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Antibiotic Pollution in the Yining Section of the Ili River: Distribution, Sources, and Ecological Risk Assessment

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Abstract

The Ili River is a transboundary water body in Central Asia and a key region along the Belt and Road Initiative, yet antibiotic pollution in this river remains unexplored. This study investigated the occurrence, distribution, and ecological risks of 14 antibiotics in the Yining section of the Ili River and the effluent of the Huocheng Wastewater Treatment Plant (HWTP). We optimized and validated an analytical method using solid-phase extraction coupled with high-performance liquid chromatography-tandem–mass spectrometry (SPE-HPLC-MS/MS). The method achieved low detection limits (0.05–1.0 ng·L^{-1}) and good recoveries (70.0–108.3%). Results showed that HWTP removed 9.8–98.3% of detected antibiotics, with negative removal observed for several compounds due to desorption or metabolite reconversion. In the Yining river section, tetracyclines dominated (55.9% of total antibiotics), followed by fluoroquinolones (33.8%), macrolides (9.7%), and β-lactams (0.6%). Ecological risk assessment using the risk quotient method revealed that the combined risk (RQ_s) in the Yining section ranged from 1.54 to 2.74, indicating a high-risk level. Chlortetracycline exhibited the highest individual risk (RQ 0.92–0.97) and is proposed as a priority pollutant. This study provides the first baseline data on antibiotic pollution in a Central Asian transboundary river and underscores the need for international cooperation in water quality management within the Belt and Road framework.

Keywords: antibiotics; HPLC-MS/MS; ecological risk assessment; Ili River; Central Asia; chlortetracycline

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1. Introduction

The discovery of penicillin in the 1940s revolutionized medicine, and antibiotics have since become indispensable for human therapy, livestock farming, and aquaculture worldwide [1]. However, the extensive and often uncontrolled use of antibiotics has led to their ubiquitous presence in the environment. China, as the world's largest producer and consumer of antibiotics, reported an annual production of 2.23×10^5 tons in 2022, with a continuous increasing trend [2]. Consequently, antibiotics are frequently detected in various environmental matrices, with concentrations ranging from ng·L^{-1} to μg·L^{-1} in surface waters and from μg·kg^{-1} to mg·kg^{-1} in sediments and soils [1]. This issue is not unique to China. Global surveys have detected antibiotics in rivers across all continents, with high-risk hotspots in Africa, South America, and Asia [3]. Moreover, a One Health assessment covering 46 countries revealed that antibiotic residues are ubiquitous across

wastewater, surface water, and other matrices, identifying high-risk hotspots in Africa, Asia, and the Americas [4].

Although environmental antibiotic concentrations are typically below therapeutic doses, chronic exposure poses significant ecological and health risks. Sub-inhibitory concentrations can induce bacterial resistance and promote the spread of antibiotic resistance genes (ARGs) through horizontal gene transfer [5]. Additionally, antibiotics can interact with co-occurring pollutants such as microplastics and heavy metals, potentially facilitating resistance dissemination and forming complex combined pollution [6–8]. Third, antibiotics have been shown to impair reproduction and growth in aquatic organisms [9], degrade soil quality [10], and threaten human health through food chain transfer and bioaccumulation [11]. The global spread of antimicrobial resistance (AMR) has been recognized by the World Health Organization as one of the top ten global public health threats, making the monitoring of antibiotic pollution in the environment a priority research area.

Reliable analytical methods are essential for monitoring antibiotic residues in complex environmental matrices. Among available techniques, high-performance liquid chromatography-tandem–mass spectrometry (HPLC-MS/MS) coupled with solid-phase extraction (SPE) has emerged as the method of choice due to its high sensitivity, selectivity, and ability to handle complex matrices [12–15]. However, the efficiency of SPE-HPLC-MS/MS methods depends on multiple factors, including sorbent type, elution solvent, sample pH, and reconstitution conditions, which require careful optimization for multi-class antibiotic analysis. While numerous methods exist for antibiotic analysis in water samples [16–20], most target specific classes or regions. Their applicability to data-scarce areas like the Ili River basin is uncertain.

In China, antibiotic pollution research has focused on eastern river basins [21], leaving western regions like Xinjiang largely unexplored. This geographical bias creates a knowledge gap. The Ili River, a transboundary river originating in Xinjiang and flowing into Kazakhstan, is a critical water resource for Central Asia and a key area under the Belt and Road Initiative. Yet no systematic investigation of antibiotic contamination has been conducted here, hindering transboundary water quality assessment and joint management.

To address this gap, this study poses three research questions: (1) What are the concentration levels and spatial distribution patterns of 14 antibiotics, namely sulfonamides (SAs), fluoroquinolones (QNs), tetracyclines (TCs), macrolides (MLs), and β-lactams (β-Ls), in the Yining section of the Ili River and in the effluent of the Huocheng Wastewater Treatment Plant (HWTP)? (2) What is the removal efficiency of HWTP for different antibiotic classes, and which treatment units contribute most to removal or negative removal? (3) What is the ecological risk level (individual and combined) posed by these antibiotics, and which compounds should be prioritized for management? We developed and validated an optimized SPE-HPLC-MS/MS method to answer these questions, thereby providing the first baseline data on antibiotic pollution in the Ili River, a transboundary water body in Central Asia. Unlike previous studies focused on eastern China's densely populated river basins, our work reveals a region-specific antibiotic fingerprint (with tetracyclines as the dominant class) and identifies chlortetracycline (CTC) as a priority pollutant. These findings underscore the need for international cooperation in water quality management within the Belt and Road framework.

2. Materials and Methods

2.1. Sample Collection

Surface water samples were collected from nine sites (S1–S9) along the Yining section of the Ili River in early August 2025 (Figure 1). Additionally, six wastewater samples were taken from different treatment units of the Huocheng Wastewater Treatment Plant (HWTP),

including influent, grit chamber effluent, anaerobic tank effluent, aerobic tank effluent, secondary clarifier effluent, and final effluent. Two downstream sites (M1 and M2) located 1.5 km and 2.5 km below the HWTP outfall were also sampled to assess the impact of wastewater discharge on the receiving river. All samples were collected at 0.5 m depth using a plexiglass sampler (Laboratory-made, China), stored in pre-cleaned 0.5 L amber glass bottles (Huaou Glass Co., Beijing, China), and kept at 4 °C during transport to the laboratory. Upon arrival, samples were processed immediately or stored at 4 °C for no more than 24 h before pretreatment.

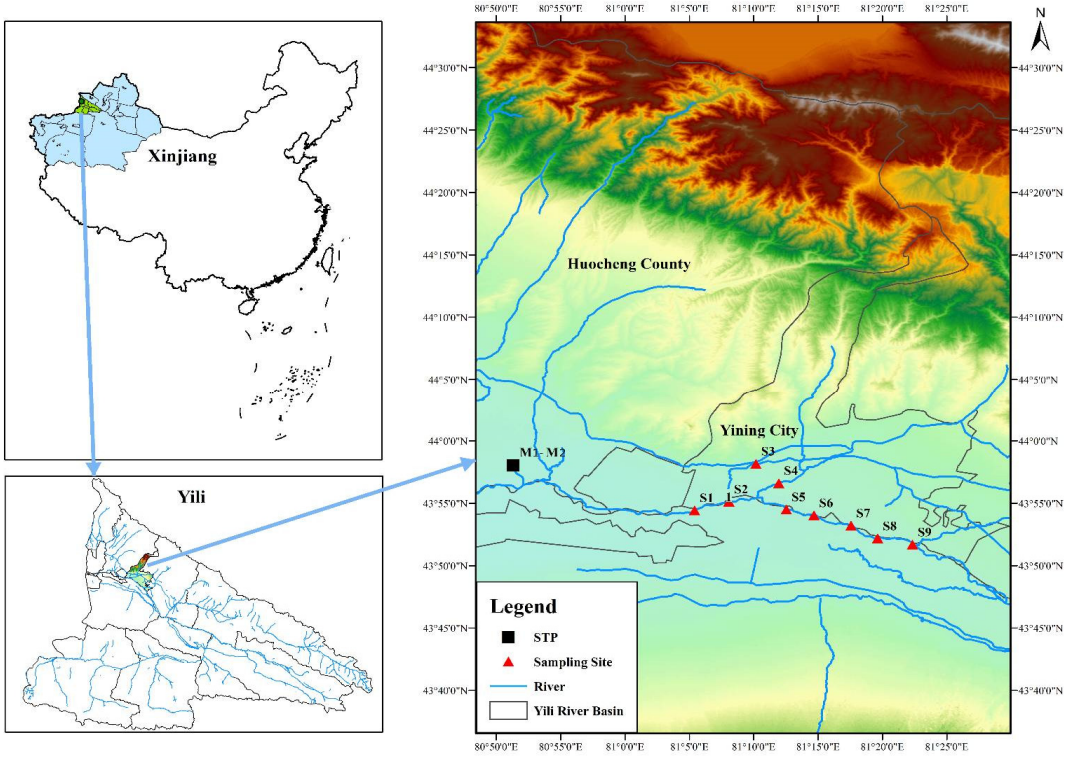

Figure 1. Map of the Ili River Basin showing sampling sites S1–S9 and M1–M2 (downstream of Huocheng WWTP).

2.2. Sample Pretreatment

We added 0.1 g of Na_2EDTA to 250 mL water samples to chelate metal ions that could interfere with antibiotic recovery. The samples were then filtered through 0.45 µm glass fiber filters (Shanghai Xinya Purification Materials Factory, Shanghai, China) to remove suspended particles. Solid-phase extraction was performed using an SPE-1000-6 fully automated solid-phase extraction system (Reeko Instrument Co., Ltd., Xi'an, China) equipped with Oasis HLB cartridges (300 mg, 6 cc). The cartridges were preconditioned sequentially with 12 mL MeOH and 12 mL Milli-Q water at a flow rate of 5 mL·min^{-1}. Filtered water samples were loaded onto the cartridges at a flow rate of 10 mL·min^{-1}. After loading, the cartridges were rinsed with 6 mL Milli-Q water to remove weakly retained impurities and then dried under nitrogen flow for 30 min. The retained analytes were eluted with 12 mL of optimized elution solvent (1% FA in MeOH–AC, 85:15, *v*/*v*) at a flow rate of 3 mL·min^{-1}. The eluate was collected in 15 mL glass tubes (Tianjin Kewei Glass Co., Tianjin, China) and concentrated to near dryness under a gentle nitrogen stream at 40 °C using an N-EVAP-112 nitrogen evaporator (Organomation Associates, Berlin, MA, USA). The residue was reconstituted with 1 mL of reconstitution solvent (0.1% FA in water–ACN, 9:1, *v*/*v*), vortex-mixed for 30 s, and filtered through a 0.22 µm membrane

filter (Shanghai Xinya Purification Materials Factory, Shanghai, China) into a 2 mL amber HPLC vial (Agilent Technologies, Santa Clara, CA, USA) for analysis.

2.3. Chemicals and Reagents

Fourteen antibiotic standards representing five major classes were selected for this study: three sulfonamides (sulfamethoxazole, SMX; sulfamethazine, SMZ; sulfadiazine, SD), five fluoroquinolones (norfloxacin, NOR; ciprofloxacin, CIP; enrofloxacin, ENR; ofloxacin, OFX; sparfloxacin, SPA), three tetracyclines (chlortetracycline, CTC; oxytetracycline, OTC; tetracycline, TC), two macrolides (erythromycin-H_2O, ETM-H_2O; azithromycin, AZM), and one β-lactam (penicillin G, PNE-G). All standards (purity > 93%) were purchased from Dr. Ehrenstorfer (Augsburg, Germany). HPLC-grade methanol (MeOH), acetonitrile (ACN), acetone (AC), formic acid (FA), and ammonium acetate (NH_4Ac) were obtained from Merck (Darmstadt, Germany). Ultrapure water (18.2 MΩ·cm) was prepared using a Millipore Milli-Q system (Merck, Darmstadt, Germany). Oasis HLB cartridges (300 mg, 6 cc) were purchased from Waters (Milford, MA, USA). Na_2EDTA was supplied by Tianjin Kermel Chemical Reagent Co., Ltd. (Tianjin, China). Glass fiber filters (0.45 μm and 0.22 μm, 50 mm diameter) were obtained from Shanghai Xinya Purification Materials Factory (Shanghai, China).

Individual stock solutions of each antibiotic (100 $mg \cdot L^{-1}$) were prepared in MeOH and stored in amber glass bottles at −20 °C in the dark. A mixed working standard solution (1.0 $\mu g \cdot mL^{-1}$) containing all 14 antibiotics was prepared by diluting the stock solutions with MeOH and stored at 4 °C. Fresh calibration standards were prepared weekly by diluting the mixed working solution with MeOH to concentrations of 0, 1, 2, 5, 20, 50, 100, and 200 $ng \cdot mL^{-1}$.

2.4. Instrumental Analysis

Chromatographic separation was performed on an ExionLC AD ultra-high performance liquid chromatography system coupled to a triple quadrupole mass spectrometer (SCIEX, Framingham, MA, USA). An Agilent ZORBAX Eclipse Plus C18 column (100 mm × 3.0 mm, 2.7 μm) (Agilent Technologies, Santa Clara, CA, USA) was used for separation with the column temperature maintained at 35 °C. The mobile phase consisted of (A) 0.1% FA in water and (B) pure ACN, delivered at a flow rate of 0.3 $mL \cdot min^{-1}$. The injection volume was 10 μL. The gradient elution program was optimized as follows: 0–1.5 min, 5% B; 1.5–6.0 min, linear increase from 5% to 95% B; 6.0–7.5 min, hold at 95% B; 7.5–7.6 min, linear decrease from 95% to 5% B; and 7.6–11.0 min, re-equilibration at 5% B.

The mass spectrometer was operated in positive electrospray ionization (ESI^+) mode with multiple reaction monitoring (MRM). The ion source parameters were set as follows: ion spray voltage, 5500 V; ion source temperature, 500 °C; curtain gas, 30 psi; ion source gas 1 (nebulizer gas), 50 psi; ion source gas 2 (heater gas), 50 psi; and collision gas, medium. Optimized MRM parameters for each analyte, including precursor ions, product ions, declustering potential (DP), and collision energy (CE), are summarized in Table 1.

Table 1. Parameters of HPLC-MS detection method.

Compound	Precursor (*m*/*z*)	Product Ion (*m*/*z*)	CE/eV	DP/(v)
SMX	253.9	155.9/92.0	13/25	70
SD	251.0	156.0/108.1	12/20	60
SMZ	279.0	185.9/91.9	13/33	75
NOR	320.1	302.1/276.2	20/12	105
CIP	332.1	314.1/231.1	20/40	100

Table 1. *Cont.*

Compound	Precursor (*m*/*z*)	Product Ion (*m*/*z*)	CE/eV	DP/(v)
ENR	360.1	342.2/316.2	20/16	75
OFX	362.0	344.1/318.1	20/16	90
SPA	393.0	375.1/349.2	16/16	100
CTC	479.0	462.0/444.0	13/17	100
OTC	461.0	443.0/426.0	5/12	95
TC	445.0	427.0/410.0	4/16	105
ETM-H_2O	734.3	576.3/158.1	16/32	110
AZM	749.5	591.4/158.1	28/40	140
PNE-G	335.0	160.1/176.0	4/12	68

Data acquisition and processing were performed using SCIEX Analyst software (version 1.7.1, SCIEX, Framingham, MA, USA). Graphs were created using OriginPro 2021.

2.5. Method Validation

The analytical method was validated for linearity, limits of detection (LOD) and quantification (LOQ), accuracy, and precision following the approaches described in previous studies [19,20]. Calibration curves were constructed by plotting peak areas against concentrations of the mixed standard solutions at eight concentration levels (0, 1, 2, 5, 20, 50, 100, 200 ng·mL^{-1}). Each concentration was analyzed in triplicate. Linearity was evaluated by the correlation coefficient (R^2) of the calibration curve. LOD and LOQ were defined as the concentrations corresponding to signal-to-noise (S/N) ratios of 3 and 10, respectively, determined by analyzing spiked blank water samples at low concentrations.

Accuracy and precision were evaluated through recovery experiments using spiked blank water samples (Milli-Q water) at three concentration levels (50, 100, and 150 ng·L^{-1}) representing low, medium, and high ranges relative to environmental concentrations. Each spiking level was prepared in triplicate and processed following the entire analytical procedure described in Sections 2.3 and 2.4. Accuracy was expressed as the percentage recovery (measured concentration/spiked concentration × 100%). Precision was expressed as the relative standard deviation (RSD, %) of triplicate measurements. Matrix effects were evaluated by comparing the peak areas of analytes spiked into water sample extracts (after SPE) with those of standard solutions at equivalent concentrations.

2.6. Quality Assurance and Quality Control

Strict quality assurance and quality control (QA/QC) procedures were followed throughout the study. Procedural blanks (Milli-Q water processed through the entire SPE procedure) were analyzed with each batch of samples to monitor potential contamination from reagents and laboratory materials. Solvent blanks (MeOH) were injected after every 10 samples to check for carryover between injections. All samples were analyzed in triplicate, and the mean values were reported. Calibration standards were analyzed at the beginning and end of each sample sequence to monitor instrument stability. A calibration curve with $R^2 > 0.99$ was required for quantification. Concentrations below the LOQ were reported as not detected (ND). Duplicate samples were collected at 10% of the sampling sites to assess sampling reproducibility.

2.7. Ecological Risk Assessment

The ecological risk posed by individual antibiotics in surface water was assessed using the risk quotient (RQ) method, which is widely applied in environmental risk assessment [22,23]. The RQ for each antibiotic was calculated as follows:

$$RQ_i = \frac{MEC}{PNEC} \quad (1)$$

where MEC is the measured environmental concentration ($ng \cdot L^{-1}$) of antibiotic i in surface water and PNEC is the predicted no-effect concentration ($ng \cdot L^{-1}$). PNEC values were derived from the literature, based on acute or chronic toxicity data for sensitive aquatic organisms (typically algae, daphnids, or fish) and applying an assessment factor of 1000 for acute toxicity data or 10–100 for chronic toxicity data [24–26], according to the European Technical Guidance Document on Risk Assessment. The PNEC values used in this study were obtained from published sources [22–26] and are listed in Table 2.

Table 2. Aquatic toxicity data and lowest PNEC values of target antibiotics.

Antibiotic	Taxonomic Group	The Most Sensitive Species Tested	NOEC ($mg \cdot L^{-1}$)	L(E)C_{50} ($mg \cdot L^{-1}$)	AF	PNEC ($ng \cdot L^{-1}$)	Reference
SMZ	Lemna	*Lemna minor*	/	1.227	1000	1277	[22]
SD	Algae	*C. vulgaris*		1.226	1000	1226	[23]
SMX	Algae		/	0.52	1000	27	[23]
NOR	Fish	*V. fischeri*	0.01038		100	103.8	[23]
OFX	Fish	*P. promelas*	500		100	5000	ECOSAR
CIP	Fish		500		1000	500	ECOSAR
ENR	Bacteria	*Vibrio fischeri*	0.00288		100	28.8	[24]
SPA	Fish					13,000	ECOSAR
OTC	Algae			0.17	1000	170	[23]
TC	Algae	*M. aeruginosa*		0.09	1000	90	ECOSAR
CTC	Algae	*C. vulgaris*			1000	9310	[25]
ETM-H_2O			2		50	40	ECOSAR
AZM	Bacteria	*P. phosphoreum*		227	1000	150	[23]
PG	Algae	*M. aeruginosa*			1000	4	[26]

Risk levels were classified according to the following criteria: RQ $\leq$ 0.01, negligible risk; 0.01 < RQ $\leq$ 0.1, low risk; 0.1 < RQ $\leq$ 1, medium risk; and RQ > 1, high risk [22,23]. To assess the combined ecological risk from multiple antibiotics at each sampling site, the total risk quotient (RQs) was calculated by summing the individual RQ values [24–26]:

$$RQ_s = \sum RQ_i \quad (2)$$

3. Results

3.1. Optimization of SPE-HPLC-MS/MS Conditions

3.1.1. Optimization of the Mobile Phase

Four mobile phase systems were compared (Figure 2): Group 1 (0.1% FA in water/0.1% FA-ACN), Group 2 (0.1% FA in water/ACN), Group 3 (0.1% FA + 5 mM NH_4Ac in water/ACN), and Group 4 (0.1% FA + 5 mM NH_4Ac in water/0.1% FA-ACN). Group 2 gave the highest overall response. Pure ACN provides stronger elution than aqueous mixtures, compressing peak widths and increasing peak heights, while also reducing carryover [27,28]. Adding NH_4Ac did not improve the responses, indicating preferential $[M + H]^+$ formation over $[M + NH_4]^+$ adducts under these conditions [29,30].

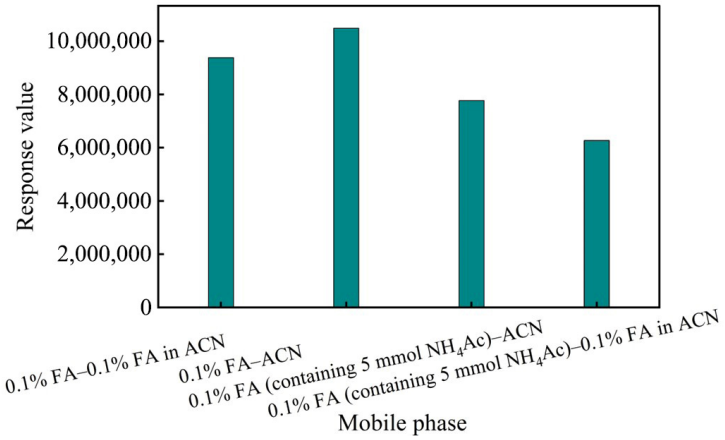

Figure 2. Total response values of 14 antibiotics.

3.1.2. Optimization of Elution Program

Two gradient programs were tested. Procedure 1 (0–1.5 min at 5% B; 1.5–6.0 min linear increase from 5% to 95% B; 6.0–7.5 min held at 95% B; 7.5–7.6 min linear decrease from 95% to 5% B; 7.6–11.0 min re-equilibration at 5% B) produced sharp peaks and high separation efficiency (Figure 3). Procedure 2 (a faster initial ramp: 0–0.5 min at 5% B, then 0.5–1 min to 50% B, and 1–6 min to 95% B) gave broader peaks and poorer resolution. The gradual gradient of Procedure 1 minimizes mass transfer resistance for hydrophobic analytes, while the 7.6–11 min re-equilibration restores hydrophilic conditions, suppressing peak tailing [31,32]. Therefore, Procedure 1 was selected.

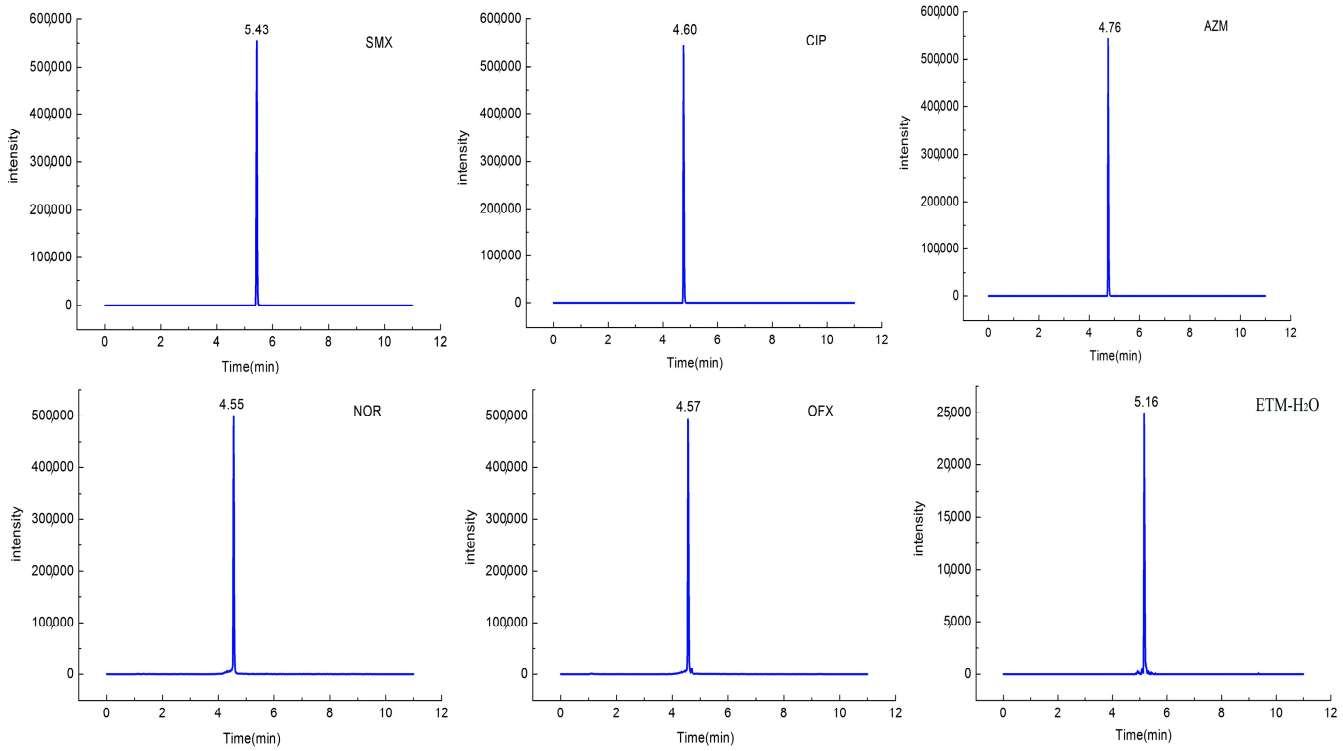

Figure 3. *Cont.*

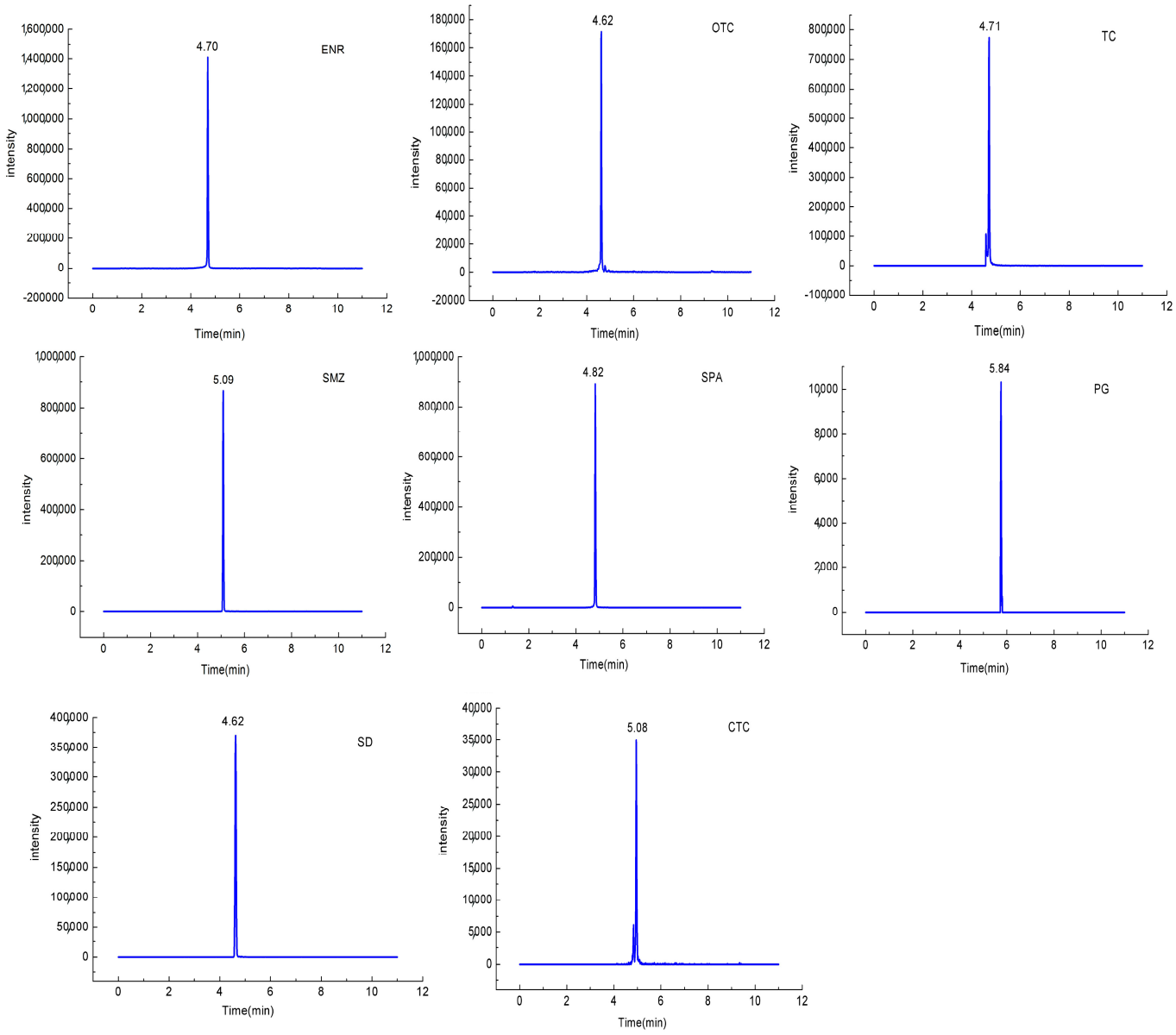

Figure 3. Ion chromatogram of 14 antibiotics.

3.2. Optimization of Sample Pretreatment

3.2.1. Optimization of Elution Solvent

Four eluents were compared (Figure 4a): MeOH, 1% FA-MeOH, MeOH-AC (85:15 v/v), and 1% FA-MeOH-AC (85:15 v/v). Sulfonamides (SAs) and erythromycin-H_2O showed good recoveries with MeOH-AC or pure MeOH (mean recoveries $\geq$75.8% and $\geq$65.1%, respectively; RSD $\leq$ 11.6%). For quinolones (QNs), the addition of formic acid significantly enhanced recoveries (79.7–93.8% in 1% FA-MeOH; 67.8–82.0% in 1% FA-MeOH-AC) because formic acid protonates carboxyl and amino groups, weakening analyte-sorbent electrostatic interactions [33,34]. The mixed solvent 1% FA-MeOH-AC gave the best overall performance across most antibiotics (mean recovery $\geq$67.5 $\pm$ 0.78%), although recoveries for SAs and ETM-H_2O were slightly lower (57.5–60.9%). These differences may arise from specific hydrogen-bonding interactions with the Oasis HLB sorbent [35]. Based on these results, 1% FA-MeOH-AC was selected.

3.2.2. Optimization of pH

Quinolones, tetracyclines, macrolides, and sulfonamides contain acidic/basic functional groups, and their ionization states control SPE recovery through pH-regulated adsorbent interactions [36–38]. Moreover, molecular variations within the same antibiotic class lead to unpredictable pH responses. The effect of pH (3, 5, 7, 9, and 11) on SPE recovery was examined (Figure 4b). The loss of SMZ is due to protonation of its sulfonamide group, which diminishes anion-exchange affinity and reversed-phase retention [39,40]; PNE-G degrades via β-lactam ring hydrolysis under acidic conditions [41]. Neutral pH (pH 7) proved to be consistently suitable for the diverse characteristics of the target antibiotics and was therefore selected as the optimal loading pH.

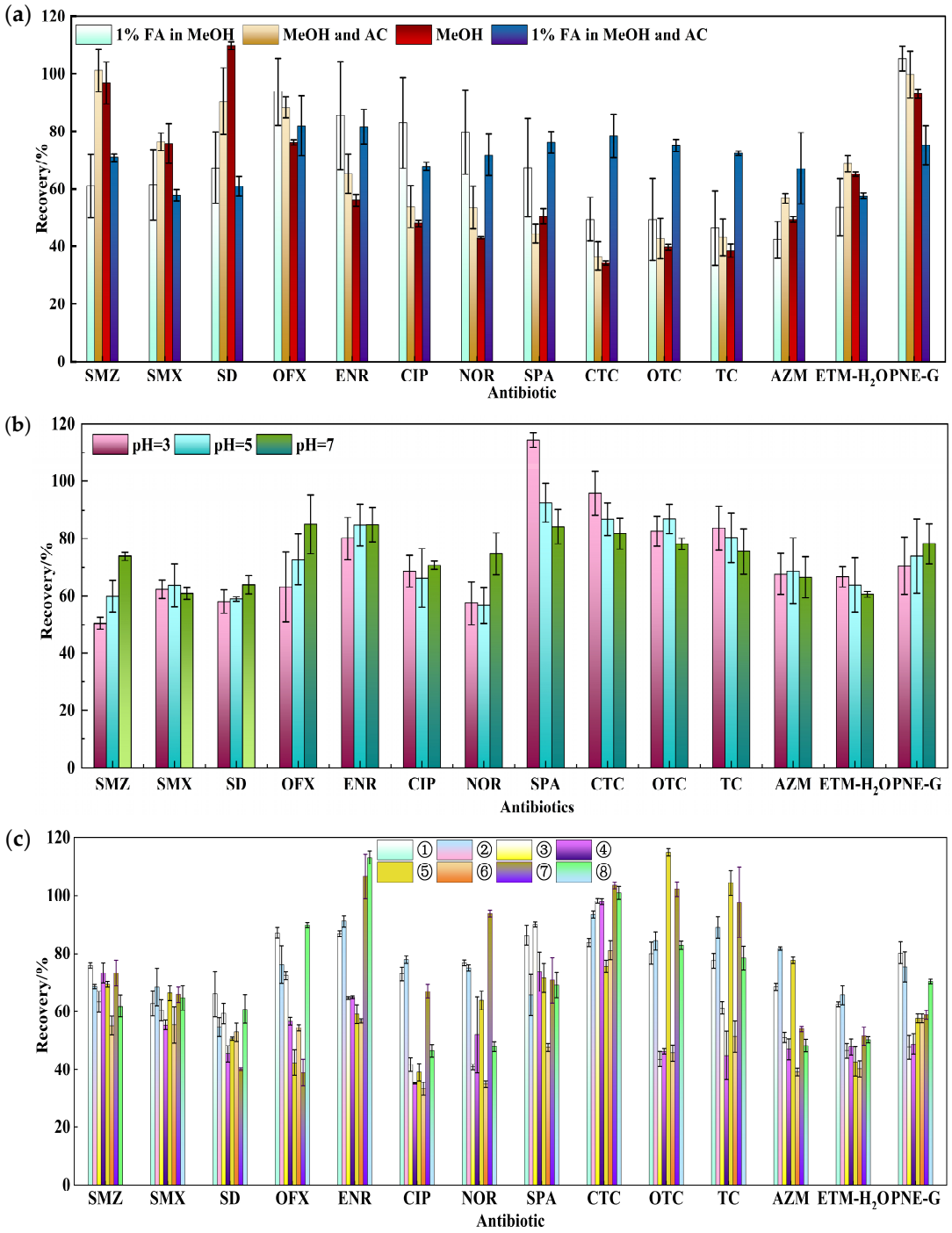

Figure 4. *Cont.*

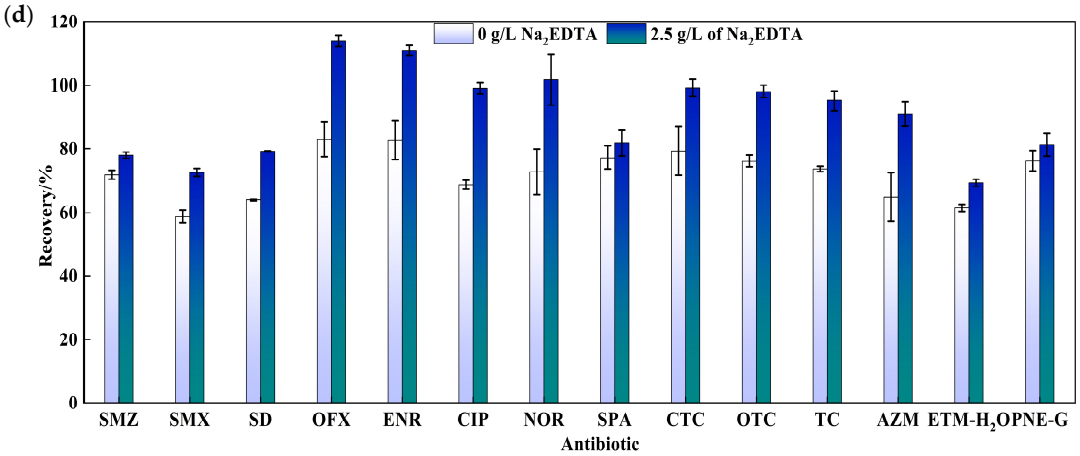

Figure 4. Optimization of sample pretreatment conditions: (**a**) effect of eluents on recovery rate; (**b**) effect of pH on recovery; (**c**) effect of constant volume solvent on recovery; (**d**) effect of Na_2EDTA on recovery.

3.2.3. Optimization of Reconstitution Solvent

Mismatch between the reconstitution solvent and the mobile phase can cause peak broadening, tailing, or splitting, reducing analytical accuracy [42,43]. Existing studies commonly use weak-elution solvents to mitigate this issue [44,45], but systematic investigations on how reconstitution solvents affect the recovery of different antibiotics are lacking [46,47]. To address this, eight solvent combinations were tested (Figure 4c): ① 0.1% formic acid in water:acetonitrile (9:1), ② 0.1% formic acid in water:methanol (9:1), ③ 0.1% formic acid in methanol:acetonitrile (1:1), ④ methanol:acetonitrile (1:1), ⑤ acetonitrile:water (1:9), ⑥ acetonitrile:water (9:1), ⑦ methanol:water (1:9), and ⑧ methanol:water (9:1). Solvent ① performed most consistently across all 14 antibiotics (recovery 67.8–110.5%), outperforming high-organic solvents. Solvents ②, ④, and ⑧ also gave acceptable recoveries for certain antibiotics, but solvent ① was selected as optimal due to its broad applicability. This effect is attributed to the synergistic action of ionization suppression and solvent focusing.

3.2.4. Effect of Na_2EDTA

According to previous studies [48,49], adding Na_2EDTA to water samples can effectively chelate metal ions, significantly reduce their interference with antibiotic analysis, and thereby increase the solid-phase extraction recovery rates of various types of antibiotics. As shown in Figure 4d, after the addition of Na_2EDTA, the average recovery rates of sulfonamides, quinolones, tetracyclines, macrolides, and β-lactams increased by 6.2–15.3%, 4.7–30.3%, 19.9–22.0%, 7.9–26.1%, and 5.1%, respectively.

The variation in recovery enhancement can be primarily explained by the differences in the number and type of electron-rich functional groups present in each antibiotic molecule. Sulfonamides only contain a few weak coordination groups such as sulfonyl amino and benzene rings and have the weakest complexing ability with metal ions, so the increase in recovery rate is the smallest [50]. Quinolones, due to containing a moderate number of functional groups such as carboxyl groups (-COOH), ketone carbonyl groups (-C=O), and piperazine groups, can combine with metal ions through bidentate chelation, resulting in an expanded fluctuation range of recovery rates [51]. Tetracyclines have the most coordination groups, such as phenolic hydroxyl groups, enol -OH, amide -C=O, dimethyl amino groups, etc., which can form multi-dentate complex networks [52]. Their high complexing ability significantly increases the recovery rate (>22.9%). This rule is consistent with the theory of "positive correlation between functional groups and complexation ability" proposed by

Seifrtová et al. [39], and the competitive chelation effect of EDTA reduces the adsorption loss in solid-phase extraction by blocking the formation of antibiotic-metal complexes.

3.3. Method Validation Performance

The analytical method was validated for linearity, sensitivity, accuracy, and precision. Calibration curves were constructed for each antibiotic at eight concentration levels. Excellent linearity was achieved with correlation coefficients ($R^2 > 0.9919$) for all analytes. The limits of detection (LOD) and limits of quantification (LOQ) ranged from 0.05 to 1.0 ng·L^{-1} and from 0.15 to 3.0 ng·L^{-1}, respectively, based on signal/noise ratios of 3 and 10 (Table S1).

Accuracy and precision were evaluated through spiked recovery experiments at three concentration levels (50, 100, and 150 ng·L^{-1}). The mean recoveries ranged from 70.0% to 108.3%, and the relative standard deviations (RSDs) were below 12.7%. Detailed recovery data for each antibiotic and spiking level are provided in Table S2. Representative MRM chromatograms of the 14 target antibiotics are provided in Figure S1.

3.4. Occurrence and Distribution of Antibiotics in HWTP

Twelve antibiotics were detected in the Huocheng WWTP process effluents (Figure 5a,b). SD and SMZ were not detected. AZM was absent in influent, but it appeared in subsequent process effluents. Influent concentrations ranged as follows: SAs ND–17.1 ng·L^{-1}, QNs 2.3–9.8 ng·L^{-1}, TCs 5.8–10.6 ng·L^{-1}, MLs ND–8.6 ng·L^{-1}, and β-Ls 4.4 ng·L^{-1}. The descending order of influent concentrations was SMX > CTC > NOR > ETM-H_2O > OFX > TC > OTC > PNE-G > CIP > ENR > SPA > AZM. The treatment system achieved 9.8–98.3% removal for these 12 antibiotics, but negative removal efficiencies were observed for almost all except CIP, similar to observations in Tianjin, China [53].

After the grit chamber, SMX, NOR, OFX, and ETM-H_2O concentrations increased, possibly due to flow fluctuations or intermittent release from grit solids. Other antibiotics decreased, likely via adsorption onto suspended solids and physical filtration [54]. SMX has a low sludge adsorption coefficient (Kd = 3.2–370 L·kg^{-1}), indicating weak adsorption. Because Kd values below 500 L·kg^{-1} favor aqueous phase retention [55], SMX removal occurs mainly via biodegradation [55–57]. However, SMX rebounded in the final effluent, likely due to deacetylation of its metabolite N^4-acetyl-SMX under hypoxic conditions [58,59].

For QNs, adsorption is the primary removal pathway [57]. Four of the five QNs decreased in the aerobic tank by 11.76–77.78%, likely due to adsorption via hydrophobic/electrostatic interactions and hydrogen bonding [60–63]. The same four QNs increased in the anaerobic tank, possibly due to reversible physisorption [64,65]; OFX and NOR increased by 111.76% and 53.38%, respectively, relative to aerobic tank levels. This suggests that returned sludge, enriched with OFX and NOR, releases these antibiotics under anaerobic conditions. Similar negative removal has been reported for CIP, ENR, NOR, and OFX in other studies. For example, Tian et al. observed negative elimination rates for CIP (−18.3 ± 124.2%), ENR (−27.0 ± 142.7%), NOR (−76.5 ± 281.3%), and OFX (−223.2 ± 339.2%) in wastewater from a WWTP [44].

For TCs, removal followed, CTC (54.72%) > TC (47.95%) > OTC (10.34%), consistent with previous reports [66]. Aerobic and anaerobic processes had little effect on TC, OTC, and CTC removal, likely due to their complex chemical structure resisting biodegradation [67]. Two main mechanisms have been proposed: (i) photodegradation and hydrolysis converting tetracyclines to 4-epimers [68] and (ii) sludge adsorption via electrostatic interactions between zwitterionic tetracyclines and negatively charged sludge surfaces, which is pH-dependent [69].

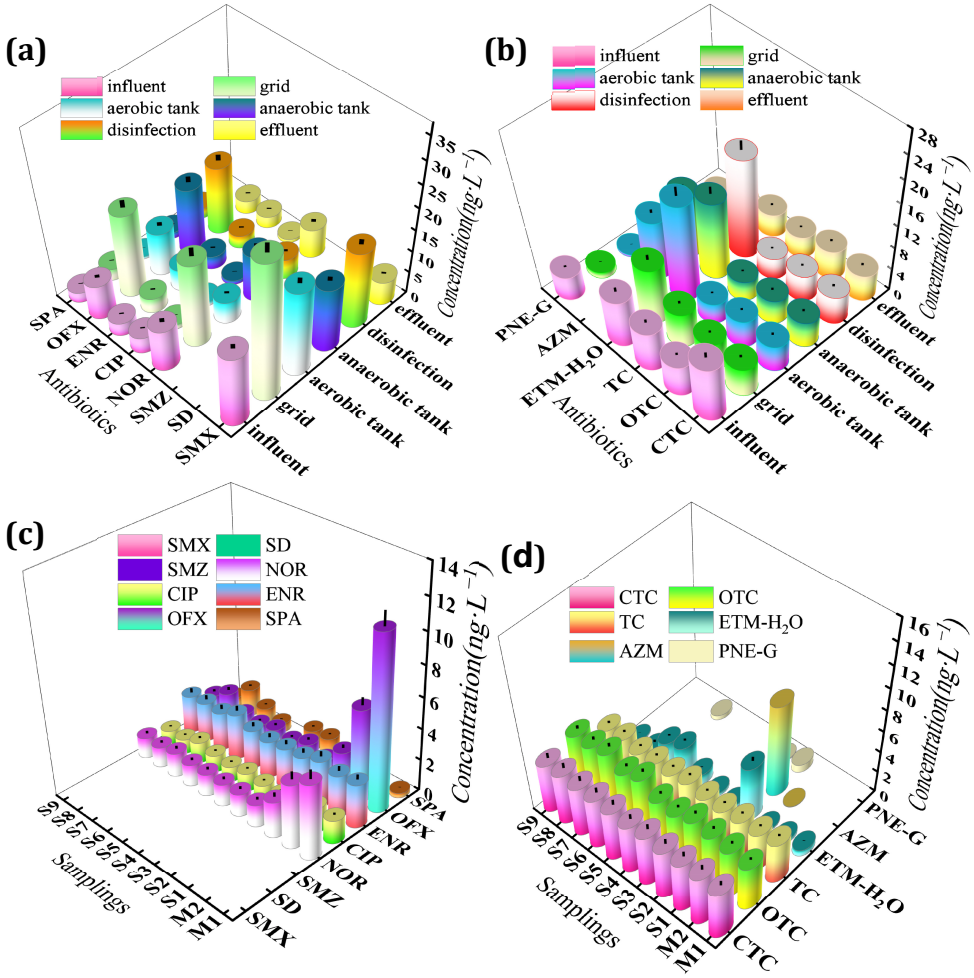

Figure 5. Antibiotic concentrations in water samples. (**a**,**b**) Concentrations of 12 detected antibiotics across six treatment units of Huocheng WWTP. (**c**,**d**) Concentrations at 11 sampling sites (S1–S9, M1, M2) in the Yining section. Error bars: SD (n = 3).

For MLs, concentrations of ETM-H_2O increased in the aerobic tank, while AZM increased in the anaerobic tank. Several factors may explain this. First, macrolides are primarily excreted via bile/feces; during biological treatment, fecal organic matter hydrolysis releases bound antibiotics into the liquid phase [57]. Second, microbial β-glucosylase may hydrolyze glucuronic acid conjugates, converting metabolites back to parent compounds [70]. Third, matrix effects in raw wastewater can suppress MS detection, underestimating influent concentrations; after secondary treatment, reduced matrix effects lead to apparent concentration increases [71]. Fourth, intracellular MLs released during cell lysis or sludge hydrolysis can further elevate aqueous concentrations, especially in anaerobic digestion [72].

3.5. Antibiotic Distribution in the Yining River Section

As shown in Figure 5c,d, the M1 site exhibited significantly higher antibiotic concentrations (up to 11.2 ng·L^{-1}) than other locations, with OFX as the primary contaminant. At the remaining sites, concentrations were relatively stable, ranging from below the detection limit to 8.79 ng·L^{-1}. Within the Yining River section, eight distinct antibiotics were ubiquitously detected (100% detection frequency). Though SMX is frequently reported as the dominant compound in global monitoring studies [73], it was conspicuously absent in this study. This divergence potentially reflects region-specific pharmaceutical usage patterns or selective environmental degradation mechanisms. The exceptionally low contamination

levels (maximum: 8.79 ng·L^{-1}) observed throughout the study area are likely attributable to stringent governmental controls on industrial and agricultural pollutant discharges.

Antibiotic concentrations across sites S1–S9 followed a descending order: OTC (4.3–5.68 ng·L^{-1}) > CTC (4.6–4.87 ng·L^{-1}) > TC (3.45–3.85 ng·L^{-1}) > ENR (2.36–2.99 ng·L^{-1}) > OFX (1.37–11.2 ng·L^{-1}) > NOR (1.31–4.8 ng·L^{-1}) > ETM-H_2O (0.13–5.19 ng·L^{-1}) > CIP (0.92–1.6 ng·L^{-1}) > SPA (0–2.89 ng·L^{-1}) > AZM (0–8.79 ng·L^{-1}) > PNE-G (0–0.74 ng·L^{-1}). TCs dominated the antibiotic burden (55.94%), followed by QNs (33.75%), MLs (9.73%), and β-Ls (0.57%), aligning with global trends of veterinary antibiotic predominance in agricultural catchments [9,56].

3.6. Ecological Risk Assessment Results

Considering the worst-case scenario, this study employed minimum PNEC values of 14 antibiotics for conservative risk assessment. Calculated RQ values (Figure 6a) indicated that 42.21% of antibacterial compounds posed negligible risk, 32.47% low risk, 25.32% medium risk, and 0% high risk. Specifically, SMX, SD, SMZ, SPA, AZM, NOR, ETM-H_2O, and PNE-G were classified as negligible-risk compounds. ENR, OTC, and TC constituted low-risk compounds, while CTC, OFX, and CIP represented medium-risk compounds. AZM exhibited low risk at S2 but negligible risk elsewhere. NOR, ETM-H_2O, and PNE-G showed medium ecological risk at 27%, 18%, and 9% of sampling sites, respectively, with remaining sites indicating low or negligible risk. Notably, CIP, OFX, and CTC consistently demonstrated RQ values > 0.1 (medium risk), with CTC showing the highest values among all detected antibiotics (0.92–0.97, still within the medium risk category) in both effluents and river water.

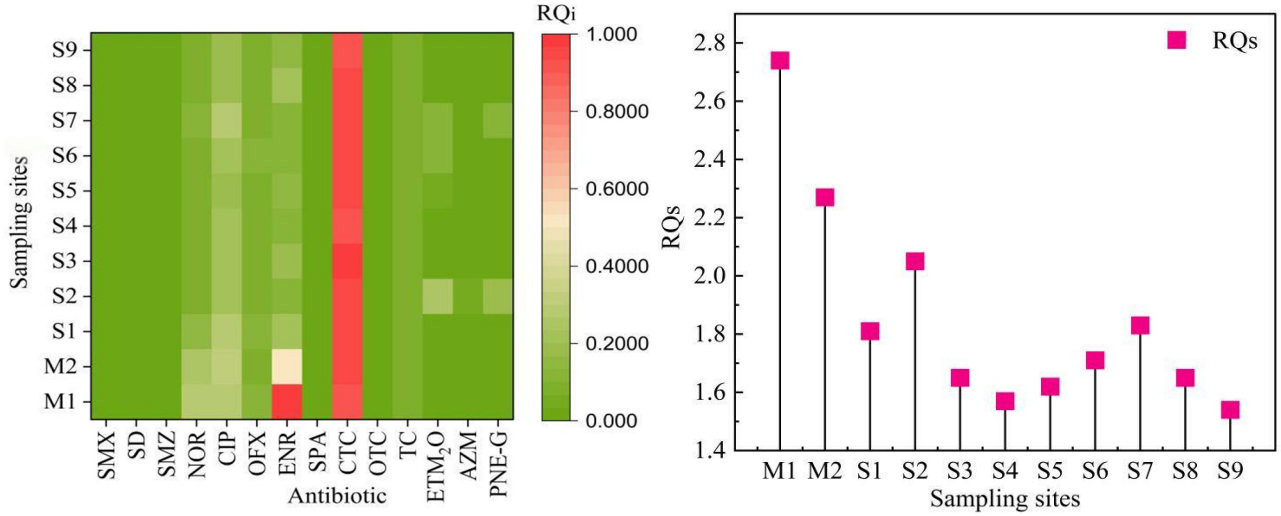

Figure 6. Ecological risk assessment. (**a**) Individual risk quotients for each antibiotic across all sampling sites. (**b**) Combined risk quotients at each sampling site.

Among all 11 sampling points, the measured comprehensive risk quotient values RQs ranged from 1.54 to 2.74, indicating that the combined ecological risk from 14 antibiotics in the Yining section falls into the high-risk category (Figure 6b). The M1 and M2 sites, located near the HWTP outfall, showed elevated RQs (2.05–2.74). This suggests that the discharge from the HWTP is a probable major contributor, although other diffuse sources (e.g., untreated sewage, agricultural return flow) cannot be excluded. Point S2, situated in the park area on the south bank of the Ili River, exhibited similarly high RQs; these may be influenced by a combination of tourism, surface runoff, and potentially landfill leachate.

However, direct evidence (e.g., chemical tracers or isotope analysis) is needed to confirm these source contributions.

The RQ and ΣRQ method used here assumes concentration addition, i.e., that the combined effect of multiple antibiotics is the sum of their individual effects. This approach does not account for potential synergistic (more-than-additive) or antagonistic (less-than-additive) interactions among the 14 antibiotics. Furthermore, the PNEC values are derived from single-species toxicity tests with application of assessment factors, which introduces additional uncertainty. Therefore, while our ΣRQ > 1 indicates a potential for adverse ecological effects, the actual risk may differ due to these unaddressed mixture interactions and data gaps. This assessment should be viewed as a conservative, screening-level evaluation.

4. Discussion

4.1. Comparison with Global Antibiotic Pollution Studies

To contextualize our findings, we compared antibiotic concentrations and class compositions in the Ili River with those reported in major rivers globally (Table 3). The total antibiotic concentrations in the Yining section were one to two orders of magnitude lower than those in major Chinese rivers (Yangtze, Yellow, Pearl, Haihe) and also below global median concentrations for QNs (2.47 ng·L^{-1}) and TCs (2.05 ng·L^{-1}) [5]. However, the proportion of TCs was substantially higher than in most other regions, indicating intensive veterinary antibiotic use. This tetracycline dominance contrasts with the global pattern where sulfonamides are the most widely distributed class [5] and also differs from the SAs and QNs dominance in Chinese coastal waters such as Jiaozhou Bay, where concentrations ranged from 15.0 to 650 ng·L^{-1} [74].

Globally, SMX, CIP, and ETM-H_2O are among the most frequently detected antibiotics in rivers [3]. In freshwater reservoirs, SAs, TCs, MLs, and QNs show high detection frequencies, whereas β-Ls are less common [75]. Our findings align with the low β-Ls detection but diverge in the dominance of tetracyclines over sulfonamides. This compositional signature distinguishes the Ili River from human-dominated watersheds and underscores the need for source-specific management.

Table 3. Comparison of antibiotic concentrations in the Ili River with major rivers worldwide.

		SAs	TCs	QNs	MLs	β-Ls	Ref
China	Hong Kong	ND–79.9	ND–31.5	ND–75.5	ND–2.8	ND–25.7	[76]
	Yangtze River	ND–940.0	ND–1454.8	ND–990	ND–2796.6	—	[77]
	Yangtze River and Jialing River	ND–142.8	ND–10.1	ND–117.7	ND–263.7	—	[78]
	Liaohe River Basin	ND–14.8	ND–57.9	ND–105.3	0.83–203.1	ND–331.6	[79]
	Nanming River	ND-289.7	ND-76.7	ND-645.1	—	—	[80]
	Sanya's rivers and bays	ND–48.6	ND–230.4	ND–213.4	ND–223.8	—	[81]
	Yellow River	59.3–100	31.8–264	61.8–100	30–100	–	[82]
	Mountain rivers in Chongqing	ND–60	ND–70.3	ND–73.6	ND–20.6	—	[83]
	Yangtze River	ND–12.5	ND–15	4.27~91.8	ND~73	—	[84]
	Bohai Sea	ND–7.5	ND–1515.1	ND–64.8	ND–193.1	—	[85]
	Dongjiang River	ND–36	ND–63.9	ND–99.3	ND–9.7	—	[86]
	Wenyu River	–	0.31~5.3	0.65~8.8		—	[87]
Spain	Ter River	ND–29.2	ND	ND–80.1	ND–173.3	ND–14.8	[88]
Germany	Reservoir	0.01–0.4	ND	ND	0.01–0.6	ND	[89]
Brazil	Belém and Barigui rivers	ND–1.8	ND	ND–0.1	0.08–0.7	0.18–4.6	[90]

Table 3. *Cont.*

		SAs	TCs	QNs	MLs	β-Ls	Ref
Argentina	Suquía River	ND–3.8	ND–34	ND–706	ND–336	—	[91]
India	Cirata reservoir and river	—	ND–10	ND–112	—	—	[92]
India	Sabarmati River	ND–5.3	—	ND–12.4		ND–1.9	[93]
Spain	Ter River	ND–76.3	—	ND–131	ND–115.9	ND–165.6	[94]

—: not reported.

4.2. Source Interpretation Based on Spatial Patterns and Antibiotic Profiles

The absence of SMX, a common marker of domestic sewage, combined with the predominance of TCs (55.9% of total antibiotics), suggests that livestock farming may be a major source of antibiotic pollution in the Yining section. The consistently high–risk quotient of CTC is consistent with this hypothesis. Spatially, the elevated concentrations at S2 could be attributed to local human activities, potentially including tourism, surface runoff, or landfill leachate, although direct evidence is lacking. The elevated levels at downstream sites M1 and M2 are highly likely influenced by HWTP discharge. Furthermore, the presence of OFX as a main contaminant at M1 tentatively points to contributions from hospital or domestic wastewater sources, a possibility that requires further investigation given the absence of large hospitals in the immediate vicinity. We stress that these source inferences are qualitative and based on spatial patterns and antibiotic profiles; quantitative source apportionment was not feasible due to the high proportion of non-detects in our dataset.

Quantitative source apportionment (PCA or correlation analysis) was not feasible due to the high proportion of non-detects in the dataset. Therefore, the source interpretation above is based on qualitative lines of evidence.

It should be noted that TCs are susceptible to alkaline hydrolysis, which may generate not only 4-epimers but also nitrogen-containing degradation products such as nitrite [69]. The release of nitrite into water bodies could potentially contribute to eutrophication, an indirect ecological risk beyond the direct toxicity of the parent antibiotics. Although the present study did not quantify these transformation products, their possible environmental effects warrant attention. Future investigations should include the identification and toxicity assessment of tetracycline degradation products, especially under alkaline conditions, to fully evaluate the ecological risks associated with tetracycline pollution.

4.3. Implications for Sustainable Wastewater Management in Transboundary Rivers

The variable removal efficiencies (from 9.8% to 98.3%) and negative removal for OFX, NOR, and ETM-H_2O observed at HWTP (Section 3.4) are not unusual; similar phenomena have been reported in China and Europe. However, for a transboundary river like the Ili, discharging partially treated effluent has cross-border implications. The conventional activated sludge process, which relies on adsorption and biodegradation, is inherently unstable for antibiotics due to reversible sorption and metabolite reconversion. Therefore, upgrading WWTPs with tertiary treatment should be evaluated, especially for plants located near international borders. Furthermore, the rebound of SMX in the final effluent may result from reconversion of its metabolite N4-acetyl-SMX to the parent compound under hypoxic conditions.

The high combined risk (ΣRQ = 1.54–2.74) observed at low individual concentrations underscores that mixture effects, rather than single-compound toxicity, drive the overall ecological risk in this river section. From a sustainability perspective, our findings support three actionable recommendations: (i) inclusion of CTC in routine monitoring programs as a priority pollutant; (ii) upgrading conventional WWTPs with advanced treat-

ment technologies to address negative removal; and (iii) fostering bilateral cooperation between China and Kazakhstan under the Belt and Road Initiative for transboundary water quality management.

4.4. Limitations and Future Directions

This study has three main limitations. First, and most critically, this study is based on a single sampling campaign conducted in August 2025. The results therefore represent a spatial snapshot rather than a long-term characterization of antibiotic pollution dynamics. This single-season design cannot account for seasonal variations driven by changes in temperature, hydrological regimes (e.g., high-flow vs. low-flow periods), or agricultural cycles (e.g., veterinary antibiotic application peaks, irrigation schedules). Consequently, our conclusions regarding concentration levels and ecological risks are strictly limited to the summer low-flow period. Future multi-seasonal investigations are essential to capture the full temporal dynamics and to validate the annual risk patterns inferred from this baseline study. Second, only water samples were analyzed; antibiotics may accumulate in sediments and biota, particularly tetracyclines and fluoroquinolones which have high adsorption affinities. Future work should include sediment and organism samples. Third, we did not quantify antibiotic resistance genes, although antibiotic residues are known to promote resistance. Future research should combine chemical analysis with molecular tools to assess resistance risks. Furthermore, the summed RQ method used for combined risk assessment assumes additive effects; potential synergistic or antagonistic interactions among antibiotics were not considered, which may affect the accuracy of the risk estimates.

5. Conclusions

This study investigated the occurrence, distribution, and ecological risks of 14 antibiotics in the Yining section of the Ili River, a transboundary water body in Central Asia. Three main findings emerge from the analysis:

(1) Although total antibiotic concentrations in the river were relatively low (ND–11.2 $ng \cdot L^{-1}$) compared to major Chinese rivers, tetracyclines dominated the antibiotic burden (55.9%). This compositional signature, contrasting with the sulfonamide-dominated profiles common in human-impacted watersheds, strongly suggests that veterinary use in livestock farming is the primary source in this transboundary river.

(2) The Huocheng WWTP exhibited highly variable removal efficiencies (9.8–98.3%) and negative removal for OFX, NOR, and ETM-H_2O, revealing inherent limitations of conventional activated sludge processes in completely eliminating antibiotics.

(3) The RQs in the Yining section ranged from 1.54 to 2.74, falling into the high-risk category. CTC showed the highest individual risk (RQ 0.92–0.97, medium risk approaching the high-risk threshold) and is proposed as a priority pollutant for routine monitoring.

From a sustainability perspective, three actionable recommendations emerge: (i) inclusion of chlortetracycline in regional water quality monitoring programs; (ii) evaluation of tertiary treatment for WWTPs located near international borders; and (iii) enhanced bilateral cooperation between China and Kazakhstan under the Belt and Road Initiative for joint monitoring and data sharing. As the first comprehensive study on antibiotic pollution in a Central Asian transboundary river, this work provides essential baseline data and supports evidence-based water quality management in data-scarce regions.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/su18115591/s1; Table S1: Linear equation, correlation coefficient and limits of detection of the proposed method; Table S2: Spiked recoveries and relative standard deviation (RSD) of the 14 antibiotics in water samples (n = 3); Figure S1: Mass spectra of 14 antibiotics.

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