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Review

Review on Biogeochemical Characteristics of Typical Antibiotics in Groundwater in China

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Abstract: The problem of antibiotic contamination in the environment has attracted much attention in recent years. However, studies on antibiotic contamination in groundwater have only emerged in the last 15 years. In this study, we systematically reviewed the detection methods, distribution characteristics, risk, fate, and sources of antibiotics in groundwater in China, listed the concentrations of the main antibiotic types, and obtained the maximum concentrations by comparing the literature published in the last 10 years. The results show that 65 antibiotics were detected in groundwater in China, with sulfonamides and quinolones receiving the most attention. Antibiotic concentrations are influenced by hydrogeological conditions and seasonal variations, and the ecological risk in most areas is low to medium risk, which is relatively manageable. The highest concentrations found in most of the literatures were in the range of 10–1000 ng/L, but the maximum concentration can reach 47,444.5 ng/L, which requires extra attention. In addition, this study makes recommendations for improving groundwater monitoring surveys and protection measures to prevent the antibiotic contamination of groundwater more effectively.

Keywords: biogeochemistry; antibiotics; groundwater; source; distribution; fate; risk

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1. Introduction

Currently, antibiotics, which mainly include quinolones (QNs), sulfonamides (SAs), tetracyclines (TCs), macrolides (MCs), chloramphenicols (CPs), β-Lactams (β-Ls), and lincosamides (Lins), have been widely used in human and veterinary medicine and are consumed in huge quantities [1–5]. According to surveys, the global consumption of antibiotics in agriculture ranges from 63,000 to 240,000 tons annually, and that of antimicrobials in food animal production was 63,151 (±1560) tons by estimation in 2010 [1,3]. China is a major producer and consumer of antibiotics. In 2013, the total usage was about 162,000 tons in China, 52% of which was used for animals and 48% of which was for humans. With the implementation of China's policy, in 2020, the total usage of veterinary antimicrobials declined to 32,776.298 tons [6–8].

Unfortunately, antibiotics cannot be completely removed, and eventually they are released into the environment, affecting all kinds of organisms—even humans. Approximately 70% of antibiotics are directly or indirectly released into the environment every year in China, and according to the reports, antimicrobial resistance will cause the deaths of 300 million individuals worldwide and economic damage amounting to 60–100 trillion dollars in the next 35 years [9,10]. In terms of the impact of antibiotics, antibiotics can exhibit cytotoxic effects in cells because of the induction of apoptosis, affecting the richness of the microbial community [11,12]. When antibiotics are released into the environment they can be toxic to algae, causing a significant decrease in photosynthesis, and can adversely affect the liver, kidneys, and reproductive organs of animals over time. For example, tetracycline (TC) causes significant developmental delay in zebrafish embryos, while cefotaxime, enrofloxacin, tetracycline, and sulfamonomethoxine significantly disrupt the immune response of fish macrophages in vitro [13–15]. Moreover, according to the study of trophodynamics in a marine food web from Laizhou Bay by Liu et al., SAs and trimethoprim have the possibility of biomagnification with trophic magnification factors of 1.2–3.9, and their low metabolic transformation and effective assimilation in animals at higher trophic levels are their possible reasons for biomagnification [16]. Most antibiotics are partially metabolized in humans or animals, and whether through drinking groundwater or eating animals who have antibiotic toxicity, the intake of antibiotics can have an impact on the human body [16]. Zhang et al. suggested that chronic exposure to sulfonamides may produce cytotoxicity, reduce cellular antioxidant capacity, and cause inflammation, and may also cause genotoxicity at high concentrations. Long-term exposure to mixed sulfonamides may cause liver tissue damage and affect the intestinal flora, resulting in adverse effects on human health. [17]. Third, the occurrence of antibiotics in the environment may give rise to the occurrence of antibiotic resistance genes (ARGs) and antibiotic resistant bacteria (ARBs) in the environment, and their migration, transformation, and diffusion may also have potential effects on the environment and humans [15].

What is worse, antibiotics not only pollute surface water, but also filter into groundwater by the interaction of surface water and soil [18,19]. However, according to statistics, groundwater utilization in China is large, and its average utilization rate is close to 30% [20]. As one of the important water resources, groundwater is commonly used for irrigation, industrial applications, services, and residential use [21]. In the north, groundwater supplies about 60% of the total urban water use, about 50% of the total industrial water use, and about 25% of the total agricultural water use. In the 41 major cities in the south, 39% of the water supply is groundwater [20].

Unfortunately, less attention has been paid to antibiotic contamination in groundwater compared to the organic and inorganic indicators. In order to have a clear understanding of antibiotics in groundwater in China, our study here integrates the published research results of the past ten years, sorts out the concentrations of antibiotics detected in groundwater in China, and summarizes detection methods, concentrations, ecological risks, sources, distribution characteristics, and the fate of antibiotics so as to provide a scientific basis for the prevention and control of antibiotic pollutants.

2. Monitoring and Analysis of Antibiotics in Groundwater

2.1. Pretreatment Methods

As the concentration of antibiotics in groundwater in China is at trace level, the solid phase extraction technique (SPE) is usually used for pre-treatment enrichment. It uses selective adsorption and selective elution to enrich, separate, and purify the samples, which can be done simultaneously to improve the detection sensitivity, processing speed, and reproducibility, but the cost is high. In the studies of antibiotics in groundwater in China, the water samples go through the steps of filtration, pH adjustment, activation of the column, passing through the cartridge, washing, elution, evaporation, addition of internal standard substances, volume replenishment with methanol, and so on.

In order to determine antibiotics in groundwater more effectively, many scholars have improved and elaborated sample extraction schemes. The Oasis HLB SPE column is commonly used for sample extraction. It is a hydrophilic-lipophilic polymeric packing material that can purify and enrich compounds over a wide pH range [22]. Na_2EDTA is generally added in the pretreatment process because the concentration of metal cations in groundwater is high and easily complexed with antibiotics, and Na_2EDTA can complex the metal cations and inhibit the complexation of metal cations with antibiotics, increasing the recovery rates of antibiotics [2]. Tong et al. found that the recovery rates of TCs were enhanced nearly 20% and those of other target compounds were not more than 10% in samples with the addition of Na_2EDTA, compared with samples without the addition of Na_2EDTA [23]. For water sample filtration, 0.2 µm, 0.22 µm, 0.45 µm, and 0.7 µm filter membranes are usually used [2,5,19,23–27]. For pH adjustment, different antibiotics have different recovery rates at different pH conditions. Yang found that when pH was 7, the ionization of FQs was inhibited, so it could be better retained on the packing polymer [7]. Tong L et al. analyzed SAs, FQs, TCs, and CAP, and found that the recovery rates were within acceptable ranges from 54.2% to 98.7% under weakly acidic condition at pH 4.0 [23]. Therefore, during the pretreatment process, the pH of the water sample needs to be adjusted according to the molecular structure characteristics of the analyzed antibiotics, which helps to ensure the accuracy of the assay results. For column activation, methanol and water, or methanol and Na_2EDTA, are often used as activators. When passing through the cartridges, due to the significant impact of the drying of the extraction column on the adsorption effect of antibiotic, attention must be paid to the continuity of the water samples and try to avoid interruption of the flow so as not to damage the membrane liquid on the absorbent or affect the recovery rate and reproducibility. At the same time, it should be noted that a slow flow rate can lead to the decomposition of antibiotics [7].

Notably, a few researchers have attempted antibiotic enrichment by solid phase microextraction (SPME). Esponda, SM et al. optimized SPME with regard to time, temperature, pH, and ionic strength using a CW-TPR fiber, applied it with micellar desorption methodology to the determination of antibiotics in several environmental liquid samples, including groundwater, and the results were satisfactory with the mean recoveries of 81–116% [28]. However, Mcclure E L et al. suggested that it may not be feasible to apply SPME to waters with lower antibiotic concentrations. They used high performance liquid chromatography tandem mass spectrometry (HPLC-MS/MS) to analyze the influent and effluent of sewage treatment plants and compared the difference in extraction effectiveness between SPE and SPME. It was found that the RSD of SPE ranged from 1–19%, while that of SPME ranged from 7–50%. The LOD of SPE influent and effluent were 0.41–6.1 ng/L and 0.08 to 1.8 ng/L, while that of SPME ranged from 2.8 to 410 ng/L and 4.1 to 77 ng/L, respectively [29].

2.2. Analytical Methods

Commonly used antibiotic analysis methods in aquatic environment can be divided into enzyme-linked immunosorbent assay (ELISA), capillary electrophoresis, chemiluminescence analysis, electrochemical analysis, liquid chromatography, and their combination methods, which have different characteristics when applied to antibiotic detection [7,30–33]. Among them, liquid chromatography (LC), including LC, HPLC and ultra high-performance liquid chromatography (UPLC), is most commonly used in the detection of environmental water.

Detectors for LC include UV, fluorescence detector (FD), electrical conductivity detector (ECD), diode array detector (DAD), and MS, which have different advantages and disadvantages. Diode array detector (DAD), UV, and MS have been used in the detection of antibiotics in groundwater [26,34–36]. Among them, HPLC-MS/MS and UPLC-MS/MS are important methods for qualitative and quantitative detection, with high sensitivity and accuracy, and can simultaneously detect multiple antibiotics in samples. Because the antibiotics concentration is reduced by adsorption and degradation in groundwater and soil, the concentration of antibiotics in groundwater is much lower than that in surface water, sediments, and wastewater. In China, HPLC-MS/MS and UPLC-MS/MS are more common in groundwater antibiotics analysis.

Many authors have also elaborated and improved LC detection schemes for more efficient determination of antibiotics in groundwater. C_{18} reversed-phase chromatography is commonly used because it is suitable for the separation of neutral or non-ionic compounds that are soluble in water/organic mixtures. For elution, the most used method is gradient elution, namely the concentration ratio of the mobile phase varies to a certain extent to achieve better separation in the same analytical cycle. The mobile phase is mainly divided into organic and aqueous phases. For the aqueous phase, 0.1% formic acid water is mainly used [36–44]. Lang and Yang found that using methanol alone as the organic mobile phase resulted in significant tail peaks for most antibiotics [2,7]. Conversely, acetonitrile makes the elution of most antibiotics fast and the separation of all substances may be poor, with peak overlap. Lang et al. found that using 64 antibiotic assays with methanol/acetonitrile (1/1, *v/v*) as an organic mobile phase not only ensures that the target analytes can be separated within 15 min of detection, but also makes the peak pattern without significant tailings and strong symmetry, improving accuracy [2]. In addition, the sensitivity of antibiotic detection was significantly improved with the addition of 0.1% formic acid in the organic phase compared to no formic acid and the addition of 0.2% formic acid. However, Yang found that for the detection of FQs in isocratic elution, when the acetonitrile concentration ratio was above 50%, it could not be completely separated, and when the concentration ratio was 40%, it could be completely separated within 22 min [7]. Therefore, the concentration ratio of the eluate needs to be adjusted according to the specific assay target and assay method.

For MS detectors, the triple quadrupole mass spectrometer commonly used for measuring antibiotic concentrations in water has shown some consistency in the detection schemes of scholars. It a spatial tandem mass spectrometry detection technique which can accurately detect the mass-to-charge ratio of the parent ions of the target compound and the characteristic daughter ions of the target compound with a low LOD, suitable for multi-component trace analysis [2]. It is usually equipped with an electrospray ionization (ESI) source. ESI is the most commonly used ionization method in antibiotic analysis which is excellent for manipulation and suitable for ionizing polar and non-polar compounds [45]. For MS/MS monitoring mode, the positive ionization mode and the multiple reactions monitoring mode (MRM) are usually operated.

3. Distribution of Typical Antibiotics in Groundwater

The distribution of antibiotics in the environment can be influenced by many factors. Due to the different residence time and distance from the contamination source to the sampling well, groundwater has different degrees of attenuation and dilution. Therefore, the detected concentration may be affected by various factors such as the contamination source, sampling location, sampling depth, etc. [46,47]. Based on the investigations of many scholars, we found that the concentrations of antibiotics in groundwater can vary greatly due to different sampling seasons, different hydrogeological conditions, and the inherent properties of antibiotics (such as water solubility, adsorption, degradation, and so on). This chapter compiles the concentrations of antibiotics in the retrieved literature, as well as the effect of seasonal variation and hydrogeological conditions on the concentration of antibiotics in groundwater.

3.1. Levels of Typical Antibiotics in Groundwater

This study summarizes the concentrations of antibiotics detected in groundwater in China from published reviews. The main types of detection (QNs, SAs, TCs, MCs, which we consider typical antibiotics) and their corresponding concentrations in different regions are shown in Tables 1–4. To date, a total of 64 antibiotics have been detected over the period 2007–2020, with the study areas being in northern and southern China. In the north, there are more studies on groundwater in Beijing area, and in the south, there are more studies on Jianghan Plain. TMP was classified as SAs in most studies because many scholars used TMP as a sulfonamide potentiator in their studies [48]. QNs received the most attention and are frequently detected, followed by SAs, MCs, TCs, CPs, β-Ls, and Lins when TMPs are classified as SAs. Nitroimidazoles, aminocyclitols, and diaminopyrimidines have not received much attention but can be detected in groundwater.

Table 1. Comparison of QNs antibiotics in different regions.

Study Area	Kinds of Detectable Compounds	Corresponding Concentration (ng/L)	Reference
North China			
North China	Difloxacin	ND-22.05	[49]
North of the North China Plain	Norfloxacin Ciprofloxacin Enrofloxacin	ND-7.92 ND-10.71 ND-33.29	[50]
Harbin	Norfloxacin Ofloxacin Ciprofloxacin Enrofloxacin	0.15–0.89 0.02–0.05 0.59–1.06 0.19–0.64	[5]
Xinjiang	Pefloxacin Norfloxacin Ofloxacin Ciprofloxacin Marbofloxacin Fleroxacin Danofloxacin Sarafloxacin	2.34–17.60 2.91–9.85 0.75–3.55 2.10–3.35 0.85–14.85 1.10–17.15 0.92–4.82 0.36–2.35	[38]
Beijing	Norfloxacin Ofloxacin Ciprofloxacin Enrofloxacin Difloxacin Lomefloxacin	ND-657.7 ND-152.1 ND-27.4 ND-307.3 ND-9.2 ND-261.4	[7,26,36,51]
Tianjin	Ciprofloxacin	ND-42.5	[41]
Xiong'an New Area	Norfloxacin Ofloxacin Ciprofloxacin Enrofloxacin Flumequine Enoxacin Nalidixic acid Danofloxacin Sarafloxacin	ND-0.18 ND-1.6 ND-6.38 ND-0.24 ND-3.01 ND-7.52 ND-7.41 ND-0.17 ND-0.29	[27]
Shijiazhuang	Norfloxacin Ofloxacin Ciprofloxacin Enrofloxacin Difloxacin Oxolinic Acid Flumequine Pipemidic Acid Marbofloxacin Enoxacin Fleroxacin Sarafloxacin Lomefloxacin Moxifloxacin Nalidixic acid Danofloxacin Cinoxacin Sparfloxacin	ND-32.2 ND-382.2 ND-26.8 ND-182.2 ND-17.50 0.42–4.13 1.23–52.20 ND-14.20 ND-1.44 ND-11.30 ND-14.70 ND-0.96 6.07 (Maximum) 10.00 (Maximum) 11.70 (Maximum) 12.80 (Maximum) 41.10 (Maximum) 58.40 (Maximum)	[19,42,52]

Table 1. *Cont.*

Study Area	Kinds of Detectable Compounds	Corresponding Concentration (ng/L)	Reference
Qingdao	Norfloxacin Ofloxacin Ciprofloxacin Enrofloxacin Difloxacin Flumequine Pipemidic Acid Enoxacin Fleroxacin Lomefloxacin Moxifloxacin Nalidixic acid Danofloxacin Cinoxacin Sparfloxacin	23.5 (Maximum) 25.3 (Maximum) 19.4 (Maximum) 13.2 (Maximum) 19.1 (Maximum) 14.9 (Maximum) 25.4 (Maximum) 57.7 (Maximum) 25.2 (Maximum) 22.1 (Maximum) 4.8 (Maximum) 20.9 (Maximum) 15.0 (Maximum) 9.2 (Maximum) 10.9 (Maximum)	[2]
South China			
Changzhou	Norfloxacin Ofloxacin Ciprofloxacin Enrofloxacin Difloxacin Lomefloxacin	40.6–108.5 1.0–3.0 ND-61.5 ND-39.4 6.2–32.6 ND-12.6	[36]
Jianghan Plain	Norfloxacin Ofloxacin Ciprofloxacin Enrofloxacin Enoxacin Fleroxacin Lomefloxacin Gatifloxacin Sparfloxacin	ND-142 ND-42.66 ND-28.2 ND-41.8 ND-24.10 ND-10.94 ND-15.6 ND-21.61 ND-39.49	[24,25,39,46,53,54]
Kaiyang	Norfloxacin Ofloxacin Ciprofloxacin Enrofloxacin Oxolinic Acid Difloxacin Flumequine Pipemidic Acid Enoxacin Fleroxacin Lomefloxacin Moxifloxacin Nalidixic acid Danofloxacin Cinoxacin Sparfloxacin Sarafloxacin	442.0 (Maximum) 1200.0 (Maximum) 86.4 (Maximum) 4.4 (Maximum) 9.43 (Maximum) 2.6 (Maximum) 22.6 (Maximum) 7.4 (Maximum) 34.0 (Maximum) 8.00 (Maximum) 23.23 (Maximum) 26.9 (Maximum) 20.5 (Maximum) 8.9 (Maximum) 508.6 (Maximum) 8.4 (Maximum) 9.10 (Maximum)	[2,43]
Jinjiang and Yuanhe River Basins	Ofloxacin Enrofloxacin Enoxacin Fleroxacin Sparfloxacin	ND-5.89 ND-47.47 ND-3.02 ND-6.41 ND-0.23	[4,55]

Table 1. *Cont.*

Study Area	Kinds of Detectable Compounds	Corresponding Concentration (ng/L)	Reference
Anshun	Norfloxacin Ofloxacin Ciprofloxacin Oxolinic Acid Enoxacin Nalidixic acid	230 (Maximum) 46.7 (Maximum) 17.9 (Maximum) 60.6 (Maximum) 12 (Maximum) 12.6 (Maximum)	[9]
Bijie	Norfloxacin Ofloxacin	2.37–5.29 5.32–14.63	[56]
The Pearl River Delta	Ofloxacin	9.1–44.2	[57]
	North China and South China		
Typical Cities in China that Use Reclaimed Water for Groundwater Recharge	Norfloxacin Ofloxacin Ciprofloxacin Enrofloxacin Difloxacin Lomefloxacin	ND-503 ND-80 ND-155 ND-49 ND-35 ND-159	[40]
the Northern and Southwestern Regions of China	Norfloxacin Ofloxacin Ciprofloxacin Enrofloxacin Difloxacin Oxolinic Acid Flumequine Pipemidic Acid Enoxacin Fleroxacin Lomefloxacin Moxifloxacin Nalidixic acid Danofloxacin Cinoxacin Sparfloxacin	442.0 (Maximum) 1199.7 (Maximum) 100.6 (Maximum) 48.5 (Maximum) 5.8 (Maximum) 24.6 (Maximum) 22.6 (Maximum) 126.4 (Maximum) 59.5 (Maximum) 10.8 (Maximum) 9.1 (Maximum) 26.9 (Maximum) 20.5 (Maximum) 16.9 (Maximum) 15.4 (Maximum) 13.4 (Maximum)	[44]
Beijing and Changzhou	Norfloxacin Ofloxacin Enrofloxacin	10.4–96.8 1.00–36.2 3.03–70.9	[37]

Table 2. Comparison of SAs antibiotics in different regions.

Study Area	Kinds of Detectable Compounds	Corresponding Concentration (ng/L)	Reference
	North China		
North China	Sulfamonomethoxine Sulfisoxazole Sulfamethoxazole Trimethoprim Sulfamethazine Sulfathiazole Sulfachloropyridazine Sulfamerazine	3.43–12.92 1.51–255.07 7.45–54.19 0.23–4.89 0.49–56.47 2.24–54.40 2.48–12.40 0.66–2.89	[49]

Table 2. *Cont.*

Study Area	Kinds of Detectable Compounds	Corresponding Concentration (ng/L)	Reference
North of the North China Plain	Sulfachloropyridazine Sulfadiazine Sulfamethazine Trimethoprim Sulfamethoxazole	ND-0.44 ND-45.4 ND-1.61 ND-3.18 ND-11.13	[50]
Harbin	Sulfamerazine Sulfathiazole Sulfapyridine Sulfadiazine Sulfamethizole Sulfaphenazole Sulfameter Sulfamethoxazole Sulfamonomethoxine Sulfamethoxypyridazine Sulfamethazine	0.08–15.3 1.55–612.0 0.34–0.43 0.09–68.6 0.05–12.4 0.19–2.61 0.29–4.35 ND-6.95 0.13–1.94 7.20–29.29 ND-0.55	[5,58]
Xinjiang	Sulphaguanidine Sulfadimethoxine Sulfamerazine Sulfathiazole Sulfapyridine Sulfaquinoxaline Trimethoprim Sulfadoxine Sulfamonomethoxine	1.00–1.70 ND-2.30 0.41–0.50 0.10–4.20 0.50–30.00 ND-12.82 ND-55.19 ND-27.86 ND-44.27	[38]
Beijing	Sulfadiazine Sulfamethazine Trimethoprim Sulfamethoxazole	ND-96.8 ND-236 ND-8.7 ND-9.41	[26,51]
Tianjin	Sulfadoxine Sulfamethoxazole	ND-78.3 7.2–9.5	[41]
Xiong'an New Area	Sulfadimethoxine Sulfamerazine Sulfamethoxypyridazine Sulfathiazole Sulfapyridine Sulfadiazine Sulfaquinoxaline Sulfamethazine Trimethoprim Sulfadoxine Sulfamethizole Sulfamethoxazole	ND-1.67 ND-0.17 ND-0.97 ND-1.72 ND-3.60 ND-0.83 ND-1.53 ND-1.74 ND-0.59 ND-2.21 ND-0.08 ND-3.69	[27]
Shijiazhuang	Sulphaguanidine Sulfamonomethoxine Sulfachloropyridazine Sulfapyridine Sulfacetamide Sulfadiazine Trimethoprim Sulfamethoxazole	3.87 (Maximum) 8.20 (Maximum) 1.33 (Maximum) 9.95 (Maximum) 1.95 (Maximum) 46.3 (Maximum) 9.2 (Maximum) 105.7 (Maximum)	[19,42]

Table 2. *Cont.*

Study Area	Kinds of Detectable Compounds	Corresponding Concentration (ng/L)	Reference
Qingdao	Sulfadimethoxine Sulfachloropyridazine Sulfapyridine Sulfamethazine Sulfadoxine Sulfamethizole Sulfameter Sulfisoxazole Sulfacetamide	19.6 (Maximum) 26.5 (Maximum) 21.9 (Maximum) 13.4 (Maximum) 38.6 (Maximum) 46.5 (Maximum) 35.1 (Maximum) 21.2 (Maximum) 20.3 (Maximum)	[2]
Jinan	Sulfadiazine Sulfamethazine Sulfamethoxazole	ND-56.3 ND-54.1 ND-2.7	[59]
South China			
Jianghan Plain	Sulfamerazine Sulfamethoxypyridazine Sulfathiazole Sulfapyridine Sulfadiazine Sulfaquinoxaline Sulfamethazine Sulfameter Trimethoprim Sulfamethoxazole	ND-7.0 ND-2.06 ND-1.50 ND-4.6 ND-14.89 ND-26.2 ND-15.9 ND-2.29 ND-5.2 ND-39.54	[24,25,39,46,53,54]
Shanghai	Sulfadimethoxine Sulfamerazine Sulfameter Sulfamethoxazole	23.8 38.5 123.3 241.5	[60]
Kaiyang	Sulphaguanidine Sulfamethoxypyridazine Sulfachloropyridazine Sulfapyridine Sulfamethazine Trimethoprim Sulfadoxine Sulfamethizole Sulfameter Sulfamethoxazole Sulfamonomethoxine Sulfacetamide	6.33 (Maximum) 7.50 (Maximum) 1.7 (Maximum) 45.33 (Maximum) 3.9 (Maximum) 433.40 (Maximum) 1.0 (Maximum) 19.3 (Maximum) 1.0 (Maximum) 1090.40 (Maximum) 123.20 (Maximum) 1.5 (Maximum)	[2,43]
Jinjiang and Yuanhe River Basins	Sulfathiazole Sulfaquinoxaline Sulfamethazine Sulfamethoxazole	ND-1.15 ND-0.14 ND-0.31 18.1–29.72	[4,55]
Bijie	Sulfadiazine Sulfamethazine	0.24–3.47 1.03–10.37	[56]
Guilin	Sulfadimethoxine Sulfamerazine Sulfamethoxypyridazine Sulfachloropyridazine Sulfamethazine Trimethoprim Sulfamethoxazole	ND-1.81 ND-8.20 ND-45.06 0.34–13.25 0.49–56.64 ND-4.32 ND-11.58	[61]
The Pearl River Delta	Trimethoprim Sulfamethoxazole	3.3–10.5 28.7–124.5	[57]

Table 2. *Cont.*

Study Area	Kinds of Detectable Compounds	Corresponding Concentration (ng/L)	Reference
North China and South China			
Typical Cities in China that Use Reclaimed Water for Groundwater Recharge	Sulfamerazine Sulfachloropyridazine Sulfathiazole Sulfamethazine Trimethoprim Sulfamethoxazole Sulfisoxazole Sulfamonomethoxine	ND-15 ND-117 ND-32 ND-49 ND-40 ND-250 ND-8.4 ND-29	[40]
the Northern and Southwestern Regions of China	Sulfadimethoxine Sulfachloropyridazine Sulfapyridine Sulfamethazine Sulfadoxine Sulfamethizole Sulfameter Sulfisoxazole Sulfacetamide	65.5 (Maximum) 153.4 (Maximum) 56.4 (Maximum) 3.9 (Maximum) 4.2 (Maximum) 28.7 (Maximum) 15.6 (Maximum) 9.2 (Maximum) 3.7 (Maximum)	[44]

Table 3. Comparison of TCs antibiotics in different regions.

Study Area	Kinds of Detectable Compounds	Corresponding Concentration (ng/L)	Reference
North China			
Harbin	Doxycycline	0.35–3.91	[5]
Xinjiang	Doxycycline	0.10–0.30	[38]
Beijing	Oxytetracycline	ND-3.2	[51]
Tianjin	Tetracycline	ND-5.2	[41]
Shijiazhuang	Oxytetracycline Tetracycline Chlorotetracycline	1364.7 (Maximum) 1082.5 (Maximum) 47,444.5 (Maximum)	[42]
Qingdao	Oxytetracycline Tetracycline Chlorotetracycline Doxycycline	22.7 (Maximum) 15.5 (Maximum) 11.7 (Maximum) 3.2 (Maximum)	[2]
South China			
Jianghan Plain	Oxytetracycline Tetracycline Chlorotetracycline Doxycycline	ND-28.7 ND-170.6 ND-86.6 ND-64.2	[24,25,39,46,53,54]
Kaiyang	Oxytetracycline Tetracycline Chlorotetracycline	237.0 (Maximum) 184.0 (Maximum) 7.1 (Maximum)	[2,43]
Jinjiang and Yuanhe River Basins	Oxytetracycline Tetracycline Chlorotetracycline Doxycycline	ND-2.65 0.21 (Maximum) ND-4.18 (Maximum) ND-1.56 (Maximum)	[4,55]

Table 3. *Cont.*

Study Area	Kinds of Detectable Compounds	Corresponding Concentration (ng/L)	Reference
North China and South China			
Typical Cities in China that Use Reclaimed Water for Groundwater Recharge	Oxytetracycline Tetracycline Chlorotetracycline Doxycycline	ND-39 ND-48 ND-76 ND-39	[40]
The Northern and Southwestern Regions of China	Oxytetracycline Tetracycline Chlorotetracycline	237.3 (Maximum) 184.2 (Maximum) 8.0 (Maximum)	[44]

Table 4. Comparison of MCs antibiotics in different regions.

Study Area	Kinds of Detectable Compounds	Corresponding Concentration (ng/L)	Reference
North China			
North China	Erythromycin	ND-1.71	[49]
Harbin	Roxithromycin Erythromycin	0.16–1.58 0.24–23.3	[5]
Xinjiang	Roxithromycin Erythromycin Clarithromycin	ND-19.87 0.31–1.50 ND-0.43	[38]
Beijing	Erythromycin	ND-1.21	[26]
Shijiazhuang	Roxithromycin Erythromycin	146.2 (Maximum) 3.90 (Maximum)	[19,42]
Qingdao	Roxithromycin Erythromycin Spiramycin Josamycin	26.5 (Maximum) 11.1 (Maximum) 6.8 (Maximum) 24.1 (Maximum)	[2]
Jinan	Azithromycin	ND-28.0	[59]
South China			
Jianghan Plain	Roxithromycin Erythromycin Spiramycin Clarithromycin Azithromycin	ND-97.13 ND-377.8 ND-18.2 ND-115.28 ND-13.10	[24,25,39,46,53,54]
Kaiyang	Tilmicosin Roxithromycin Erythromycin Clarithromycin Spiramycin Josamycin Azithromycin	7.70 (Maximum) 84.0 (Maximum) 117.7 (Maximum) 48.80 (Maximum) 167.07 (Maximum) 1.5 (Maximum) 146.97 (Maximum)	[2,43]
Jinjiang and Yuanhe River Basins	Roxithromycin Clarithromycin	ND-0.07 ND-5.10	[4,55]
Anshun	Roxithromycin Erythromycin	1.63 (Maximum) 22.5 (Maximum)	[9]
The Pearl River Delta	Erythromycin	5.6–12.4	[57]

Table 4. *Cont.*

Study Area	Kinds of Detectable Compounds	Corresponding Concentration (ng/L)	Reference
	North China and South China		
Typical Cities in China that Use Reclaimed Water for Groundwater Recharge	Erythromycin Azithromycin	ND-143 ND-73	[40]
The Northern and Southwestern Regions of China	Roxithromycin Erythromycin Spiramycin Josamycin	54.5 (Maximum) 345.7 (Maximum) 11.8 (Maximum) 16.5 (Maximum)	[44]

Accordingly, some scholars have not only detected antibiotic concentrations but have also assessed the ecological risk of antibiotics in groundwater by risk quotient (RQ). The results show that the current concentration of antibiotics in groundwater is ng levels with a controllable ecological risk, mainly between medium and low values. The highest concentrations found in most of the literature were in the range of 10–1000 ng/L, but the maximum concentration can reach 47,444.5 ng/L, which is chlorotetracycline (belongs to TCs) from the Wangyang River area. It is assumed that groundwater in this area is largely influenced by infiltration of treated or untreated sewage or river water containing sewage [42]. The highest concentrations of QNs, SAs, and Lins were detected in the karst area of Guizhou. The corresponding maximum concentration values and compounds are 1200 ng/L for ofloxacin, 1090.4 ng/L for sulfamethoxazole, and 861 ng/L for lincomycin, which may be influenced by their specific hydrogeological conditions [2]. For MCs, the highest concentration was detected in the Jianghan Plain, and the corresponding maximum concentration values and compounds is 377.8 ng/L for erythromycin, presumably related to surface water pollution [54].

Notably, we cannot ignore the potential ecological risks in groundwater. Because most antibiotics in groundwater decay slowly, their concentrations can accumulate over time, and there are also potential human health risks associated with long-term antibiotic exposure. What is worse, there are no reliable methods to estimate the risk of mixing synergistic or antagonistic effects in mixtures [61]. Ecological evaluation methods do not take the characteristics of the groundwater aquifer into account, the interactions between the whole system consisting of lake, groundwater, and sediments, and the risk of developing bacterial resistance [25]. Therefore, the ecological evaluation methods of antibiotics need to be improved, and the risk of using antibiotics in groundwater remains a concern.

3.2. Seasonal Variation of Typical Antibiotics in Groundwater

Several surveys have shown that the concentration and type of antibiotics in groundwater in the same area vary from season to season. The reasons for seasonal variations are complex. Combined with existing studies, we found the following three possible reasons for the seasonal variation of antibiotics.

The first is physical or chemical change caused by a change in temperature. For groundwater, temperature was the main factor affecting antibiotic distribution compared to ORP, pH, DO, and DOC. Temperature can affect antibiotic-related environmental behavior in surface water and soil, such as adsorption, hydrolysis, photodegradation, and biodegradation, making the concentration of antibiotics in groundwater changes [53]. For example, Yao, L. et al. found that the sorption coefficient K_d of NOR was lower at higher temperatures, indicating stronger mobility in spring than in winter [39].

The second is the variation of water volume caused by hydrological factors. This situation usually occurs in areas with strong interaction between surface water and groundwater. During the dry season, surface water levels drop and antibiotic concentrations increase, resulting in changes in groundwater concentrations. For example, Qin, L. T. et al. detected the groundwater in the Huixian wetland located in a karst region and found that the groundwater level decreases during the dry period under the influence of the level of surface water whose concentration increase because the water level drops [61]. During the rainy season, rain can dilute the concentration of antibiotics and induce antibiotics into the groundwater. Due to this duality, the concentration of antibiotics in groundwater may increase or decrease. For example, in an investigation of Jianghan Plain, Tong, L. et al. found that compounds such as SAs are heavily diluted due to continuous rain [54]. Liu, X. et al. found that the continuous rainfall in rainy summer may take responsibility for the transport of antibiotics, leading to higher antibiotic concentrations in summer than in winter [53].

The third is the seasonal use of antibiotics. In some areas, the concentration of antibiotics in groundwater is significantly influenced by human activities and the use of antibiotics varies from season to season. For example, Qin, L. T. et al. found that SAs were used during the wet period for the fast growth of fishes, whereas medicines are unused during the dry period [61]. Hu, X. et al. found that because winter was the most important season of antibiotics manured to organic vegetable bases, the residues of antibiotics in winter were higher than those in summer [41]. Wang believes that one of the reasons why the concentration of antibiotics in the Dingqi Underground River is higher in the spring and winter than in the summer is that there is a higher incidence in the spring and winter, which leads to more antibiotic use, resulting in changes to the concentration of antibiotics in groundwater [9].

Therefore, it can be seen that the concentration of antibiotics in groundwater varies from season to season due to different reasons. In the same area, the detection of antibiotics in groundwater in different seasons of the same year is very important for obtaining representative sample data. Therefore, seasonal factors should also be considered when formulating preventive and control measures for antibiotic pollution in groundwater.

3.3. Distribution of Typical Antibiotics by Influence of Hydrological Settings

The migration and transformation process of contaminants in groundwater is also influenced by the characteristics of aquifers, especially karst aquifer. Karst aquifer is a highly permeable soil or rock system with special hydrogeological conditions and complex groundwater environment. It has large voids, high transport velocities, low residence time, high heterogeneity, and high anisotropy, high hydraulic conductivity, and more frequent exchange between surface water and groundwater, so precipitation can quickly penetrate the ground [9,43,62–64].

In the underground rivers in the karst area of Guizhou, antibiotics are degraded in the environment while new sources of pollution are available to replenish them, and the presence of underground rivers can accelerate the migration of substances [2]. Lang found that the detection rate and concentration of antibiotics in karst groundwater samples in Guizhou were higher than those in pore groundwater samples in Dagu River when the same antibiotics were discharged in Guizhou area and Dagu River area [2]. Moreover, ofloxacin, sulfamethoxazole, and lincomycin in karst groundwater samples in Guizhou had the highest concentration for QNs, SAs, and Lins in the retrieved literature [2]. Chen L also detected oxyfloxacin at concentrations up to 1199.7 ng/L in groundwater samples from karst-landform, and such high concentrations have posed ecological risks to algae and fish [44]. In addition, TC, ERY, and CIP had high RQ values for algae, and OFL had high RQ values for plants in these samples [44].

Therefore, the sensitivity of groundwater to contamination by antibiotics is different due to hydrogeological differences. Before delineating the functional areas, the hydrogeological characteristics of the area need to be investigated and protective measures should be taken during construction and operation.

4. Source of Typical Antibiotics in Groundwater

The source of antibiotics is often discussed in studies of antibiotic detection, and we have found that there is a pattern to their migration pathways. Antibiotics are produced in pharmaceutical factories and then sent to research institutions, agriculture, livestock production, aquaculture, hospitals, households, etc. Wastewater from these areas is sent to sewage treatment plants (STPs) for disposal and solid waste is sent to landfills for disposal. The STP effluent may be discharged to surface water, reused as reclaimed water, or recharged directly to groundwater. Due to incomplete treatment in STPs, antibiotics can enter groundwater indirectly or directly, and leaks in the pipeline network during transportation, interaction between surface water and groundwater, and infiltration from agriculture, livestock production, and aquaculture can also contaminate groundwater, resulting in the occurrence of antibiotics in groundwater. Figure 1 illustrates the pathway of antibiotics migration in the environment. This chapter describes the sources of antibiotics in groundwater, including hospital and pharmaceutical factories, agriculture, livestock production, aquaculture, landfills, reclaimed water from STPs, and surface water.

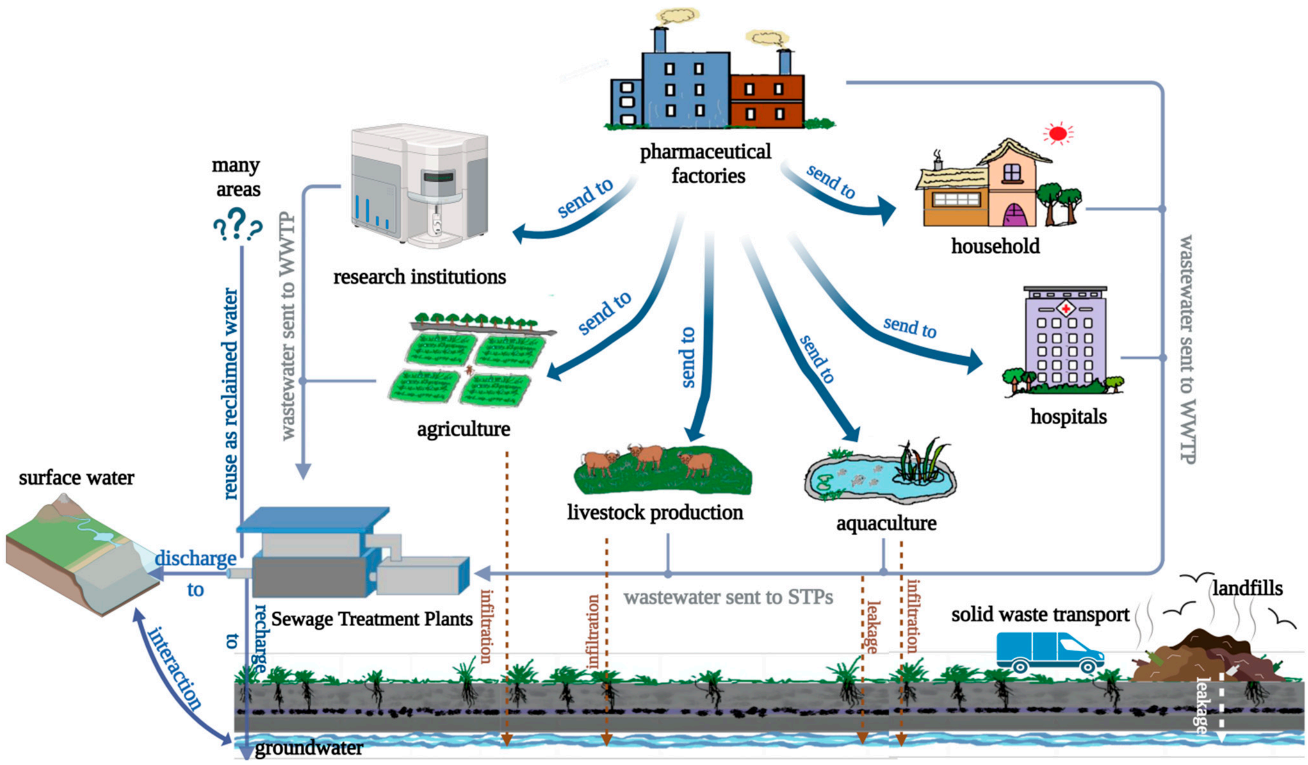

Figure 1. Antibiotics migration in the environment (Created with BioRender.com).

4.1. Hospital and Pharmaceutical Factories

Hospitals wastewater and wastewater of pharmaceutical factories are the main sources in the aqueous environment, and their migration pathways are generally of three types. First, antibiotics are not completely absorbed by organisms. H. Stass et al. studied the pharmacokinetics of mofloxacin and its metabolites in healthy male volunteers and found that after giving a single 400 mg dosage of moxifloxacin, more than 96% of the dose was recovered from urine and feces after oral dosing, and >98% was recovered following iv administration of the drug [65]. Granneman, GR et al. also collected urine for assay of temafloxacin and its metabolites in healthy adult male volunteers and found the recovery of unchanged temafloxacin at 0 to 60 h was 56.5 $\pm$ 10.5% of the dose, less than 1% of the dose remained to be excreted at the end of the 60-h interval [66]. E. Cribb et al. collected urine from healthy volunteers who have ingested 1000 mg sulfamethoxazole and found that sulfamethoxazole hydroxylamine constituted 3.1 $\pm$ 0.7% of the drug excreted in the urine in 24 h, fifty-four percent of the ingested dose was excreted during this same time [67]. Feces and urine containing antibiotics and antibiotic metabolites can be released into the environment. Secondly, unreasonably-disposed-of medical waste and medical equipment containing antibiotics can cause antibiotics to enter the environment [55,68]. In addition, wastewater from hospitals, scientific research institutions, and pharmaceutical companies contains a significant amount of antibiotics and their metabolites. They can enter the wastewater treatment plants, which cannot degrade them completely, and can be discharged into the environment [55,69–71].

In the current reports on the investigation of antibiotics in groundwater in China, many scholars point out that the high concentrations of antibiotics in their sampling sites are associated with pharmaceutical enterprise wastewater and hospital wastewater. Ma et al. analyzed the antibiotics in groundwater in Harbin and found that the sources of SAs and TCs were mainly influenced by biopharmaceutical enterprise and medical emissions [5]. Ju et al. analyzed the antibiotics in groundwater in Shijiazhuang City and found that the high concentration of QNs in groundwater in the central region may also be related to many hospitals and pharmaceutical enterprises in this region [52]. Shi et al. found that in high-density urban areas, hospital wastewater is one of the main sources of antibiotics [50]. Zuo et al. found that the highest sulfonamide concentrations in the Limin area in northern Harbin was observed in the site located near the pharmacy factories [58].

In summary, the treatment of antibiotics in wastewater from pharmaceutical enterprises and hospitals is particularly important. When designing relevant sewage treatment facilities, the degradation efficiency of antibiotics should be considered as much as possible.

4.2. Agriculture, Livestock Production, and Aquaculture

Antibiotics have been not only used for the treatment of human diseases, but have also been used in agriculture, livestock production, and aquaculture. According to the survey, 48% of antibiotics are used annually in China for agriculture and livestock production every year [72]. Antibiotics contamination in groundwater near agriculture, livestock production, and aquaculture has become a hot topic in the detection of antibiotics in groundwater.

In agriculture, antibiotics are heavily used in China and can be detected in nearby groundwater. The most used antibiotics in agriculture today are oxytetracycline and streptomycin, which are used to treat citrus "Huanglongbing" and plant pathogens in edible vegetables, such as bacterial wilt of tomatoes [73]. Unfortunately, antibiotics can contaminate groundwater, whether absorbed by crops and entering the food chain, or through sewage irrigation and fertilization. Among these pathways, sewage irrigation has received a great deal of attention. At present, 15 antibiotics have been detected in the sewage irrigation area of Taiyuan, with a maximum concentration of 114.38 ng/L [74]. Studies have shown that sewage irrigation has input more types and quantities of antibiotics into groundwater than groundwater irrigation [75]. Wu et al. found that TMP and SMX concentrations were 42% and 61% higher, respectively, in reclaimed water irrigated soils than in groundwater irrigated soils [76]. Chen et al. detected groundwater in Beijing and found that the antibiotic concentration in the sewage irrigation area was much higher than the groundwater, which was recharged by the water of South-to-North Water Diversion Project [51].

Feed antibiotics were mainly used as feed additives to promote the growth of animals and improve the productivity of livestock production and aquaculture for more than 70 years before the policy issued by the Ministry of Agriculture and Rural Affairs of the People's Republic of China that stopped the production of growth-promoting drug used for feed additives (except traditional Chinese medicine) was implemented [7,77]. The use of antibiotics not only directly enters the food chain and indirectly affects the environment, but also contains antibiotics in the manure of livestock production, contaminating the soil and water of farmland and causing antibiotics to infiltrate the groundwater. Moreover, some rural areas in China do not have centralized wastewater treatment facilities, and some wastewater-containing antibiotics are directly discharged into the environment after simple treatment, posing a threat to the environment. Hong et al. detected the groundwater of Chongming Island and concluded that the high concentration of SAs in groundwater may be due to the large number of livestock and poultry farms in urban areas [60]. Ma et al. detected the groundwater in Harbin and found that the concentration of SAs in groundwater sampling points around chicken farms and pig farms operated by villagers was higher than 1 ng/L [5]. Gao et al. detected the groundwater in BoBai located in Jiangxi Province and found that pig farming can cause groundwater contamination of antibiotics and even pollute the nearby domestic well water [78]. Li et al. also found that antibiotic residues could spread from swine feedlots and feed into groundwater environments in surrounding villages through principal component analysis and hierarchical clustering [79]. Notably, the concentration of antibiotics in groundwater may vary significantly from farm to farm in the vicinity. Gu et al. found that the maximum total concentration of SAs (27.24 ng/L) was detected in groundwater from duck farms, the highest total concentration of FQs (29.83 ng/L) was detected in the groundwater from chicken farms, and the maximum total concentration of MCs (23.02 ng/L) was detected in the groundwater from cattle farms [47].

Long-term aquaculture activities have an impact on the spread of antibiotics in the groundwater environment. Fish ponds can act as reservoirs for antibiotics and can eventually allow them to enter groundwater [24]. Tong et al. detected the groundwater in Jianghan Plain and found that the concentration of TCs in samples collected around fishponds has increased [54]. Jiang et al. detected the groundwater in Wangyang River and its adjacent area and found that high-intensity aquaculture activities could contribute to the increasing levels of antibiotic in the area [42].

Even though the production of growth-promoting drug feed additives (except Chinese medicine) has been banned since 2020, the large amount of antibiotics from agriculture, livestock production, and aquaculture that can be detected in groundwater is a cause for concern. We should take certain protective measures against the migration of antibiotics because antibiotics need to be used as medicine for treatment and prevention. Additional measures need to be developed to prevent antibiotics from entering the groundwater. For example, the addition of fresh organic matter to the soil has been reported as a promising measure [80]. Notably, many researchers have started to research developing degradable antibiotics. For example, Huang et al. developed antimicrobial peptides and their mimics as alternative disinfectants in agriculture and aquaculture, which have excellent potency and low drug resistance generation rates [81]. The development of these high-toxicity and degradable antibiotics should receive attention.

4.3. Landfills

The conclusion that the main source of antibiotics in groundwater in China is that landfills are less well-reported but also deserve our attention. It is important to mention that China has only recently implemented solid waste sorting in some major cities, which means that municipal solid waste-containing antibiotics may be put into landfills without pretreatment, where they release landfill leachate [57]. Untreated leachate can be discharged directly, and the composite liner pipe of the leachate collection system may break and leak during long-term operation, polluting the groundwater environment [59]. Dai et al. analyzed the sources of antibiotics in civilian wells around the Bijie Ganjiawan landfill and concluded that it was human excrement, antibiotic-containing food, and other items that were washed by surface runoff or infiltrated into surrounding civilian wells through rainwater on a short-term basis [56]. Wang K et al. detected the emerging organic contaminants (including antibiotics) in groundwater adjacent to the landfill in Jinan City and found that they had a similar composition pattern to raw leachates [59]. Therefore, it is important to reduce leachate infiltration into groundwater. The leakage of antibiotics from solid waste should be considered when developing impermeability measures for landfills. In addition, the separation and recycling of medical waste needs to be further implemented.

4.4. The Effluent from Sewage Treatment Plants

Because conventional sewage treatment plants are not designed to remove antibiotics, influenced by compound-specific properties, treatment process, hydraulic retention time, and solid retention time, the effluent still contains significant amounts of antibiotics in different degrees, and these antibiotics end up in the groundwater [82]. Meanwhile, leaks can also occur during sewage transport through the pipe network due to pipe cracks and defective joints, causing antibiotics to seep into groundwater [83]. Several studies have shown that the discharge of sewage treatment plant is one of the major sources of antibiotics in groundwater. Ma found that the pollution of karst groundwater in Kaiyang County was mainly comes from domestic waste with the impact of the STP and wastewater treatment plant on the river [84]. Chen L et al. found that one of the main sources in the northern and southwestern regions of China was the discharge of sewage treatment plants [44]. Shi et al. found that the occurrence of high concentrations at individual sites in the northern part of the North China Plain may be caused by local sources from leakage in the sewage pipe network [50].

The effluent of some STPs containing advanced treatment processes will not only be discharged into surface water, but can also be reused as reclaimed water. Some areas recharged groundwater with reclaimed water by using wells, surface spreading, and riverbank filtration (RBF), which can reduce, stop, or even reverse declines of groundwater levels, protect underground freshwater in coastal aquifers against saltwater intrusion and store surface water [85,86]. However, many scholars believe that groundwater mixes more antibiotics when reclaimed water is recharged. Ma Y et al. detected 15 typical cities using reclaimed water to recharge groundwater and found that the detection frequency in groundwater samples was almost the same as that in reclaimed water samples [40]. Ding et al. found that the concentrations of ENR, NOR, and CIP increased significantly by 56.4% to 143.9% after the injection of reclaimed water in half a month from Gaobeidian Wastewater Treatment Plant in Beijing. Moreover, compared with the surface spreading into groundwater in Changzhou, the reclaimed water had a greater impact on the concentration of FQs in groundwater [36].

Therefore, the risk of groundwater contamination from effluent should not be ignored due to incomplete removal of contaminants from STPs. Antibiotic removal should also be taken into account when designing the standards and treatment processes for STPs.

4.5. Surface Water

There are strong interactions between groundwater and surface water due to factors such as climate, hydrogeological conditions, and hydraulic gradients [46]. For example, when the concentration of antibiotics in surface water is significantly higher than that in groundwater, the former can be considered as a source of contamination for the latter [27]. Many scholars have pointed out that the interaction between groundwater and surface water is an important source of pollution. Liu, X. et al., Yao, L. et al., and Ma, N. et al. found that surface water is an important source of pollution in the Jianghan Plain, and there is a risk of migration of antibiotics from surface water or its sediments to groundwater [25,39,53]. Wang, J. et al. investigated the alluvial-diluvial fan of the Hutuo River in north China and found the antibiotic pollution in the lightly polluted area primarily originated from the river recharge input [19]. Jiang, Y. et al. investigated Wangyang River area and suggested that the riverine runoff and river water percolation were possible antibiotics sources to groundwater [42].

Many studies have compared the antibiotic concentrations in surface water and groundwater. Numerous studies have found that the concentration of antibiotics in surface water is usually higher than that in groundwater, sometimes by 1–2 orders of magnitude, by reason of physicochemical reactions such as soil adsorption, filtration, and degradation [26,40]. However, due to the characteristics of groundwater such as slow changes in water quality parameters and difficulties in recovery from pollution, sometimes the concentration of antibiotics in groundwater, the type of antibiotics detected, and the detection rate is higher than that in surface water. Tong L et al. found the concentration of CAP in the samples of lake water and groundwater was around 2.0 ng/L but was not detected in any wastewater samples, perhaps because CAP has been banned in livestock production since 2002, but its early use and slow degradation led to the detection [23].

Therefore, the relationship between groundwater and surface water in certain areas is very close. It is necessary to understand in detail the interaction between surface water and groundwater in each area, and to treat and detect surface water and groundwater as a whole system in these areas. When the concentration of antibiotics contained in surface water is high, measures should be taken as soon as possible to reduce the concentration in surface water and prevent antibiotics in surface water from entering groundwater.

It is noteworthy that in many cases the source of contamination may not be single. We found that in most cases there is a compound contamination at the same sampling site and the contribution of antibiotic concentrations at the same point was different. For example, Ma et al. found that the contribution of SAs in Harbin from small to large is village farms, residents health care, and biopharmaceutical companies [5].

5. Fate of Typical Antibiotics in Groundwater

The migration of antibiotics in the underground environment not only depends on the environmental characteristics such as microbial community, lithology, soil texture, residence time of groundwater, redox state, and hydraulic characteristics, but also depends on the physico-chemical properties and concentration of antibiotics [87,88]. Due to the physicochemical properties of antibiotics, reactions such as adsorption, hydrolysis, and biodegradation can occur in the process of entering the underground environment (Figure 2).

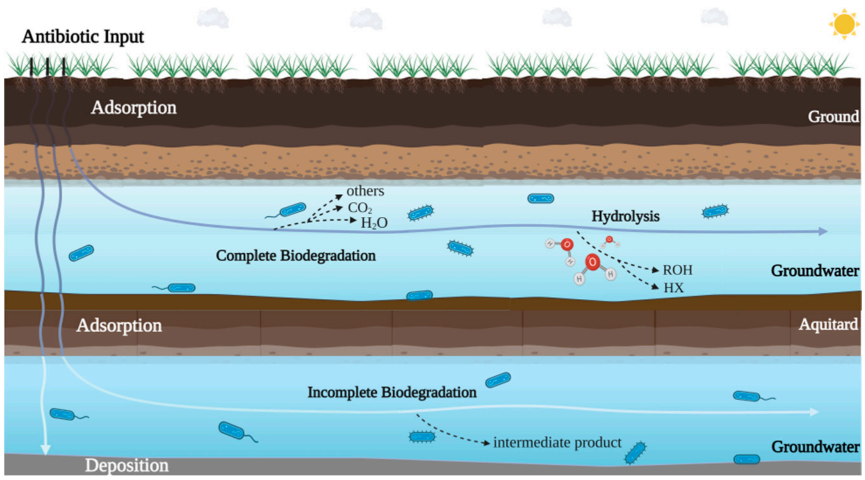

Figure 2. Fate of antibiotics in the groundwater (Created with BioRender.com).

5.1. Adsorption

The unique environment in groundwater and the physicochemical properties of antibiotics determine that adsorption is one of the important factors affecting the migration and transformation of antibiotics in groundwater [87]. In general, the stronger the adsorption capacity, the more stable in the environment, and the easier the deposition, the weaker the adsorption capacity, the easier the migration with water [55].

Adsorption can be divided into physical and chemical adsorption. Antibiotics can be physically adsorbed in the aqueous environment, and they can also react with other substances to form complexes. The soil in the aquifer mainly was sand with low organic matter content and cation exchange capacity. Therefore, its sorption capacity was low, causing less antibiotics to be retained in the soil [36,37]. Furthermore, one or more hydrophilic polar functional groups exist in antibiotics, which easily combine with water to form hydrates, causing antibiotics to enter the groundwater faster [44]. These two aspects allow antibiotics to leak and leach from the soil and sediment of the vadose zone.

The adsorption capacity of soil for antibiotics is influenced by many factors, such as soil and environmental conditions and the physicochemical properties of antibiotics. The adsorption behavior environmental conditions such as soil, organic matter content, ionic strength, temperature, and pH are important influencing factors [89,90]. In the reviewed literature, many studies on groundwater antibiotic sorption have focused on the effect of soil, antibiotics properties, and coexisting ions on antibiotics.

For soil, generally speaking, the finer of the medium particles are, the more adsorption sites can provide, and the higher the antibiotic adsorption capacity [58,91]. For the adsorption of antibiotics varies with different soil textures, and in related experiments, more research has been done on SAs. For example, Thiele-Bruhn, S. et al. and Zuo et al. found that adsorption of SAs increased in the sequence: sand < clay < fine silt [58,92]. Correspondingly, Doretto et al. also suggested that sulfonamides tend to be leached from soils with high sand and low organic carbon contents [93].

Since different antibiotics have different physicochemical properties, they may behave differently even if different antibiotics are under the same environmental conditions or the same antibiotics under different environmental conditions. In general, due to the ionic structures and their pK_a values, FQs and TCs showed higher adsorption to sediments in water studies with K_d (sorption coefficient) values of 54,600 and 7600 L/kg compared to SAs and MCs with K_d values of 130 and 1.37 L/kg [89]. For FQs, they can interact differently in the environment because they are zwitterionic species and have pH-dependent speciation [94]. For MCs, because of the ionizable dimethylamino and hydroxyl group in the molecular structure, the pH of the environmental media determines the cationic, zwitterionic, or anionic form, which further determines the adsorption mechanisms. When pH < pKa, the dominant form of MCs tends to be cationic and the main adsorption mechanisms are cation exchange and hydrogen bonding. When pH > pKa, the dominant forms of MCs tend to be zwitterions and anions, and the main adsorption mechanisms are surface complexation and cation bridging [95]. For SAs, because of their low Kd values, SAs are very mobile, which enables them to enter the groundwater easily [40,96].

Several studies have shown that coexisting metal ions can influence antibiotic adsorption. For example, M. Ötker Uslu et al. found that the competition of fluoroquinolones and Ca^{2+} ions for negatively charged clay minerals could also be a reason for lower sorption coefficients of ENR and CIP in the case of sandy loam soil [97]. Zuo et al. found that coexisting ions, such as iron, manganese, and ammonia nitrogen, promote the adsorption of SAs [58]. Zhao et al. found that the presence of metal cations promoted TC adsorption through an ion bridging effect in the order Cu (II) > Pb (II) > Cd (II) [98]. Li et al. found that the sorption of MCs can also be affected by ionic environments, such as Na, K, Ca^{2+}, Mg^{2+}, Al^{3+}, and other common metal ions in the soil and sediment [95]. In China, metals, especially heavy metals, have been used as detection targets in some of today's detection literatures on the occurrence of antibiotics, and the relationship between antibiotics and heavy metals has been studied. For example, Gao et al. found antibiotic concentrations in the urban soil were positively correlated with heavy metal contents [99]. Guo et al. and Chen et al. studied surface water and found that positive correlations existed between the antibiotics and tested heavy metals [100,101]. Chen et al. suggested that it was likely driven by their common source of contamination and the complexation [101]. Therefore, for the detection of groundwater, we can take into account the metals in the water at the same time, which will enable us to get more research findings.

5.2. Hydrolysis

Hydrolysis, an act that alters the concentration of antibiotics in groundwater by reacting with water, also has many influencing factors. During the hydrolysis process, the parent structure of antibiotics is broken, and one or more degradation products are generated [102]. The process is affected by water environment factors such as temperature, pH, and contact with soil organic matter and the physicochemical properties of antibiotics, such as the solubility of antibiotics [55,102,103]. Among them, temperature and pH value are the main factors that contributed to the hydrolysis of antibiotics [104]. Notably, hydrolysis reactions have different degrees of effect on different types of antibiotics. Studies showed that β-lactams, MCs, TCs, and SAs are susceptible to hydrolysis, but the hydrolysis reactions of MCs and SAs at a neutral pH range are very slow [105,106], and QNs are difficult to hydrolyze [107,108].

5.3. Biodegradation

Generally, when antibiotics enter the biosphere, the interaction between antibiotics and bacteria can be divided into various types, some cells cannot tolerate the toxicity of antibiotics and die, some cells use some mechanisms to resist the toxicity of antibiotics, and some cells use the xenobiotic compound as a source of energy, nutrients (C, N, S, etc.), or as a final electron acceptor, and even mineralize antibiotics to convert them into CO2 and other products, which have the effect of biodegrading antibiotics [109–111]. Biodegradation, which is the use of microorganisms, microbes, and enzymes to break down antibiotics in the environment, has received high attention in the studies of antibiotics in groundwater and has been influenced by many factors [109].

Environmental conditions such as temperature, pH, oxygen, and antibiotics themselves affect the activity and availability of microorganisms in the environment to varying degrees, which in turn affects the rate of antibiotic degradation [112–114]. In the literature retrieved concerning groundwater in China, more attention has been paid to the effect of oxygen on biodegradation. In higher DO environments, microorganisms can metabolize organic matter more efficiently. Liu X et al. and Wu S et al. found that most antibiotic concentration showed a negative correlation with DO [38,53]. Yao L. also found that the SM-2 and SMZ these two compounds are sensitive to the redox conditions [39]. However, the sensitivity of ORP, which indicates the redox state of groundwater, is higher than DO in groundwater environment [25]. Wu S et al. found that ORP had a strong negative effect on the concentrations of FQs and TCs but had no relationship with CPs and MLs [38].

Compared to the microorganisms present in the soil, the groundwater environment has fewer microorganisms, lower temperatures, less oxygen, and less light, which is not conducive to the rapid degradation of antibiotics, so antibiotics in groundwater may not be completely degraded [115]. The result is that antibiotics in groundwater may be converted to harmful metabolites or remain in the groundwater for a long time. For example, N^4-acetylsulfamerazine were detected more frequently than its parent compound sulfamerazine, which could be explained by having higher solubilities and higher persistence than the parent, and some metabolites of QNs in the environment are more toxic than the parent [116]. However, some antibiotics degrade more readily in anoxic environments. For example, erythromycin (ERY) would be degraded to anhydroerythromycin (ERY-H_2O) immediately in the environment, while the ERY-H_2O was reported to undergo more effective degradation under anoxic conditions, so ERY have low concentration in groundwater in many cases [39,105,117–119].

Therefore, antibiotics may be adsorbed, hydrolyzed, and biodegraded when they enter groundwater and migrate in groundwater, and the effects to different antibiotics are different. We need to further study the behavior of different types of antibiotics, paying extra attention to antibiotics with high water solubility, poor adsorption, poor degradability, and high toxicity, and formulate policies accordingly.

6. Conclusions

In this paper, we systematically reviewed the occurrence of antibiotics in groundwater in China and the relevant findings obtained from the literature, including the detection methods, concentrations, ecological risks, sources, distribution characteristics and fate of antibiotics, and found the following patterns:

(1) In terms of monitoring tools, most studies used SPE as the pretreatment technique and HPLC/MS/MS and UPLC-MS/MS as the analytical techniques. The researchers performed some specific technical optimizations, such as adding chemicals and adjusting the flow rate, for the instrument operation scheme and the target compounds to ensure reliable results.

(2) In terms of monitoring concentrations and ecological risks, 64 antibiotics were detected until the detection time of 2020, most of the concentrations were 10–1000 ng/L, and risks were between low and medium, but the highest value could reach 47,444.5 ng/L. There were more relevant studies in Jianghan Plain and Beijing, and QNs and SAs received more attention. In terms of influencing factors, antibiotic concentrations can be affected by seasonal changes for various reasons, and hydrogeological conditions, especially karst aquifers, have a greater impact on antibiotics in groundwater.
(3) In terms of source, scholars believe that the detected antibiotics originate from pharmaceutical companies, research institutions, hospitals, domestic sewage, livestock production, fish ponds, agriculture, landfills, sewage treatment plant effluent, and surface water. Among them, those receiving more attention are surface water, sewage treatment plant effluent, livestock production, and agricultural wastewater.
(4) In terms of their fate in groundwater, antibiotics can undergo processes of adsorption, hydrolysis, and biodegradation in groundwater, and they are affected both by themselves and by the environment, with different antibiotics having different sensitivities to different reactions.

In summary, we believe that there are relatively few studies on antibiotics in groundwater in China, and the scope and frequency of antibiotic detection need to be increased. Due to the influencing factors of the distribution of antibiotics in groundwater, the basic water quality of groundwater, such as pH, water temperature, and the presence of ions, especially the presence of heavy metal ions, need to be tested at the same time. The season at the time of monitoring, the geological conditions of the groundwater, and potential nearby point sources also need to be recorded.

At the same time, we should optimize the detection scheme according to the actual situation, some new and efficient detection means deserve to be developed comparatively, and the ecological risk evaluation methods need to be improved to identify more precisely. Additionally, when developing policies, special attention needs to be paid to antibiotics in groundwater that are high in toxicity, hard to degrade, and have high mobility in order to develop reasonable control measures for the occurrence of antibiotics in groundwater.

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