% | High cost of functional materials; complex mechanism of multiphase interfaces | 111–115 |
| Microalgae technology | Combined treatment technologies | Multiple technical units are connected in series to achieve deep removal and risk control | Pretreatment + biodegradation, physicochemical treatment + biodegradation can achieve removal of antibiotics and heavy metals (more than 90%) | System complex, design and control challenging; investment and operation costs increase | 52, 114, and 116–119 |
| | Microalgae perform photosynthesis to degrade pollutants and convert resources into biomass | Microalgae perform photosynthesis to degrade pollutants and convert resources into biomass | Removal rate of chloramphenicol can reach 94.27%; synergistic purification of algal-bacterial system | Efficiency is greatly affected by environmental factors; high cost of biomass recovery | 16, and 120–124 |

Table 2 Comparative removal of major antibiotic classes in different treatment systems

| Antibiotic class | Representative compound | Treatment system | Removal efficiency | Key operating conditions | References |
|------------------|--|---|--------------------------|---|----------------------------|
| Sulfonamides | Sulfamethoxazole | Anaerobic degradation | 20–60% | Sulfate as electron acceptor | 89 |
| | Sulfadiazine | Laccase–syringaldehyde system | 94.84% | 30 °C; pH 5.32; laccase 0.5 mL L ⁻¹ ; syringaldehyde 0.15 mM | 27 |
| | Sulfamethazine | Fixed-film activated sludge membrane bioreactor | 87% | HRT 10 h; SRT 80 days | 81 |
| | Sulfamethazine/sulfathiazole | Oxygen-based membrane biofilm reactor | 77%/87% | 32 hollow-fiber membranes | 84 |
| | Sulfadiazine/sulfamethazine | Anaerobic membrane bioreactor | 80.1–54.33%/74.12–47.66% | 0.5 g L ⁻¹ biochar; monitored from day 73 to day 86 | 91 |
| | Sulfamethoxazole/sulfadiazine/sulfamethazine | Anaerobic dynamic membrane bioreactor | 94.2%/51.2%/52.8% | HRT 40 h; 1.5 mg L ⁻¹ Cu ²⁺ /Zn ²⁺ | 92 |
| | Sulfamethoxazole | Moving bed biofilm reactor | 85.16% | Ammonia-N or nitrate-N as nitrogen source | 95 |
| | Sulfamethoxazole | Microbial-graphene hydrogel | 94.7% | Graphene oxide, <i>Pseudomonas</i> , pH 7.0; 10 mg L ⁻¹ initial conc. | 104 |
| | Sulfamethoxazole | Biogenic manganese oxides-moving bed biofilm reactors | 80% | Mn(II); COD 165 mg L ⁻¹ ; ammonia 50 mg L ⁻¹ | 119 |
| | Tetracyclines | Tetracycline | Continuous-flow reactors | 1.4 mg per g VSS per d | 35 °C; 24 h reaction cycle |
| Tetracyclines | Tetracycline | Static magnetic field-activated sludge process | 100% | Sludge loading 3 mg TC per g MLSS per d; static magnetic field 5 mT and 25 mT | 78 |
| | Tetracycline | Immobilized bacteria + algae | 93.87% | <i>Alcaligenes faecalis</i> strain R1 + <i>Tetradosmus obliquus</i> | 103 |
| | Tetracycline | Nonradical process | 92% | N-doped graphene nanosheets; carbon nanotubes | 112 |
| | Tetracycline/sulfamethoxazole | Polyurethane foam biological trickling filter with vertical-flow constructed wetlands | >94% | HRT 72 h; HLR 0.050 m ³ m ⁻² day ⁻¹ ; <i>Canna indica</i> L. | 114 |
| | Chlorotetracycline | H ₂ – membrane biofilm reactors | 96% | 5 h HRT; 2 psi H ₂ pressure | 85 |
| | Ciprofloxacin | Aerobic activated sludge | 39.69% | 25 °C; HRT 11 h; glucose as co-substrate | 79 |
| | Ciprofloxacin | Submerged attached biofilter | 95% | Dextrose 500 mg L ⁻¹ | 87 |
| | Ciprofloxacin | Partial nitrification-moving bed biofilm reactor | 98% | FNA level 0.056 mg N L ⁻¹ | 34 |
| | Ciprofloxacin | Moving bed biofilm reactor | 27.11% | Ammonia-N or nitrate-N as nitrogen source | 95 |
| | Enrofloxacin | Microbial | 80.8% | <i>Nitrobacter</i> sp.; initial enrofloxacin 5 mg L ⁻¹ | 66 |
| Others | Quinoline | <i>Achromobacter</i> sp. strain JWJ-09 | 99.39% | 100 mg L ⁻¹ methanol | 98 |
| | Chloramphenicol | Cyanobacteria | 94.27% | <i>Synechocystis</i> sp. | 123 |
| | Chloramphenicol | <i>Raoultella ornithinolytica</i> CC12 | 99.32% | Magnetic biochar | 105 |
| | Amoxicillin/erythromycin | Expanded granular sludge bed | 78%/72% | 30 °C, HRT 24 h | 90 |
| | Lincomycin | Bacterium–algae consortium | 98.54% | <i>Bacillus subtilis</i> strain | 106 |



inherent bacteriostatic or bactericidal nature of these compounds. The response of biological systems is strictly concentration-dependent and often exhibits hormetic behavior. At trace levels (ng L^{-1} to low $\mu\text{g L}^{-1}$), antibiotics may undergo partial removal through sorption and biotransformation without causing measurable inhibition.¹²⁵ However, as concentrations rise to high $\mu\text{g L}^{-1}$ or mg L^{-1} levels, systemic toxicity emerges through the disruption of key metabolic enzymes and cell membrane integrity. The sensitivity of different biological processes varies considerably, making toxicity thresholds highly process-specific. For instance, sulfonamides at concentrations above $100 \mu\text{g L}^{-1}$ have been shown to disrupt amino acid synthesis, cofactor production, and purine/pyrimidine metabolism in anammox bacteria, eventually leading to community collapse and performance deterioration. In addition to direct metabolic inhibition, antibiotics can also reshape microbial community composition.¹²⁶ Exposure to sulfamethoxazole may suppress conventional heterotrophic denitrification such as *Phycisphaera* and *Winogradskyella* while enriching sulfur-autotrophic denitrifiers such as *Sediminicola* and *Thiogramnum*.¹²⁷ In contrast, CIP and amoxicillin have been reported to inhibit *Proteobacteria* and promote *Bacteroidetes* and fungi in denitrification systems.¹²⁸ Such community shifts often occur at the expense of original treatment functions, including nitrogen and phosphorus removal, thereby threatening the long-term stability and efficiency of biological processes. Therefore, the toxicity turning point of antibiotics should be understood not as a fixed value, but as a process-dependent concentration range closely linked to microbial ecology, antibiotic type, and operational conditions.¹²⁹ This constitutes one of the fundamental challenges in the biological treatment of antibiotic-containing wastewater.

The dissemination of ARGs driven by antibiotic residues and the associated secondary risks represent one of the most severe environmental challenges for biological treatment technologies.⁵¹ Antibiotics in the environment exert strong selective pressure on microbial communities. Biological treatment systems, especially wastewater treatment plants, serve as hot-spots for ARG enrichment and HGT. Due to their high microbial density and frequent exposure to antibiotics.^{6,70} A more complex and concerning issue is that many key degradation enzymes, such as hydrolases and modifying enzymes, are encoded by specific genes. These genes are often located on mobile genetic elements (MGEs), including plasmids, transposons, or integrons. Importantly, these MGEs frequently co-carry ARGs.⁵⁸ It implies that a bacterium may simultaneously acquire the capability to degrade a particular antibiotic and resist other antibiotics through the acquisition of one plasmid. Consequently, biological treatment processes may inadvertently select for microorganisms harboring multifunctional enzymes alongside ARGs. These processes can also enrich such microorganisms. As a result, the treatment systems may effectively transform into amplifiers and dissemination of ARGs. Studies have demonstrated that antibiotics such as sulfamethoxazole and TC can induce the expression of integrons. Thereby accelerating the dissemination of multiple ARGs within bacterial populations, including *intI1*, *sul1*, *dfrA12*, *mexB*, and *mexF*.

Moreover, ARGs are often associated with MGEs, including transposons, insertion sequences, integrons, and plasmids, which can disseminate resistance determinants among bacteria through HGT pathways, mainly conjugation, transformation, and transduction.¹²⁸ The induction of MGEs by antibiotics, coupled with the efficient operation of these HGT pathways, creates a powerful engine for ARG dissemination.^{130,131}

Transitioning from laboratory validation to engineering application represents a critical leap for biological treatment technologies for a process often hindered by multiple practical obstacles. The primary challenge arises from the interference present in actual water bodies. Coexisting contaminants such as organic matter and heavy metals may exhibit synergistic or antagonistic effects with antibiotics, competing for microbial metabolic resources or directly inhibiting the activity of key enzymes. Consequently, treatment efficiency in real systems is often significantly lower than those achieved under laboratory conditions.^{132,133} Introduced high-efficiency degrading bacteria or enzymes frequently undergo rapid inactivation in dynamic natural environments. This instability is caused by difficulties in adapting to fluctuations in pH, temperature, and other environmental factors. Additionally, these bacteria or enzymes face competitive disadvantages compared to indigenous microorganisms. They are also vulnerable to predation by protozoa. All of these factors prevent sustained, long-term degradation function. Although many enhanced materials and novel processes can improve treatment efficacy, their high preparation and operational costs limit large-scale implementation. Collectively, these factors constitute significant bottlenecks for the efficient, stable, and safe application of biological treatment technologies in complex real environments.

4.2 Frontier countermeasures and innovative

4.2.1 Process intensification and stress-resistance regulation.

To proactively mitigate the inhibitory effects of antibiotics on biological treatment systems, various strategies have been developed. The focus is on process intensification and stress-resistance regulation. Micro-electric field stimulation is a promising physical intensification method. For example, applying a low-intensity voltage of 0.3–1.5 V has been shown to effectively alleviate the inhibitory effects of sulfamonomethoxine on anammox systems. The underlying mechanism involves stabilizing microbial cell membrane structure, promoting the synthesis of key cofactors such as cytochrome *c*, and enhancing purine and pyrimidine metabolism, thereby shortening the recovery time of inhibited systems by more than one week.¹³⁴ Quorum sensing regulation is achieved by adding or interfering with signaling molecules. This regulation can coordinate microbial community behavior and enhance collective stress response. Furthermore, it improves the cooperative degradation capability.¹³⁵ Meanwhile, the addition of trace elements and cometabolic substrates, such as iron and sodium acetate, supplies essential cofactors or extra energy for functional enzyme synthesis. As a result, it directly promotes antibiotic degradation pathways dominated by cometabolism.¹³⁶ These



strategies optimize microbial survival environments and metabolic states through external interventions. As a result, it improves the tolerance, resilience, and degradation performance of biological treatment systems under antibiotic stress. Additionally, it offers diversified technical options to ensure stable operation.

The efficiency of antibiotic degradation is intrinsically tied to the precision of electron transfer efficiency (ETE). However, ETE does not automatically guarantee selective antibiotic degradation, because electrons may also be consumed by competing pathways such as methanogenesis and sulfate reduction. Therefore, stabilization of electron flow is essential for maintaining selective antibiotic transformation. Practical strategies include optimizing redox potential and electron donor dosage, limiting competing electron acceptors, enriching target functional microorganisms, and using conductive carriers or redox-active materials to direct electron transfer toward antibiotic-transforming pathways.^{137,138}

Residual sub-inhibitory levels may still impose selective pressure on wastewater microorganisms and induce ARG expression. Functional microbes, including nitrifiers, may serve as ARG hosts can spread to indigenous microbiota through HGT.¹³⁹ Therefore, the risk mechanism involves not only microbial inhibition, but also residual antibiotic selection, ARG maintenance, and HGT-mediated dissemination. Control strategies should extend beyond operational regulation and include quorum quenching, phage therapy, improving sludge management, integrating polishing technologies for ARG and extracellular DNA removal, and adopting monitoring frameworks that couple antibiotic removal with ARGs and MGEs.¹⁴⁰

4.2.2 Synergistic treatment using novel materials and coupling technologies. The development of multifunctional materials and the integration of different technological processes represent a significant trend for achieving synergistic enhancement. The advancement of novel functional materials, such as modified biochar and gel-immobilized carriers, extends beyond traditional adsorption functions. These materials can provide refuges for microorganisms to against antibiotic stress and serve as electron mediators to activate catalytic processes. For example, the addition of biochar has been shown to increase the removal rates of various sulfonamide antibiotics by 53% to 88%.¹⁴¹ Nano zero-valent iron and granular activated carbon significantly enhanced system stability and tolerance.⁸⁸ The deep integration of materials with biological processes can generate synergistic enhancements. In anaerobic digestion systems, the application of modified biochar or granular activated carbon not only adsorbed antibiotics but also enriched functional microbial communities and promotes interspecies electron transfer through porous structures. This dual function synchronously enhanced methane production and inhibited the proliferation of resistance genes like *tetA*.¹⁴² Additionally, incorporating physical field regulation into biological systems could activate microbial oxidative phosphorylation and electron mediator synthesis, resulting in a 1.46-fold increase in the degradation of sulfamethoxazole.⁵³ Phosphorus-modified biochar-MoS₂/alginate hydrogel beads could efficiently adsorb and concentrate antibiotics. It also activated persulfate to

generate reactive oxygen species, enabling *in situ* advanced oxidation degradation of pollutants and material regeneration. Collectively, these advances highlight that interdisciplinary integration aimed at optimizing materials and multi-technology processes is a key pathway to advancing water treatment technologies toward higher efficiency, intelligence, and sustainability.

4.2.3 Synthetic biology and precise biological tools. The application of synthetic biology and precise biological tools has introduced breakthrough paradigms of green catalysis and intelligent bioremediation for antibiotic pollution control. Researchers have identified highly active and specific enzymes from nature, such as nitroreductase, and employed protein engineering to enhance the performance.¹⁴³ Furthermore, one representative example is the FerTiG complex, a modular protein assembly that integrates Tet(X4) for TC decomposition, glucose dehydrogenase for cofactor regeneration, and ferritin for enzyme protection, with the aim of improving catalytic efficiency and operational stability. The biomimetic design significantly enhanced catalytic efficiency, environmental stability, and operational safety.¹²² The artificial design and synthesis of novel biocatalysts also demonstrate great potential. For instance, Co_{0.5}Fe_{0.5}Fe₂O₄ with enzyme-like activity has been developed to efficiently catalyze the degradation of various antibiotics under mild conditions. This process achieved deep mineralization while preventing the accumulation of toxic intermediates.¹⁴⁴ Moreover, intelligent engineered strains or synthetic microbial consortia have been constructed through metabolic pathway editing and the introduction of genetic circuits. The modifications endow microorganisms with high and specific degradation capabilities. Additionally, it confers intelligent sensing–response regulatory functions that respond to specific pollutant concentrations in the environment.

4.2.4 Resource recovery and turning waste into wealth. Advancing biological treatment from simple pollutant removal toward resource recovery and recycling represents a forward-looking strategy for addressing antibiotic pollution and improving process sustainability. Pollutants in wastewater are increasingly regarded as misplaced resources, and emerging technologies seek to achieve both contaminant removal and value recovery. Under light-driven conditions, microalgal systems can effectively degrade antibiotics while assimilating nutrients such as nitrogen and phosphorus into biomass enriched in lipids and proteins, which can be further utilized as feed, fertilizer, or converted into biodiesel.¹²¹ Anaerobic digestion and related enhanced processes not only contribute to antibiotic removal but also convert organic pollutants into biogas, while optimization through functional materials such as biochar can further improve methane yield and treatment performance.¹¹¹ In addition, anaerobic fermentation can produce short-chain fatty acids, and specific microorganisms may further convert antibiotic degradation intermediates into bio-based chemicals. Beyond these conventional recovery pathways, biological treatment processes may also enable the recovery of high-value products such as EPS-derived biopolymers. As EPS contains polysaccharides, proteins, and other macromolecular components with diverse functional groups, it



has potential for valorization in bio-based materials, flocculants, adsorbents, and related polymeric applications.^{145,146} In antibiotic treatment systems, this pathway could further enhance sustainability by coupling pollutant removal with the recovery of value-added biomaterials. However, its practical implementation remains constrained by EPS heterogeneity, extraction efficiency, and possible contamination by residual antibiotics, resistance genes, or related transformation products, highlighting the need for further evaluation of product safety and process feasibility.¹⁴⁷ Collectively, these strategies support a green circular model that integrates pollution control, energy recovery, and material valorization, thereby enhancing both the economic and environmental sustainability of wastewater treatment processes.

4.2.5 Process control and models. To achieve stable, efficient, and low-risk operation of antibiotic bioprocessing, the development of advanced process control and predictive model strategies is essential. Comprehensive risk management throughout the entire process is the central guiding principle. It is essential to establish a continuous risk assessment system that uses the abundance, transmission potential, and driving factors of ARGs as key indicators for evaluating process success or failure. This foundation enables the development of targeted regulatory strategies to suppress ARGs dissemination. To achieve the goal, the in-depth application of multi-omics technologies including metagenomics, meta transcriptomics, and metabolomics is critical. These approaches allow precise identification of key functional microorganisms and degradation enzyme genes, elucidation of complete metabolic pathways, and systematic revealing of ARGs transmission networks.^{148,149} Building upon this knowledge, advanced control based on mathematical model and artificial intelligence offers a means to achieve precise regulation. Given the highly nonlinear of biological systems, emerging dissipation-based control methods can better coordinate internal processes. Meanwhile, machine learning algorithms such as random forests, support vector machines, and neural networks can be employed to mine stress-response markers from multi-omics big data. The algorithms can also be used to construct predictive models that link antibiotic concentration, process parameters, and nitrogen removal performance. It facilitates risk early-warning and parameter optimization.^{150,151} Furthermore, tools like graph neural networks can decode complex microbial interaction networks and identify core microbial communities and critical ecological niches that maintain system functional stability.³⁰ In summary, through the deep integration of mechanistic knowledge and artificial intelligence, biological treatment systems can be propelled toward a more intelligent, precise, and predictive-controlled.

5 Conclusions

Biological treatment technologies are considered a central strategy for addressing antibiotic pollution due to cost-effectiveness and environmental friendliness. The biological removal of antibiotics is primarily driven by microbial cometabolism, involving complex microbial communities composed

of AOB, microalgae, heterotrophic bacteria. These communities collaboratively execute a series of biochemical transformations such as hydrolysis, oxidation, reduction, and SMC. Emerging enhancement technologies including bioaugmentation, immobilization, bio-material coupling, and integrated processes have demonstrated significant advantages in improving removal efficiency and operational stability. However, the inherent inhibitory effects of antibiotics on functional microorganisms can disrupt microbial community structures and treatment performance. What's more, the treatment processes may become hotspots for the proliferation and dissemination of ARGs, posing serious secondary environmental risks. Therefore, there is a pressing need to shift from mere contaminant removal toward resource recovery, such as microalgal biomass production and biogas energy. Concurrently, advancing the deep integration of multi-omics technologies with mechanistic knowledge and artificial intelligence, ARGs process control and predictive model is essential. These approaches will lay the foundation for developing next-generation sustainable biological treatment technologies that are intelligent, efficient, and capable of simultaneously mitigating resistance risks.

Author contributions

Xiangtao Zhao: writing – original draft, and conceptualization. Enhui Xie: writing – original draft. Huina Xie: writing – review & editing, supervision, funding acquisition.

Conflicts of interest

There are no conflicts to declare.

Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

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