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Transformation products of antibiotics: overlooked drivers for enhancing the environmental spread of antibiotic resistance

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Abstract

Humans have released thousands of antibiotics into the environment, which is a primary driver of the global dissemination of bacterial resistance. Parent compounds can generate various transformation products (TPs), many of which remain unidentified and lack comprehensive microbial risk assessments. The TPs formed during the process may exhibit structural similarities to the parent compounds, and they can induce antibiotic-like resistance transmission despite lacking the bactericidal/antibacterial properties of the parent compounds. However, assessments of antimicrobial resistance hazards predominantly emphasize parent compounds while largely neglecting their TPs. Here, we highlight that TPs warrant greater attention regarding chemical structure identification and the risk of resistance transmission. This perspective summarizes TPs' potential, mechanisms, and challenges in triggering the risk of resistance transmission.

Keywords: Antibiotic resistance, transformation products, resistance transmission, horizontal gene transfer, antibiotic-like effects

INTRODUCTION

Driven by population growth and the rising demand for veterinary drugs, global antibiotic consumption has been steadily increasing[1]. The global annual consumption of antibiotics is estimated to be between 100,000 and 200,000 tons[2]. However, due to poor intestinal absorption or incomplete metabolism, many antibiotics are excreted in their unchanged form or produce some potentially toxic transformation products (TPs) that ultimately enter the environment[3,4]. Environmental residues of TPs may exhibit antibiotic-like effects, such as inhibiting the growth and activity of microorganisms, exerting toxic effects on plants and animals, and presenting a potential risk to ecosystem stability[5-7]. Furthermore, TPs can also disseminate antibiotic resistance genes (ARGs) through environmental media such as water, soil, and air, as well as within plants and animals, thus posing a significant exposure risk and human health threat[8]. The identification of the resistance transmission risk posed by TPs remains inadequate. This is primarily due to the fact that research on drug resistance has predominantly centered on parent antibiotics. Additionally, TPs' complex and heterogeneous nature introduces considerable uncertainty when assessing their risks.

EFFECTS AND MOLECULAR MECHANISMS OF ANTIBIOTIC-INDUCED RESISTANCE TRANSMISSION

Antibiotics are widely used in medicine, agriculture, animal husbandry, *etc.* However, their extensive use is a major driver of antibiotic resistance and also causes exposure risks to humans[9]. Antibiotic resistance can arise either through the induction of gene mutations or via vertical gene transfer and horizontal gene transfer (HGT). Antibiotics can induce the overproduction of reactive oxygen species (ROS) in bacterial cells, damaging DNA. Errors during the repair process may introduce mutations that enable bacteria to acquire antibiotic resistance[10]. In particular, HGT can make bacterial resistance transfer between different strains or even between different communities, mainly including four ways: conjugation, transformation, transduction, and vesiduction [Figure 1][11]. Conjugation is through direct contact between bacteria; resistant bacteria pass ARGs to other bacteria through the plasmid, which is the HGT process with the highest frequency[12]. For example, tetracycline at subinhibitory concentrations (e.g., 3.9-250.0 ng/mL) promoted HGT frequency by 1.47- to 3.19-fold[13]. In addition, bacteria can promote antibiotic resistance transmission through antibiotic target changes, efflux pump enhancement, enzyme degradation processes, and metabolic pathway changes[14]. Pu *et al.* found that enhanced efflux pump activity, especially multi-drug efflux genes *TolC*, can promote drug tolerance in dormant bacterial cells[15]. Modifications in metabolic pathways allow bacteria to circumvent the mechanisms of antibiotic action and sustain their growth[16]. The alterations in these biological processes increase the risk of resistance transfer mainly indirectly. Since antibiotic TPs may exhibit characteristics of both parent compounds and other substances, the underlying mechanisms of the risk of transmission of resistance are complex and deserve comprehensive consideration.

MIGRATION AND TRANSFORMATION OF ANTIBIOTICS IN THE ENVIRONMENT

The primary sources of antibiotics in the environment include industrial wastewater, medical wastewater, livestock farming, and aquaculture[17]. However, the existing treatment processes cannot eliminate antibiotics, resulting in the presence of antibiotic residues. Antibiotics are redistributed across environmental media through various biochemical processes, including adsorption, migration, and degradation, posing exposure risks to humans[18]. Adsorption is a key process in the interaction of antibiotics with various environmental media, directly influencing their migration/degradation[19]. Sulfonamides remain at high levels due to electrostatic repulsion with negatively charged sediments, potentially becoming the source of groundwater contamination[20]. Additionally, antibiotics undergo various natural degradation reactions, such as abiotic degradation (hydrolysis and photolysis) and microbial degradation[21]. For example, β-lactam, amphenicol, and macrolide antibiotics are soluble in water and prone to hydrolyzed[22]. In addition to hydrolysis, most antibiotics can also undergo photolysis in surface water and

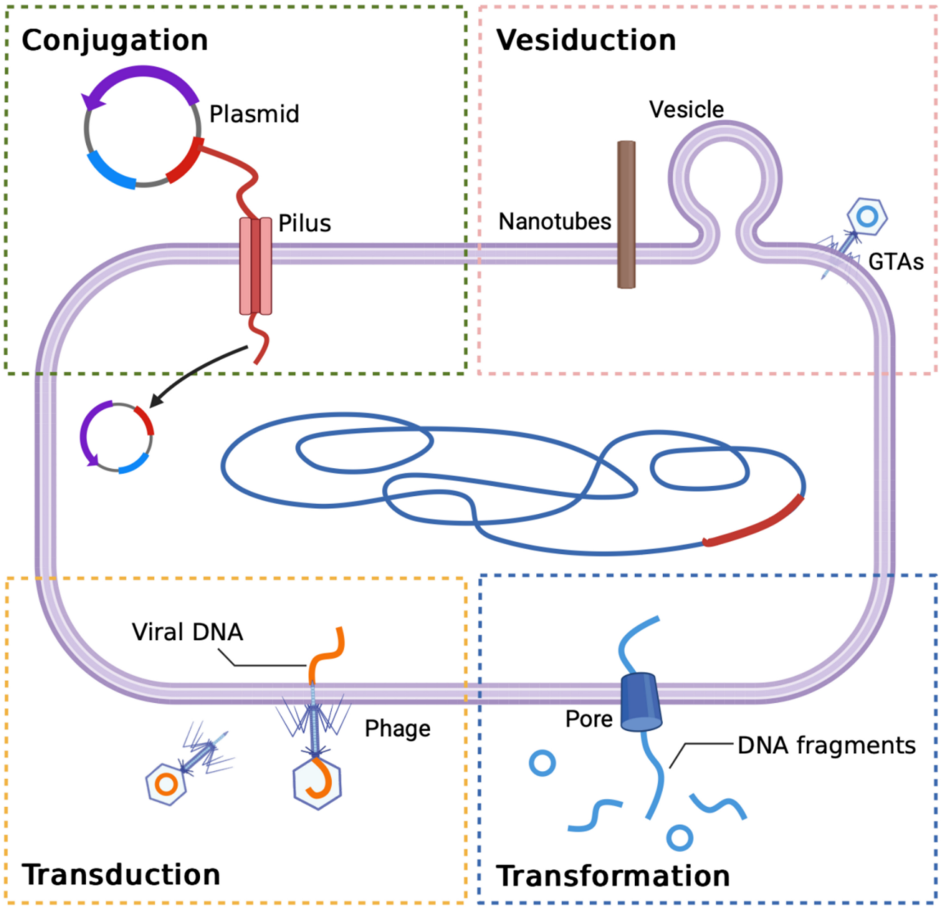


Figure 1. Illustrations of HGT via conjugation, transduction, transformation, and vesiduction. HGT: Horizontal gene transfer.

on soil surfaces. Direct photodegradation refers to the breakdown of antibiotic molecules through electronic transitions induced by ultraviolet radiation[23]. Research showed that sulfamethoxazole and sulfadiazine exhibited good photodegradation effects in ultrapure water, with half-lives of 6.76 and 0.86 h, respectively[24]. Indirect photodegradation involves various natural photosensitizers in water bodies (such as humus, algal organic matter, *etc.*), which convert light energy into ROS and promote the degradation of antibiotics[20]. The efficiency of this process is influenced by the types and concentrations of photosensitizers, while different photosensitizers can promote or inhibit the degradation of antibiotics. Furthermore, the biodegradation of antibiotics plays an important role in aquatic environments, mainly relying on the activities of coexisting microorganisms. In the activated sludge, microorganisms can break down antibiotics into smaller molecules by enzymatic catalysis, such as N-oxidation and hydrolysis of macrolide rings[25]. The migration and transformation of antibiotics are also influenced by environmental factors such as water temperature, pH, light intensity, and water mobility[26]. For example, influenced by seasonal river flow, a significant increase in summer runoff results in a faster photolysis rate and lower antibiotic residues than in winter[27]. The classification of antibiotic TPs is determined by the specific transformation processes of their parent compounds, and environmental factors and water treatment processes significantly increase the complexity of the conversion process.

THE CONTRIBUTION OF OVERLOOKED ANTIBIOTIC TPS TO ANTIBIOTIC RESISTANCE DISSEMINATION

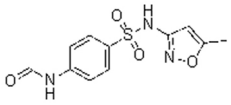
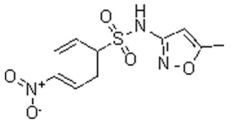
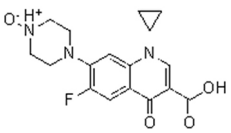
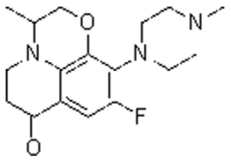
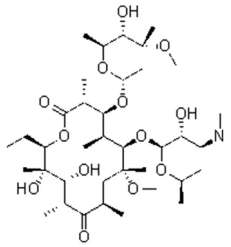
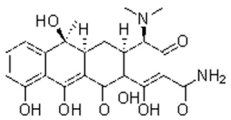
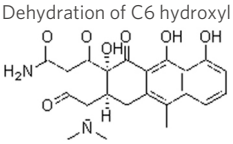
TPs are increasingly detected in various environmental media, forming through both natural processes and anthropogenic activities like wastewater treatment. They may accumulate over time, leading to long-term environmental exposure and posing significant risks of ecotoxicity and resistance gene induction [Table 1][28].

Many studies have been conducted to investigate the ecotoxicity of antibiotic conversion products. Some of the TPs may have stronger toxic activity than the original antibiotics. For example, the accumulation of certain TPs (such as chlorinated or brominated products of sulfamethoxazole) is prone to bioaccumulation in aquatic environments due to poor hydrophilicity, resulting in death or stunted growth of aquatic species, thus disrupting the food chain[50]. Zhang *et al.* found that after biodegradation in the wastewater system, the TPs of ciprofloxacin (CIP) retain partial toxicity and antibacterial activity. Notably, TPs generated through decarboxylation, hydroxylation, and cleavage of the piperidinyl substituent exhibit higher toxicity compared to the parent CIP[51]. However, there are few studies on the transmission of TPs-related resistance genes, with most research focusing only on the induction of ARGs and their bactericidal/antibacterial effects, and even few studies on transmission, such as HGT, and it is easy to ignore the overall effect of maternal compounds and TPs. Fluoroquinolone degradation products can bind to DNA gyrase, interfere with DNA replication, and stimulate resistant mutations in *E. coli*[38]. Degradation products like tetracycline can enhance the expression of oxidative stress gene *lexA*, promote the production of ROS, and the membrane-associated efflux pump protein encoding *otrC* to induce bacterial resistance genes[52]. Changes in bacterial metabolism caused by TPs are consistent with the previously discussed mechanism that indirectly causes the spread of resistance. However, this aspect has not been extensively explored in the current study, and the risk of HGT is often ignored. Furthermore, in our investigation of sulfamethoxazole TPs, we observed that although these TPs do not retain the bactericidal properties of the parent compound, they significantly enhance conjugative HGT by over 70-fold. This enhancement is primarily driven by the induction of ROS, increased cell membrane permeability, and upregulation of bacterial secretion systems[32]. Due to the wide variety of TPs, the current lack of uniform standards for the characterization and management of TPs, and the research preference of researchers focusing on TPs toxicity, research on the risks associated with TPs-mediated resistance transmission remains limited. Future studies should highlight the influence of TPs on the development of bacterial resistance, especially in the spread of AGRs, and how to better use theoretical approaches to predict the toxicity and resistance of TPs. An in-depth study and comprehensive evaluation of the induction and transmission ability of TPs-related resistance genes, along with strengthening the identification and management of TPs, is an important task to reduce the environmental problems of antibiotics.

PERSPECTIVES

The existing literature has commonly suggested the worldwide occurrence of antibiotic TPs in multiple environmental matrices, while their ecological risks have been largely documented. In particular, most TPs possess molecular structures similar to the parent antibiotics and their modes of action may be similar in inducing antibiotic resistance. While standardized protocols for systematic TP identification are lacking, recent analytical advancements (e.g., non-targeted screening, high-resolution mass spectrometry, and stable isotope analysis) have enabled pragmatic identification of TPs and their ecological risks[53,54]. To better determine its molecular structure, and identify or predict its toxicity and drug resistance, it is essential to effectively integrate TPs into chemical management frameworks. This can be achieved by enhancing the identification of TPs' structures and broadening the discussion on resistance transmission mechanisms. Several key topics warrant focused attention following:

Table 1. Main antibiotic TPs' structural features, environmental concentration, transfer pathway, and resistance mechanism

Antibiotic class	TP name	Structural features	Environmental concentration	Transfer pathway	Mechanism of resistance
Sulfonamides	N^4-acetyl sulfamethoxazole	N-acetylation 	Surface water: ng/L~μg/L[29] Sediment: μg/kg[30]	Micro-biological degradation[30], chemical oxidation degradation[31]	Promote conjugation, enhance ROS, cell membrane permeability, secretion system, *etc.*[32]
	4-nitro sulfamethoxazole	Nitro substitution on the benzene ring 	WWTP effluent: ng/L~μg/L[31,33]		
Quinolones	CIP N-oxide	Oxidation of the piperazine ring 	Soil: μg/kg[34] Surface water: μg/L~mg/L[35]	Photocatalytic degradation[36], micro-biological degradation[37]	Enhance resistant mutations, random errors during DNA replication, activate SOS response, and increase intracellular ROS[38]
	Decarboxy ofloxacin	Decarboxylation of carboxylic group 	River sediment: μg/kg[39]		
Macrolides	Clathromycin	Hydroxylation at C14 	Surface water: ng/L~μg/L[40] Pharmaceutical wastewater: mg/L[41]	Photochemical degradation[42], adsorption and migration[43], micro-biological degradation[44]	Change the target of macrolide (i.e., ribosome) and upregulation of efflux pump[45]
Tetracyclines	4-epi-tetracycline	Epimerization at C4 	Livestock manure: mg/kg[46]	Micro-biological degradation[47], chemical oxidation degradation[48]	Enhance resistant mutations, enhance target protection, metabolic adaptations, and reduce membrane permeability[49]
	Anhydrotetracycline	Dehydration of C6 hydroxyl 	Compost product: μg/kg[46]		

TPs: Transformation products; ROS: reactive oxygen species; WWTP: wastewater treatment plant; CIP: ciprofloxacin.

1. The development of non-targeted analysis, high-resolution mass spectrometry, and stable isotope analysis is conducive to effectively predicting the potential molecular formula of TPs and even determining their chemical structure.

2. Integrating diverse antibiotic TPs into the chemical management framework is needed. Leveraging the accumulation of big data, machine learning technologies can ultimately be utilized in the toxicity assessment and prediction tools for TPs. How to better use theoretical methods to predict toxicity and resistance of TPs becomes the future direction.

3. Attention should be given to the risk of resistance transmission induced by the antibiotic-like effect, as TPs frequently lose their parent compounds' bactericidal or bacteriostatic efficacy against bacteria while introducing additional toxic risks.

4. Laboratory-oriented strategies for mitigating resistance risks from TPs: Future research should focus on developing selective advanced oxidation processes (e.g., solar/chlorine and chlorination/bromination treatment[55,56]) and functional nanostructured adsorbents [e.g., metal-organic framework (MOFs)] for selective TP capture. Integrated technologies synergistically suppress HGT in multi-pollutant matrices, weakening environmental persistence and resistance-driven ecological threats.

DECLARATIONS

Authors' contributions

Methodology, investigation, writing - original draft, writing - review and editing: Zhang, Y.
Methodology, investigation, writing - original draft: Jiang, J.
Conceptualization, methodology, investigation, writing - original draft, writing - review and editing, project administration, funding acquisition: Feng, M.; Ye, C.

Availability of data and materials

Not applicable.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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