

The Silent Menace: Antibiotics In The Aquatic System And The Need For Action

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Abstract: Antibiotics have revolutionized modern medicine, but their availability and indiscriminate use have led to persistent contamination of aquatic ecosystems. Significant quantities of domestic sewage. Reports suggest that antibiotic concentrations range from nanograms per liter (ng/L) to several micrograms per liter (µg/L) in surface waters globally. Such contamination has significantly contributed to the development and spread of antibiotic-resistant microorganisms and genetic determinants of resistance, often through mechanisms such as horizontal gene transfer. This poses a serious risk to aquatic life and human health. Hence, this review focuses on the major sources of antibiotic pollution and their toxicological effects on model organisms, such as *Daphnia magna*, zebrafish, and *C. elegans*, as well as current detection methods, including LC-MS/MS and biosensors. We also discuss remediation strategies like advanced oxidation processes (AOPs), membrane filtration, and bioremediation. Despite technological progress, regulatory enforcement and public awareness remain limited. Hence, this review also describes an in-depth discussion on the areas requiring future research and the urgent need for integrated policy, advanced analytical monitoring, and sustainable management practices to mitigate antibiotic contamination in aquatic environments.

Keywords: antibiotics; aquatic environment; toxicology; monitoring; remediation; pollution.

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1. Introduction

The chemical substance generated by bacteria to kill other bacteria or germs was characterized as an “antibiotic”, as stated by S.A. Waksman in 1947. However, the various methods by which modern antibiotics are produced and used have significantly altered this concept. Now, antibiotics are defined as any chemical, synthetic, natural, or organic material that stops the development of infections [1].

Antibiotics are a group of drugs used to treat bacterial illnesses [2]. They function by eradicating or slowing the growth of bacteria, thereby empowering the body's immune system to fight off various illnesses. These pharmaceuticals adhere to bacterial cells and interfere with their molecular mechanism for protein production, nucleic acid synthesis, or metabolic pathways [3]. They interfere with vital functions and disrupt the bacteria's ability to replicate, grow, or survive, ultimately leading to their elimination by the immune system [4].

In downstream water, the concentration of antibiotics is higher due to the discharge from wastewater treatment plants. Similarly, the antibiotic concentration in river water is higher in areas near urban regions than in rural areas due to the high population and various anthropogenic activities [5]. Additionally, when surface water is considered, the antibiotic concentration is comparatively lower due to dilution from water or adsorption in suspended solids. Moreover, the occurrence of these antibiotics varies considering different seasons [6]. When the marine environment is considered, the concentration is lower due to the dilution process through deposition, degradation, and/or exchange of antibiotics between coastal waters and the open sea. Finally, the association of antibiotics with groundwater depends on the variability of the season. For example, during the season of heavy rainfall, there is potential for groundwater runoff into surface water, which may create a dilution effect leading to low antibiotic concentrations.

A study highlighted the importance of monitoring emerging contaminants and developing efficient treatment options to mitigate antimicrobial resistance (AMR) and remove these toxins from water sources [7]. Also, a reported study found that antibiotic concentrations were discovered to be in the low to medium range. Yet, they could still pose a hazard to the environment and contribute to the development of antimicrobial resistance. Moreover, it was also reported that more than 70% of all medications used on animals and 6% in the case of people were antibiotics [8].

To select the most suitable antibiotics, it is essential to consider various parameters, including the nature of the infection, bacterial susceptibility, and safety considerations. Antibiotic medication was originally used to treat bacterial infections in humans, animals, and plants. Some of these illnesses are infections of the respiratory pathways, infections in the urinary tract systems, dermatosis, Sexually Transmitted Infections, Surgical Prophylaxis, and Bacterial Meningitis [9]. According to a study, Eastern Europe and Central Asia had the greatest rates of antibiotic use, while Sub-Saharan Africa had the lowest rates [10]. According to a 2016 study, the estimated global consumption of antibiotics is 14.3 billion, with a 95% consumption rate. Additionally, research conducted in North Africa, the Middle East, and South Asia revealed high consumption rates for particular antibiotic classes [11].

The production of antibiotics is increasing rapidly due to high population growth in Asia, the USA, Africa, Europe, and Australia. Certain wastes (antibiotic residues) generated during the manufacture of antibiotics in the pharmaceutical industries are sent to treatment facilities, while others are released straight to water sources without sufficient treatment. These antibiotics can break down into a variety of metabolites on water surfaces, interact with other metabolites, or react with other substances, forming complexes or other toxic agents that can give rise to cancer-causing chemicals, which can be extremely lethal to humans and aquatic life [12].

Although less harmful than other contaminants, the presence of antimicrobials in water habitats can nonetheless alter the habitat or ecosystem of microorganisms and other aquatic animals in these environments, resulting in the encouragement of multidrug resistance in bacteria. According to studies, antibiotics present in aquatic environments can lead to modifications in bacterial communities, which can create and spread drug-resistant genes [13].

The current review sheds light on the occurrence of antibiotics in aquatic environments from various sources and their toxicological consequences on different model organisms, followed by a detailed discussion about the risks of antibiotics found within aquatic ecosystems. Subsequently, we describe the advanced techniques currently applied for the

identification of antibiotics. Further, this paper has also discussed the remediation methods currently available to tackle antibiotic pollution. Moreover, in-depth discussions have also been conducted on areas requiring further improvement and research regarding the present topic.

2. Sources of Antibiotic Contamination in the Aquatic Environment

Antibiotics can enter our environment from various sources, potentially leading to deleterious effects on humans and animals [14–17]. Figure 1 below highlights the various routes of antibiotic contamination in the aquatic environment and its impact on humans and animals.

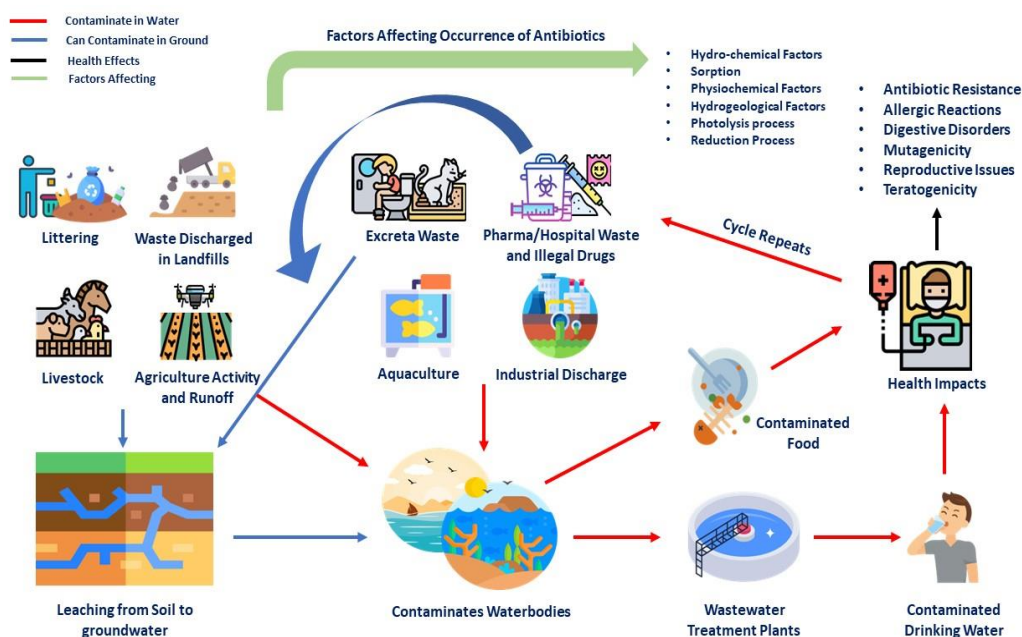


Figure 1. Sources of antibiotic contamination in the aquatic environment and their impact.

2.1. Household and municipal wastes.

The term "municipal waste" refers to garbage produced or discarded within a city and subsequently disposed of at a municipal landfill. In addition to debris from building and demolition operations, this garbage also includes waste from homes, companies, hospitals, and other organizations. Over time, certain medications, such as antibiotics, may be inadvertently combined with other types of municipal waste that have been discarded, posing a risk of environmental contamination and potential harm to living organisms. The danger of acquiring antibiotic resistance rises when outdated or unused drugs are improperly disposed of in the environment [18]. Antibiotics and antibiotic-resistant bacteria may be present in areas where municipal waste is disposed of. These antibiotic-resistant bacteria may spread through leachates, posing a serious threat to the ecosystem. Inevitably, it is not possible to determine the susceptibility of antibiotics in bacterial communities due to the widespread transfer of municipal waste in terminals nationwide [19].

A study found that in low-income settings, wastewater is primarily composed of feces and urine, which contain excreted pharmaceuticals and often end up in on-site sanitation systems, such as pits, latrines, septic tanks, and even the environment in the case of open defecation [20]. However, there is a possibility of pharmaceutical pollution in groundwater sources, including those used for drinking water supply, due to strong hydrological connections between pit latrines and groundwater systems [21].

Furthermore, customers may run the risk of health problems if they dispose of their unwanted pharmaceutical waste in the toilet or washbasin. In a study conducted in the Malaysian town of Selangor, it was found that the vast majority of participants, approximately 81.6% of respondents, admitted that storing their unused and expired medications at home is a risk. Regarding the notion that improperly discarded pharmaceutical waste may impact surface water, 73.4% of participants agreed with this concept [22].

2.2. Agricultural sources.

The degree to which pharmaceutical residues adhere to soil solid fragments, such as organic matter, influences their behavior and persistence in the soil. The amount of sorption influences the accessibility of the medication's active ingredients as well as their persistence in the soil [23].

In a study conducted in Pakistan, it was discovered that a significant majority (85%) of the farms lacked a proper wastewater drainage system. As a consequence, poultry waste and antibiotic residues were directly released into the surrounding environment. Antibiotics seep into the soil and subsequently reach the groundwater [24]. Antibiotic drugs administered to livestock are present in their manure and are used as fertilizers for agricultural purposes, which may result in veterinary medicines entering water bodies through leaching [25]. Soil leaching, wastewater discharge into surface waterways, and agricultural runoff result in antibiotics being present in groundwater, indicating that they have been filtered through the soil strata and influenced by rainfall events [26].

In another research report, it was found that 66% of poultry farmers also maintained other kinds of animals. The majority of individuals store their medications in cabinets or drawers and in a convenient location, such as a refrigerator. Furthermore, improper disposal of unused medications in household trash can result in antibiotics ending up in landfills [27]. Over time, leachate from these landfills can carry residues that infiltrate the nearby soil and water bodies [28].

Different farming techniques have been adopted to meet the demand for animal proteins in emerging countries. This has led to the inclusion of residual antibiotics in goods obtained from animals, resulting in an increase in antibiotic resistance. Such resistant bacteria can lead to serious public health issues because these diseases are transmissible from animals to humans via the food supply distributed in the natural world [29].

Agricultural runoff can lead to the pollution of terrestrial water and groundwater aquifers [30]. Similarly, in aquaculture, antibiotics are used to prevent infections in fish populations, and these compounds can escape from fish farms into surrounding water bodies, contributing to contamination. Urban areas with dense populations often exhibit significant antibiotic usage. During rainfall, stormwater runoff can carry antibiotics from urban surfaces into nearby water bodies. This runoff has been observed to contribute to the introduction of pharmaceutical residues into water surfaces, including dams, rivers, and lakes [31].

2.3. Medical wastes.

People's health was at risk when medical wastes were improperly disposed of during the pandemic [32]. To avoid direct discharge into aquatic bodies, medical waste is conventionally treated via landfill and incineration. Improper medical waste disposal can lead

to contaminants entering groundwater and surface water through infiltration and runoff, potentially contaminating these water supplies [33].

It is now known that improper handling of medical waste can lead to environmental contamination and pose risks to water, air, agricultural products, the food chain, and livestock. Proper management and disposal of medical waste have become a debated and significant issue due to the ongoing rise in pharmaceutical use, and the disposal of leftovers or outdated pharmaceuticals ending up in sewage systems. In response to this issue, several nations have put in place pharmaceutical waste collection systems [34]. The necessity of measuring public awareness of this issue, as well as educating consumers about responsible drug use and the proper disposal of leftover or expired pharmaceuticals, must be critically addressed [35].

A previous study found that approximately 53.9% of respondents disposed of their stored medications in conventional trash cans alongside other solid waste. The most typical way for individuals to dispose of unneeded medications is in standard trash cans [36]. Comparatively, the study found that the practice of flushing unwanted medications down the toilet or draining or disposing of them with regular solid waste (3%) is uncommon in developed countries [37].

Medical waste belongs to a unique group of hazardous contaminants, and during public health emergencies, improper treatment might lead to secondary environmental pollution. Even in the absence of a pandemic, the large population expansion is expected to drive more than a 50% rise in medical waste output by 2030. Due to a significant portion of the larger population and gross domestic product (GDP), the eastern region generated more medical waste than the western region. However, the amount of household consumption alone determines the per capita medical waste output, which is not impacted by any regional features [38].

2.4. Industrial wastes.

The pharmaceutical industry has experienced significant growth in recent years due to the high demand for drugs to treat various diseases worldwide. This increased demand is a result of the growing global population and the prevalence of acute and chronic illnesses [39]. Unfortunately, the growth of these industries has led to the pollution of surface water through multiple means. During the manufacturing processes of pharmaceutical products, a wide range of chemicals, solvents, and reagents are utilized. When these substances mix with wastewater, they can come into contact with surface water after being discharged from wastewater treatment points [40]. In certain scenarios, pharmaceutical waste is partially treated and released, increasing the likelihood of environmental contamination with pharmaceutical residues [41].

Spills and leaks from pharmaceutical manufacturing industries can also lead to environmental contamination from these residues. Leaked pharmaceutical ingredients may eventually be washed into rivers, lakes, or oceans by running water [42]. Additionally, the presence of pharmaceutical compounds in drinking water can originate from two sources: the production processes of the pharmaceutical industry and the common use of pharmaceutical compounds, resulting in their presence in urban and agricultural wastewater [43].

Wastewater in pharmaceutical manufacturing industries arises during the synthesis and production of drugs. The production of active pharmaceutical ingredients involves various chemical reactions, leading to the generation of wastewater. The quantity and composition of this wastewater can vary based on factors like plant location, raw materials used, and the manufacturing processes employed [44]. The diversified nature of the pharmaceutical industry

makes it challenging to implement a standardized treatment system for managing these wastewater streams [45]. Inadequate treatment of these effluents can lead to the direct release of antibiotics into the aquatic environment. The pharmaceutical industry's rapid growth has led to various pollution pathways in surface water. To mitigate this issue, pharmaceutical companies need to implement proper waste management practices and invest in effective wastewater treatment technologies to minimize the environmental impact of their operations.

Table 1 below highlights some important examples of the most commonly used antibiotics globally, along with their associated contamination. The table highlights the specific antibiotics studied and the maximum concentration of antibiotics detected from that source. For example, in Korea, the composting aquatic system from swine manure detected the highest concentrations of tetracyclines and sulfonamides. In India, multiple locations, including Delhi, Kota City, and Ujjain, exhibit significant antibiotic contamination from the sewage system and hospital wastewater, with residues such as ampicillin and cefpodoxime detected at the highest concentrations. In Africa, sewage treatment plants and hospital wastewater have been identified as the primary sources of antibiotic contamination in the environment, with high levels of sulfonamides and fluoroquinolones. Furthermore, regions such as Southeast Queensland, Australia, and Buenos Aires, Argentina, have reported significant amounts of fluoroquinolones, sulfonamides, and macrolide antibiotics in rivers and industrial discharges. In Europe, the most commonly detected antibiotics are macrolides and beta-lactams in the wastewater system. These observations highlight the presence and distribution of antibiotics in various aquatic systems within our environment.

Table 1. Some examples of the most commonly used antibiotics globally & their contamination.

Country/continent	Sources of antibiotic contamination	Studied antibiotics	Maximum detected concentration	References
Korea (Asia)	Swine manure composting	Tetracyclines, Sulfonamides	Tetracycline (254.82µg/L)	[46]
Delhi, India (Asia)	Sewage system	Beta-lactams	Ampicillin (104.2 µg/L)	[47]
Bangladesh (Asia)	Aquaculture	Sulfonamides, Beta-lactams	Trimethoprim (41.67µg/L)	[48]
Kenya (Africa)	Sewage treatment plant	Sulfonamides, Fluoroquinolones, Beta-lactams	Norfloxacin (56µg/L)	[49]
South-East Queensland, Australia	Hospital samples	Beta lactams, Quinolones, Macrolides, Tetracyclines, Lincosamides, Sulphonamides	Ciprofloxacin (>64 µg/L)	[50]
Bangzhou Bay, China	Estuary aquaculture	Sulfonamides, Quinolones, Tetracyclines, Amphenicol	Tetracyclines (39.59 ng/L)	[51]
Bushehr City (Iran)	Wastewater treatment plant	Macrolide	Azithromycin (896 ng/L)	[52]
Kota City (India)	Hospital wastewater samples	Beta-lactams, Cephalosporins, Fluoroquinolones, Penicillins	Cefpodoxime (3.24 mg/L)	[53]
Ujjain (India)	Kshipra is affected by industrial pollutants	Sulfonamide, Fluoroquinolones	Sulfamethoxazole (4.66 µg/L)	[6]
Delhi-India	Yamuna River	β-lactam, Fluoroquinolone, Cephalosporin	Amoxicillin 13.75µg/L	[47]
China	Songhua River	Macrolide, Cephalosporins, Fluoroquinolones	Sulfamethoxazole (73.1ng/L)	[54]

Country/continent	Sources of antibiotic contamination	Studied antibiotics	Maximum detected concentration	References
Buenos Aires-Argentina	Rivers and farm wastewater	Fluoroquinolones	Enoxacin (22.1 µg/L)	[55]
Nairobi County, Kenya	HWW	Sulfonamides, β -lactams, Macrolides, Aminoglycosides	Sulfamethoxazole (20.6 µg/L)	[56]
Kharkiv region-Ukraine	Surface water	Macrolides	Azithromycin (30 µg/mL)	[57]
Africa	Wastewater	Aminoglycoside, Macrolides, Quinolones, Tetracycline, Trimethoprim	Sulfamethoxazole (39 µg/L)	[58]
European	Waste water	Macrolides, Fluoroquinolones	Azithromycin (1577.3 ng/L)	[59]
Yellow Sea in China	Surface water	Tetracyclines, Sulfonamides, Fluoroquinolones	Ciprofloxacin (6.6 ng/L)	[60]
Mekong Delta, Vietnam-Asia	Freshwater aquaculture,	Sulfonamides, Fluoroquinolones	Sulfamethoxazole (21 ng/L)	[61]
Terahan-Iran	Wastewater treatment plant (From hospital water)	Cephalosporins, Fluoroquinolones	Cephalexin (977.7 ng/L)	[62]
BRAZIL-South America	Wastewater treatment plant	Metronidazole, Tetracyclines, Sulfonamides, Fluoroquinolones	Sulfamethoxazole 1.374 µg/L	[63]
USA-North America	Waste water	Macrolides, Fluoroquinolones, Sulfonamides, Cephalosporins	Cephalexin (13.818 µg/L)	[64]
Nigeria-Africa	Hospital Wastewater Treatment Plants	Fluoroquinolones	Ciprofloxacin (561 µg/L)	[65]

Chemicals used in the manufacturing process of pharmaceuticals are not completely filtered out, allowing pollutants to leak into nearby water bodies and open fields. This results in pollution when effluent from pharmaceutical facilities contaminates adjacent water bodies and open fields, thereby increasing the amount of pharmaceutical waste in the ecosystem [66]. Most municipal wastewater treatment plants are unable to remove these chemicals from drinking water, so they end up in rivers after being flushed down the toilet or excreted from the body. This can lead to chronic exposure and major health problems [67,68].

Active pharmaceutical chemicals are found in over 50% of all the world's rivers at concentrations that can have a serious negative influence on health. Significant pollution, primarily from fluoroquinolones, was identified in a supplementary investigation that assessed active pharmaceutical ingredients in the surface, groundwater, and drinking water, both upstream and downstream of industrial discharge. Ciprofloxacin, for instance, was detected in quantities ranging from 2500 to 10000 µg/L in rivers and lakes, and between 44 and 14000 ng/L in wells, indicating that pharmaceutical manufacturers' effluents can pollute water bodies past the discharge point [69].

Other studies conducted in the Musi River, India, have pointed out that water bodies typically contain antibiotics, and drinking water from these water bodies is crucial for human survival. However, this contamination poses a significant health risk. The above study found Fluoroquinolones at an alarming concentration; for instance, the concentrations of ciprofloxacin, ofloxacin, and norfloxacin were 5015 µg/L, 542.4 µg/L, and 251 µg/L, respectively [70]. It is noteworthy that the amount of antibiotics found in aquatic bodies exceeds the EPA's (Environmental Protection Agency) recommended draft notification thresholds, raising a red flag for water's antibiotic regulatory bodies [71].

For instance, in the investigation conducted in the Kshipra River in 2020 during the pandemic, sulfamethoxazole was detected at a concentration of $>4.66 \mu\text{g/L}$. The scientists found that it was crucial to routinely check the Kshipra River for antibiotic residues to prevent the emergence of resistance, which jeopardizes the health of humans and other animals, as well as the entire ecosystem [72]. In autumn, studies conducted on the river water found that sulfamethoxazole was more prevalent in the water. Researchers also discovered norfloxacin and ofloxacin in amounts of 0.66 g/L and $0.99 \mu\text{g/L}$, respectively. In the fall season, the values ranged from $(0.74 - 5528 \mu\text{g/L})$, and ciprofloxacin was identified as the most prevalent antibiotic [73]. A similar study reported fluoroquinolone antibiotic concentrations in Musi River water samples up to $6278 \mu\text{g/L}$ [70].

3. Antibiotic Contamination in the Aquatic Environment

Antibiotic residues enter our environment through various pathways, including the removal of unmetabolized pharmaceuticals from organisms, such as humans and veterinary animals, limited biodegradation capacity in microorganisms, inadequate disposal of medical waste, and the release of pharmaceutical manufacturing waste [74]. Once present in our habitat, antibiotics have serious negative effects on the ecology and facilitate the emergence of antibiotic resistance, resulting in the spread of environmental contamination from antibiotic residues [75].

Levofloxacin and azithromycin were identified as the primary contributors to contamination in a study conducted in India. It's conceivable that the high concentration of these drugs was caused by residents' use of drugs to treat seasonal ailments, including colds, fever, and respiratory infections that are common in the winter [64].

In a study conducted by analyzing the Seine River in France, the authors reported the presence of three antibiotics, namely Ofloxacin, Norfloxacin, and Sulfamethoxazole, at higher concentrations. All antibiotics identified in this analysis exceeded the Ministry's draft notice limitations, despite the investigation's limited sample size. The main source of antibiotic residues in this river may be treated and untreated sewage from point and non-point sources [76]. According to a reported study in Jiangnan Plain, China, Erythromycin had the highest detection frequency among all other antibiotics in water samples from surface sources in different seasons, including winter, summer, and spring, with concentrations of $0.546 \mu\text{g/L}$, $1.60 \mu\text{g/L}$, and $0.772 \mu\text{g/L}$, respectively. The issue of a smaller number of sewage systems in lower-income countries can impact the exposure pathways [77]. Additionally, middle-income countries discharge untreated sewage into water bodies and then use the water for irrigation [78]. Manure spread on farms and runoff from agricultural fields introduce antibiotics to surface and groundwater. In countries where manure is stored in manure lagoons, heavy rainfall can cause antibiotics to enter the aquatic system. Moreover, accidental spillage of antibiotics, their disposal, and atmospheric dispersal of manure and feed dust contaminated with antibiotics can also be small sources of antibiotic contamination [79].

Residues of several antibiotics, including erythromycin (320.5 ng/L), ciprofloxacin (3 ng/L), metronidazole (1195.5 ng/L), clarithromycin (320.5 ng/L), norfloxacin (10 ng/L), tetracycline (23 ng/L), ofloxacin (179 ng/L), trimethoprim (424 ng/L), and sulfamethoxazole (326 ng/L), were detected in rivers like Tagus, Guadarrama, Jarama, Henares, Manzanares [80] providing valuable insights on antibiotics pollution in these rivers. Similarly, the largest rivers in Spain, such as the Llobregat and Ebro, were also reported to be contaminated with traces of antibiotics [81]. Antibiotic contamination, including ciprofloxacin (653 ng/g), norfloxacin

(5770 ng/g), oxytetracycline (652 ng/g), and ofloxacin (1290 ng/g), has been detected in the Pearl, Hai, Liao, and Yellow Rivers in China [82]. Studies have also found varying concentrations of antibiotics, such as ciprofloxacin, azithromycin, and sulfamethoxazole (SMX), in wastewater, surface water, soil, and even drinking water, which could contribute to the emergence of antimicrobial resistance in bacteria and pose a risk to both human and animal health [21, 83, .

Even though one of the strongest natural filters for preventing contaminants from entering freshwater is soil, due to anthropogenic activities, urban aquifers have become a primary source of antibiotic pollution, contributing to the presence of antibiotic residues in underground water. Nevertheless, the soil's proficiency in contamination, the extent of retardation is determined by a combination of factors, including the physicochemical properties, ambient concentration, and environmental nature of the pollutant [28]. For instance, the highest concentration was found for ciprofloxacin (1.270 µg/L), followed by levofloxacin (0.177 µg/L) and amoxicillin (1.50 µg/L) antibiotics in the groundwater of Spain. Additionally, a study found that wastewater treatment plants (WWTPs) are the primary source of contaminated drinking water, according to a study that revealed 72 distinct pharmaceutical residues in Barcelona's underground water[85]. Additionally, the Llobregat delta (Catalonia, Barcelona, Spain) was the subject of a three-year continuity study that confirmed contamination, with the highest concentrations of ciprofloxacin (323.57 ng/L) in the delta, due to poor sanitation, improper wastewater treatment, and the misuse of agricultural antibiotics [86].

Furthermore, seawater has been found to have a lower concentration of antibiotics compared to wastewater treatment plants and sewage water, with river confluences being the primary source of antimicrobial pollution in rivers. Previous research has identified such instances in Bohai Bay coastal waters, providing insight into how Bohai Bay's ecological disturbance was caused by the discharge of rivers contaminated with antibiotic residues [60].

Table 2 below highlights various contaminations of antibiotics in various aquatic matrices. Wastewater samples revealed the highest detection of antibiotics, including amoxicillin, ciprofloxacin, ofloxacin, sulfamethoxazole, and ampicillin, with concentrations ranging from non-detectable to 495 µg/L. Followed by the hospital wastewater with the highest concentration of antibiotics, including amoxicillin, ceftriaxone, amikacin, ofloxacin, and ciprofloxacin, with concentrations up to 236.6 µg/L. Groundwater was mostly contaminated with antibiotics, including sulfonamides, chloramphenicol, tetracycline, β-lactams, and erythromycin, with concentrations ranging from 0.0001 µg/L to 100 µg/L. Surface water was found to contain a wide range of antibiotics, including azithromycin, clarithromycin, trimethoprim, ciprofloxacin, ceftriaxone, and metronidazole, with concentrations reaching up to 5528 µg/L.

Table 2. Examples of Antibiotic Contamination in various aquatic matrices.

Matrix	Detected antibiotics	Concentration (µg/L)	References
Wastewater (Sewage system)	Amoxicillin, Ciprofloxacin, Ofloxacin, Sulfamethoxazole, Norfloxacin, Ampicillin, Naproxen, Trimethoprim, Levofloxacin, Azithromycin, Metronidazole	ND- 0.1726, ND-5.75, ND-17.84, 0.024-7.3, ND-2.75, ND-51.82, 4.5-495, ≥0.023, ≤1.374	[7,47,63,64,73]
Hospital wastewater	Amoxicillin, Ceftriaxone, Amikacin, Ofloxacin,	ND-236.6 43	[87,88]

Matrix	Detected antibiotics	Concentration (µg/L)	References
	Ciprofloxacin, Norfloxacin, Levofloxacin, Clarithromycin, Trimethoprim, Sulphapyridine, Sulfamethoxazole		
Groundwater	Sulfonamide, Chloramphenicol, Tetracycline, β-Lactams, Erythromycin, Ciprofloxacin, Ofloxacin, Sulfamethazine, Sulfamethoxazole, Azithromycin, Ciprofloxacin, Norfloxacin, Sparfloxacin, Amikacin, Trimethoprim, Clarithromycin, Trimethoprim	1-100, <0.1944, >0.1, <0.0001-0.034, 0.001- 0.816	[88–90]
Surface water	Azithromycin, Clarithromycin, Trimethoprim, Ciprofloxacin, Ceftriaxone, Ofloxacin, Norfloxacin, Sulfamethoxazole, Metronidazole, Triclosan, Carbamazepine, Ampicillin, Ciprofloxacin, Gemifloxacin, Sparfloxacin, Cefuroxime, Naproxen, Sulfamethoxazole, Trimethoprim, Erythromycin, Keflex, Tetracyclines, Roxithromycin, Clarithromycin, Clindamycin, Lincomycin, Miconazole, Thiabendazole	ND -4.66, <5528, 0.2 - 0.93, 9.44–51.6, ND-5.38, 9.5–263.3, 0.2-0.93, 4.7-2500, 0.0547-0.826, ND-35.5, ND-3., 3e-5-0.0171, 20≤50, ≤1, 0.0571 -2.7966, 0.100 µg/L- 1.60, 0.004-0.021, 0.024-7.3	[6,8,27,61,91–101]

*ND- Not Detected

4. Toxicity of Antibiotics

Antibiotics are pervasive environmental contaminants that, due to their high durability, may have effects spanning multiple generations. Unfortunately, little is known about their impacts across generations and possible pathways. Moreover, antibiotics encourage the emergence of an emerging pollutant called antibiotic resistance [102–104].

One of the major reasons for antibiotic pollution is that many countries rely on septic tanks for sewage disposal, which pollutes aquatic bodies. The leachate generated from municipal solid waste landfills containing disposed antibiotics also leaches into the groundwater, leading to the issue of antibiotic resistance genes (ARGs) and antimicrobial-resistant bacteria (ARB) [29, 105]. Additionally, another issue with antibiotics is that they can accumulate in the environment and subsequently in crops. Drugs being excreted from the human body are also entering the environment through sewage [29, 105, . These pharmaceuticals take a large amount of time to be eliminated, thus entering our food chain [105] as shown in Figure 2.

Cycle of Antibiotic Resistance in Aquatic Ecosystems

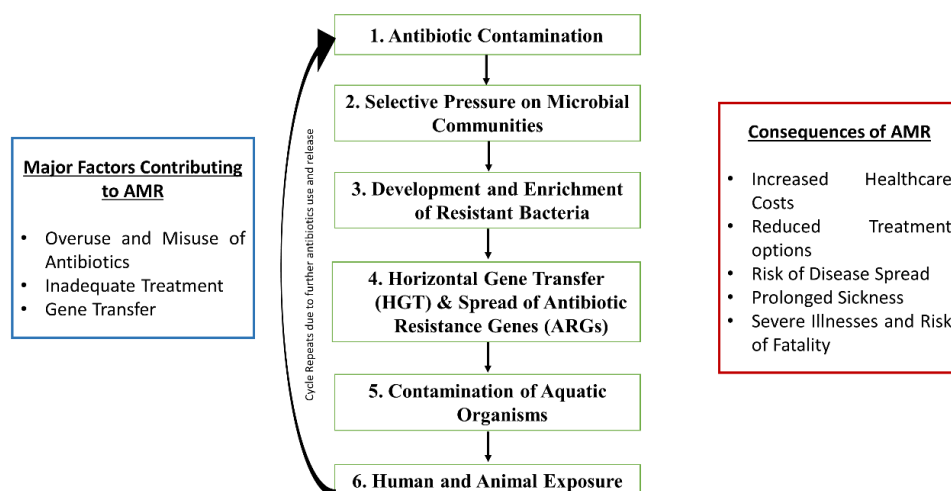


Figure 2. Schematic representation of the antibiotic resistance cycle in aquatic environments, showing entry of antibiotics into the water bodies and promoting the proliferation of resistant bacteria and subsequent exposure to living organisms.

These antibiotic-resistant bacteria can easily contaminate food and enter the bodies of biological organisms, posing a major health challenge [107]. The propagation of AMR in the environment is largely driven by Horizontal gene transfer (HGT) in natural ecosystems, which is intensified by human activities [108,109]. Horizontal Gene Transfer (HGT) is one of the most important mechanisms by which bacteria exchange genetic material, including antibiotic resistance genes (ARGs), across individuals or species, bypassing the traditional mode of inheritance. HGT occurs primarily through three mechanisms: transformation (the uptake of free DNA fragments from the environment), conjugation (the direct transfer of plasmids between bacterial cells via cell-to-cell contact), and transduction (the transfer of bacterial DNA via bacteriophages) [110,111]. These processes enable bacteria to rapidly acquire and disseminate resistance traits, contributing significantly to the spread of antimicrobial resistance (AMR) [110,111], as illustrated in Figure 3.

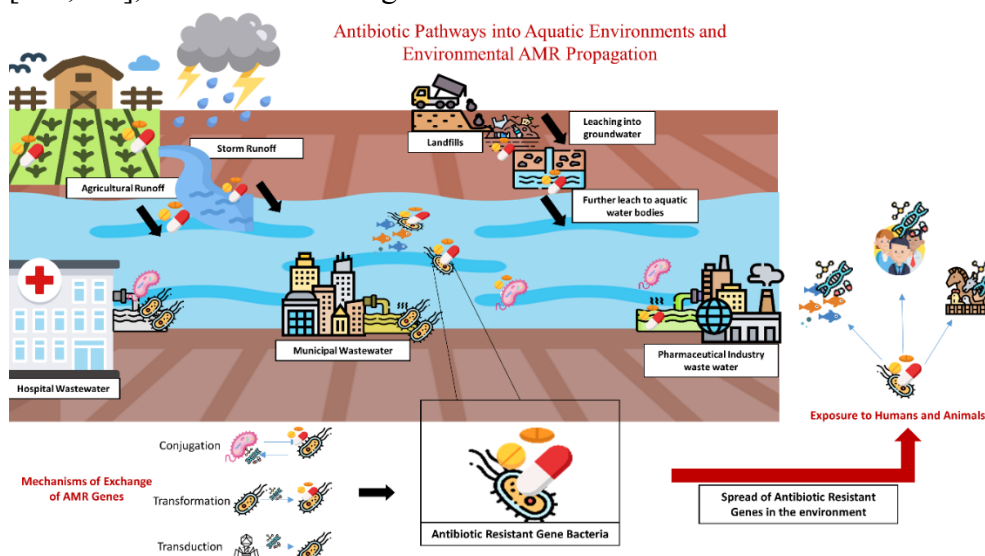


Figure 3. Illustration of environmental pathways contributing to antibiotic contamination and antimicrobial resistance (AMR) propagation in aquatic systems. (included figures are original and non-published)

Additionally, pollutants like pharmaceuticals and industrial chemicals can enhance HGT by affecting bacterial cell permeability or inducing stress responses. Furthermore, climate change factors, including rising temperatures and extreme weather events, can enhance bacterial growth and gene transfer, thereby exacerbating the spread of AMR and posing significant public health challenges [108,109].

Numerous case studies have highlighted the prevalence of antibiotic resistance genes (ARGs) in downstream of pharmaceutical facilities, underscoring the urgent need for stringent environmental regulations. In Nigeria, untreated wastewater from pharmaceutical plants has been found to harbor multiple clinically significant β -lactam resistance genes, including blaTEM, NDM-1, OXA, IMP, and CTX-M, as well as MLS resistance genes and sulfonamide resistance genes such as sul1, sul2, and sul3 [112–114]. Similarly, in Saudi Arabia's Wadi Hanifah Valley, downstream water samples exhibited a high frequency of ARGs such as tet(M), tet(B), erm(B), and sulII, indicating significant contamination from upstream pharmaceutical discharges. In Europe, studies have detected pharmaceutical pollutants, including antibiotics, in rivers within national parks, leading to concerns about the impact on freshwater organisms and human health due to the promotion of antimicrobial resistance [112–114]. According to the World Health Organization, human deaths due to antibiotic-resistant organisms are more than those of diseases [107]. These findings underscore the crucial need for intensified monitoring and regulation of pharmaceutical pollution to protect environmental and public health [112–114].

The wastes from animals carry a large number of germs that can cause human disease. Among these, many microbes can already be transformed into resistant organisms, causing different ailments. Essentials like vegetables and fruits can also be contaminated with antibiotic-resistant bacteria, posing a serious threat of food poisoning [115]. The World Health Organization (WHO) estimates that bacteria are one of the most common causes of global food poisoning. One of the reasons for this contamination may be the use of contaminated water for irrigation. Antibiotics have been used for years to treat bacterial infections, but as many of these bacteria have developed resistance, scientists are exploring ways to combat these notorious microbes. Multiple factors, including antibiotic efflux from the body and the modification of functional groups of antibiotic-modifying co-substrate enzymes, contribute to the development of antibiotic-resistant bacteria. Also, changes in the cell surface receptors, redox systems, and severe antibiotic stress lead to the production of resistant enzymes [115].

The various toxic reactions of antibiotics include skin rashes, serum sickness, thrombocytopenia, erythema multiforme, hemolytic anemia, vasculitis, acute interstitial nephritis, Stevens-Johnson syndrome, and toxic epidermal necrolysis. For example, allergic reactions have been reported in people who consumed milk, meat, and pork, all containing penicillin residues [116]. Furthermore, some studies have mentioned that aminoglycoside, sulfonamide, and tetracycline residues can also cause allergic reactions [117]. For example, a study reported that penicillin, oxacillin, cloxacillin, flucloxacillin, and amoxicillin-clavulanate could cause hepatitis [118]. At the same time, tetracyclines can mimic acute fatty liver during pregnancy.

Furthermore, a study has reported that nitrofurantoin could cause chronic hepatitis mimicking chronic autoimmune hepatitis, acute cholestatic, and hepatocellular reactions [119]. Other antibiotics like Ceftriaxone are also known to cause drug-induced gallstones and quinolone cholestasis. Sulfamethoxazole/trimethoprim is also capable of causing hepatotoxicity, especially in patients with acquired immunodeficiency syndrome [118].

Mutagenicity, reproductive disorders, and teratogenicity have also been reported in various studies [120].

Various toxicity studies examine the impact of antibiotics on different organisms. Among these, zebrafish, *Daphnia magna*, and *C. elegans* have recently been used to screen various environmental toxicants. Zebrafish is an animal model that the OECD has recommended as an indicator of the ecological toxicity of contaminants in aquatic environments. Due to its low costs, ease of maintenance, genetic capabilities, and manipulations, it has been used in toxicity studies [121]. Table 3 below highlights some recent toxicity studies using Zebrafish.

Table 3. Highlights some recent toxicity studies using Zebrafish.

Sr. No	Antibiotics	Parameters	Results	References
1	Tetracycline and Bacteriostatic antibiotics	Biochemical parameters and gene expression	Impact on zebrafish gut health with a decrease in expression of muc2.1. Moreover, a decrease in OUT numbers and alpha-diversity indexes. Further levels of mRNA in glycolipid metabolism genes like PK, FAS, ACC1, and ACO increased.	[122]
2	Bacteriostatic antibiotic	Oxidative stress, Antioxidant index, and immune-related genes	Increase in Oxidative stress activity leading to damage to the liver and gills. Activation of toll-like receptors causes inflammation and upregulation of inflammatory factors	[123]
3	Fluoroquinolone, tetracycline, and cephalosporin antibiotics	Behavioural studies	Acute exposure caused impacts on learning, memory processes, and aggression.	[124]
4	Sulfonamide, cephalosporin, tetracycline, and fluoroquinolone antibiotics	Single and combined toxicity, body length, and oxidative stress	Shortened body length, an increase in ROS levels	[125]
5	Macrolide antibiotics	Hepatotoxicity studies, cell viability, and LDH assay	Liver degeneration, alteration in the size of the liver, and liver steatosis	[126]
6	Penicillin, like diaminopyrimidines, and macrolide antibiotics	Locomotor behavioral changes	Significant increase in neurological motor impairments, movement, speed, etc.	[127]
7	Tetracycline, sulphonamide, and macrolide antibiotics	Gut microbiota and gene expression	Imbalance in gut microbiome, and alteration in immune and stress-related gene expression	[128]
8	Quinolone Antibiotics	Survival and cardiac toxicity	Dose-dependent mortality and teratogenic effects. Followed by cardiac developmental toxicity	[129]
9	Sulphonamide Antibiotics	Oxidative stress and immune disorder	Oxidative stress and immune damage to the liver and gills with a decrease in gut microbiota. Moreover, pathological changes to the liver and intestinal tissues were observed.	[130]
10	Fluoroquinolone Antibiotics	Survival, Growth, biochemical alterations, and teratogenicity	Higher doses led to growth retardation, malformations in zebrafish embryos, and biochemical alterations	[121]
11	Sulfonamide Antibiotic	Neuro-behavioural changes and Gene expression	Alteration in behavior and growth was observed. At environmental concentrations, genes for folate synthesis and carbonic anhydrase were downregulated.	[131]

In recent studies, zebrafish models have been utilized to assess the toxicity of macrolide, bacteriostatic, quinolone, sulfonamide, fluoroquinolone, and tetracycline antibiotics. Zebrafish have been used to assess organ toxicity, growth, reproduction,

neurological defects, survival rates, and molecular alterations occurring from antibiotic exposures, as shown in Table 3.

Daphnia is another important aquatic organism that is recommended by the EPA and OECD for aquatic ecotoxicological studies. The widespread presence of this species in the food web helps serve as a bioindicators for predicting health effects, due to its advantages, such as a short reproductive cycle and ease of maintenance [132–134]. Table 4 below depicts some recent toxicity studies of Antibiotics using *Daphnia magna*.

Table 4. Depicts some recent toxicity studies of antibiotics using *Daphnia magna*.

Sr. No	Antibiotics	Parameters	Results	References
1	Tetracycline, sulphonamide, aminoglycoside, and bactericidal antibiotics	Population growth and metabolic profiles	Moderate toxicity was observed in the case of sulphonamide, aminoglycoside, and bactericidal antibiotics.	[135]
2	Tetracycline antibiotic	Reproduction effects	Tetracycline antibiotic had caused modulation effects on the microbiome composition, causing changes in the reproductive cycle.	[136]
3	Tetracycline antibiotic	Effects of Diet and Antibiotics	Poor dietary effects at lower and higher concentrations impacted the overall survival rate and reproduction cycle.	[132]
4	Tetracycline antibiotic	Mortality and gut biota	Low mortality rates, but an alteration in the species diversity of the biota	[137]
5	Fluoroquinolone and sulfonamide antibiotics	Mortality and Mutagenic Potential	Fatal mortality observed with injury-related responses	[138]
6	Fluoro-quinolone antibiotics	Reproductive effects	Early oogenesis and increased brood size in the second birth at moderate doses. At higher doses, embryonic viability and offspring degradation were more prominent.	[139]
7	Antimicrobial and Bacteriostatic antibiotics	Acute toxicity at varying temperatures	Acute toxicity increased for individual and combined exposures at higher temperatures.	[140]
8	Sulfonamide Antibiotics	Mortality, Growth, Reproduction, locomotion behavior, and ingestion rate	No changes to mortality and growth. Alterations in locomotion, ingestion rate, and reproduction were observed. Further, inhibition of AChE and lipase was observed.	[134]

Recent studies on *Daphnia* with various tetracyclines, sulphonamides, aminoglycosides, bactericidal Fluoroquinolones, and sulfonamide antibiotics have shown toxicity. In various studies, it was observed that the microbiome of *Daphnia* underwent alterations, affecting its survival rate, reproductive cycle, and subsequent growth and diet-related changes, as shown in Table 4.

C. elegans has been utilized as an important animal model for environmental toxicology, as 60-80% of genes are related to humans. Few recent studies have explored the potential toxicity effects of various sulphonamides, macrolides, tetracycline, and quinolone antibiotics on *C. elegans*. Various impacts, including dose-dependent toxicity, obesogenic effects, effects on the reproductive cycle, and the generation of oxidative stress, were observed, indicating the risks posed by antibiotics, as shown in Table 5.

Table 5. Depicts some recent toxicity studies on antibiotics using *C. elegans*.

Sr. No	Antibiotics	Parameters	Results	References
1	Sulphonamide Antibiotics	Feeding, Growth, and Antioxidant Enzyme Levels with limited/high food availability	Dose-dependent inhibition is greater with higher food plates	[141]
2	Macrolide Antibiotics	Lipid accumulation, Lipid Metabolism ELISA, Glucose Metabolism ELISA, gene	Both diets stimulated body width and triglyceride levels, with higher stimulation with live bacteria. Water-borne antibiotics	[142]

		expression of daf-2, daf-16, nor-49, total carbohydrates, fatty acid levels, measurement of intestinal barrier damage, and bacterial colonization impacts with exposures in water and diet-borne antibiotics in the presence of live/inactivated bacteria.	inhibited the activities of enzymes involved in fatty acid β -oxidation, and diet-borne antibiotics inhibited the activities of enzymes involved in lipolysis, followed by stimulation of the activities of enzymes in lipogenesis. Moreover, waterborne antibiotics caused the upregulation of genes. The results pointed towards obesogenic effects with varying diets.	
3	Tetracycline and Macrolide antibiotics	Lifespan and aging parameters (feeding, accumulation of lipofuscin, and ATP levels)	Extended lifespan and potential anti-aging effects	[143]
4	Quinolone Antibiotics	Locomotion behaviors, growth, apoptosis, ROS, and expression of genes coding for heat shock proteins, tumor suppression, superoxide dismutase, and Acetylcholine esterase	Significant decline in locomotion behaviors and growth. Followed by an increase in ROS levels and apoptotic activity, indicating oxidative stress. Increase in gene expression levels indicating stress	[144]
5	Macrolide and Sulphonamide Antibiotics	Multi-trans generational impacts	Inhibited reproduction and inhibition decreased with increasing generations.	[145]

Different antibiotics, such as sulfonamides, tetracyclines, and macrolides, have been shown to exhibit potential adverse effects on the development and growth of algae [146]. Studies with sulfathiazole exposure are one example that indicates their exposure might be linked to growth retardation of the macroalgae *Lemna gibba*, whereas antibiotics like aureomycin, oxytetracycline, and tetracycline were found to affect the growth of *Microcystis aeruginosa* [147] substantially. The inducible production of abscisic acid is connected to the explicit growth-inhibiting action of antibiotics. Another theory for how antibiotics impact algae is that they hinder protein production and harm the growth of chloroplasts, as this affects metabolism and photosynthetic ability, causing the algae's cell development and multiplication to be suppressed and inhibited [148]. Additionally, bone marrow toxicity and nephropathy were also seen in some antibiotics [149]. Multiple research studies have documented the toxic consequences of analgesics, including naproxen, ibuprofen, diclofenac, and paracetamol. A study has explained that environmental exposures to diclofenac can cause gill alterations and renal lesions in rainbow trout [150]. Diclofenac is also known to cause renal failures in vultures that feed on diclofenac-contaminated dead livestock [151]. Exposures of erythromycin and oxytetracycline are also known to cause alterations in the gills [152]. In a study, atorvastatin has been found to cause alterations in the biosynthesis and utilization of dietary fats in the primary intestinal region of species bivalves and changes in the mitochondria of *Mytilus edulis* [153]. Their presence in the environment can cause mutagenic effects, leading to the formation of micronuclei and binuclei in the gastrointestinal tract of tadpoles [154]. Growth inhibition was also explored in algae and cyanobacteria when they were exposed to 5-fluorouracil [155]. The problem of antibiotic residues has been found even in animal manures, for example, Ofloxacin and Norfloxacin have been found in chickens. Moreover, Ciprofloxacin, Enfluroxacin, Oxytetracycline, Chlorotetracycline, Sulphonamides, and Nitrofurans have also been detected in swine, cattle, and chickens. Similarly, tetracyclines and macrolides have also been detected in swine [156]. Furthermore, the adverse health effects of antibiotics and their residues when they enter the human body are affected by the microbiome. This can lead to alterations in the internal microbiome composition of the human body, resulting in disorders such as colitis, colorectal cancer, and intestinal ailments [157].

5. Detection Strategies for Antibiotics from the Aquatic Environment

There are various techniques for detecting antibiotics, including chromatography, electrophoresis, and enzyme-linked immunosorbent assay. Advanced technologies have also emerged, such as sensors for detecting antibiotics [158]. Chromatography coupled with mass spectrometry has enabled the detection of certain pharmaceuticals in the environment at lower concentrations [159]. For achieving better detection, more effective extraction methods are also necessary. There are various chromatographic techniques, such as High-Performance Liquid Chromatography with Ultraviolet or Diode Array Detection [160], which enable comprehensive detection and profiling of antibiotics using advanced analytical techniques, including LC-MS, tandem LC-MS/MS, and GC-MS [161]. Table 6 below gives a summary of various studies analyzing different antibiotics from various water matrices. The most employed method of sample extraction was Solid Phase Extraction. The common analytical methods employed were LC-MS/MS, UHPLC-ESI-MS/MS, and HPLC-MS for the identification and quantification of antibiotics. The following antibiotics were examined: trimethoprim, sulfamethoxazole, amoxicillin, azithromycin, ciprofloxacin, clarithromycin, doxycycline, levofloxacin, penicillin, roxithromycin, and many more. The sensitivity of the techniques employed was demonstrated by the differences in the limit of detection (LOD) and limit of quantification (LOQ) between investigations, which ranged from as low as 0.005 ng/L to as high as 3000000 ng/l. Antibiotic recovery rates from the samples also varied, with some investigations reporting recoveries of up to 129%.

Table 6. Examples of chromatographic methods used for detecting antibiotics in various aquatic matrices.

Matrix	Antibiotics studied	Extraction method	Analytical method	LOD: LOQ (ng/L)	Recoveries (%)	Ref.
Wastewater (Sewage treatment plant)	Amoxicillin	Solid Phase Extraction	LC-MS/MS (Column size 150 mm × 2.0 mm) Particle size: 4 µm	2.8,9.	77	[162]
	Azithromycin			0.2, 0.8	78	
	Ciprofloxacin			13.5, 45.0	91	
	Clarithromycin			2.2, 7.3	69	
	Doxycycline			8.8,29.2	11	
	Levofloxacin			0.5, 1.6	89	
	Penicillin			1.1, 3.8	68	
	Roxithromycin			5.1,17.1	51	
	Sulfamethoxazole			5.1, 17.1	63	
	Trimethoprim			3.1,10.2	94	
Wastewater	Ofloxacin	Solid Phase Extraction	LC-MS Column size (125 mm×2.0 mm) Particle size 5 µm	29.3	142	[163]
	Sulfamethoxazole			16.1	33.7	
	Erythromycin			12.4	67.7	
	Carbamazepine			2.2	84	
Seawater samples	Cefotaxime	Solid Phase Extraction	UHPLC-ESI-MS-MS Column size column (4.6 mm×150 mm, 2.7 µm) Particle size: 5 µm	0.02 -2, 0.06 -2.3	66 -113	[164]
	Erythromycin					
	Sulfamethoxazole					
	Lincomycin					
	Clindamycin					
	Tetracycline					
Surface wastewater	Oxalic acid	Solid Phase Extraction	(LC-MS/MS) Column size (250x4mm) Particle size: 2.6 µm	0.02 -0.59 0.07 -1.80	97.4 96.8	[165]
	Sulphapyridine					
WWTPs	Ampicillin	Solid Phase Extraction	LC-MS (100 mm × 2.1 mm) Particle size: 1.9 µm	0.1 -167.2 0.03 -50.6	70–120	[166]
	Sulfamethoxazole					

Matrix	Antibiotics studied	Extraction method	Analytical method	LOD: LOQ (ng/L)	Recoveries (%)	Ref.
WWTPs	Clarithromycin Azithromycin Levofloxacin	Oasis HLB - Solid Phase Extraction)	LC/MS/MS C18 (Agilent, (2.1 x 150 mm) Particle size 5µm	0.37 - 8.8 1.2 - 29	46-103	[167]
HWW	Clarithromycin Cilastatin Trimethoprim Ciprofloxacin Sulphapyridine Sulfamethoxazole	Solid Phase Extraction	HPLC -MS Column size:(150mm × 2 mm) Particle size: 4 µm	550-3000000 35000-43000	61-10.0	[87]
Surface water samples	Chloramphenicol Thiamphenicol Florfenicol Sulfadiazine Sulphapyridine Sulfamethoxazole Sulfathiazole Sulfamerazine Sulfamethazine Norfloxacin Ciprofloxacin Enrofloxacin Ofloxacin Tetracycline Oxytetracycline Chlortetracycline Erythromycin Roxithromycin	Solid Phase Extraction	UPLC-MS/MS Column size (100 mm x 2.1 mm Particle size:1.8 µm	0.01-1.18 0.03-1.68	62-129	[168]
Raw and treated wastewater	Ciprofloxacin Ceftazidime Meropenem Amoxicillin Lincomycin Clindamycin Erythromycin Azithromycin Clarithromycin Tylosin Trimethoprim Tetracycline Minocycline Chlortetracycline Oxytetracycline	Solid Phase Extraction	UHPLC-MS/MS C18 (3.0 mm 100mm) Particle size: 2.7 µm	(5 -15)	84.5–105.6	[169]
Wastewater (Industrial discharge & slaughterhouse use)	Sulfadimidine Sulphapyridine Sulfadiazine Sulfamethoxazole Ofloxacin Doxycycline	Solid Phase Extraction	HPLC-ES-MS/MS C18 column (150 mm x 2.1 mm) Particle size:3.5 µm	0.02-0.08 0.05-0.2	61-89	[170]
Wastewater s	Clarithromycin Trimethoprim	Solid Phase Extraction	LC-MS/MS Column size:(50 mm × 2.1 mm) Particle size:5µm	0.76-3.6	88-91	[171]
Raw hospital wastewater	Trimethoprim Spectinomycin Ampicillin Oxacillin Sulfamethoxazole Sulfamethazine sulfadiazine Sulphonamides Penicillin Erythromycin Tetracycline	Solid Phase Extraction	LC-MS/MS Column size:(50 mm × 2.1 mm)Particle size:1.8µm	0.005-0.04 0.017-0.220	68-111	[56]
Wastewater samples (from public hospitals)	Ampicillin Sulfamethoxazole	Solid Phase Extraction	(LC-MS/MS) CS12A (4x250 mm) Particle size: 2.6 µm)	20-590 70-1800	72.1-97.4	[172]

Other modern methods also exist for detecting antibiotics. ELISA is a well-known method for screening antibiotics. The sensitivity of this test depends on the reaction's strength. Different enzymes, including D-glucose oxidoreductase, peroxidase, pyruvate dehydrogenase, alkaline phosphomonoesterase, and β -galactosidase, are employed. The color reaction occurs when the enzyme catalyzes the substrate, and based on the reaction, an observation is made. Various ELISA methods have been developed for the detection of antibiotic residues, including fluoroquinolones, chloramphenicol, tetracyclines, and sulfonamides [173]. An ELISA method has also been developed for detecting penicillin in milk samples [174]. Another sensitive ELISA method has been devised to detect 1-amino-hydantoin in fish, shrimp, pork, and chicken samples. For the detection of banned antibacterial drugs, such as bacitracin and virginiamycin, in feed, ELISA has also been utilized [175].

Immunoassays have been utilized for screening various antibiotics in food samples, which depicts a concerning area in the antibiotic contamination research. Antibiotics such as β -lactamase inhibitors, Fluoroquinolones, Aminoglycosides, tetracyclines, sulfonamides, chloramphenicol, lincosamides, and macrolides have been detected in various food matrices, including milk, beef, chicken, pig muscles, fish, eggs, honey, and different animal feeds, using the ELISA technique. There are other reports and studies utilizing different techniques, such as radio-labeled antibody assays and gold nanoparticle-based lateral flow assays, as well as other BIOCHIP/APTA biosensor methods, for detecting antibiotics in various food matrices, including milk, wastewater, honey, eggs, swine, fish, and sea cucumber. Immunoassays are utilized for the detection of antibiotics, as they offer advantages such as high sensitivity, low cost, reduced labor intensity, ease of use, on-site screening, and improved throughput [173].

A chemiluminescent immunoassay is a type of assay in which a reaction occurs between the luminescent enzyme and substrate, or between the antigen and antibody, based on a chemiluminescent reaction. This method has been widely utilized for antibiotic detection. Different labeling enzymes, such as ALP (alkaline phosphatase) and HRP (horseradish peroxidase), are used as substrates in studies involving TMB (tetramethylbenzidine)/Luminol, among others. This technique has been widely used for the determination of macrolides in plasma and phosphate-buffered saline [176]. Additionally, the use of a multi-analyte chip immunoassay for the simultaneous screening of four different antibiotics has been reported [177]. Moreover, radioimmunoassay is a type of assay that uses isotope-labeled and unlabeled antigens that react competitively with antibodies developed in a modified RIA method for the screening of TCs in serum, urine, milk, and tissue, and also in environmental samples [178].

Furthermore, fluorescence immunoassay/ fluorescence polarization immunoassay is a method that utilizes a fluorophore linked to a specific antigen to detect and identify antibiotics using a fluorescent method. This method has been used to detect sulphonamides, tetracycline β -lactamase, quinolones, Chloramphenicol, Streptomycin, Erythromycin, Spiramycin, Tilmicosin, Tylosin, Clenbuterol, and Ofloxacin [179]. A one-step method for determining fluoroquinolones based on the production of monoclonal antibodies has also been developed for detecting cefalexin, cefadroxil, clinafloxacin, and gentamicin [180]. Additionally, colloidal gold immuno-chromatographic assay (CGIA) has been employed for detecting tetracycline, sulfonamides, and quinolone residues in milk samples. Another CGIA method for detecting streptomycin residue in milk and swine urine was reported [181].

A study has also reported the development of a kit based on a lateral flow antibody-based assay for the simultaneous detection of fluoroquinolones, β -lactam antibiotics,

sulfonamide derivatives, and tetracyclines in fish samples, utilizing antigen and antibody interactions [182].

There have been major developments in the past few years in the detection of antibiotics and their residues. Techniques such as chip technology, immunosensors, and surface plasmon resonance-based immune technology have been explored for detecting antibiotic residues. Biochip assay is another emerging technique based on receptors. The biochip method has been reported for detecting residues of aminoglycosides, macrolides, and lincosamides in honey samples across various concentration ranges [183].

6. Remediation Strategies for Antibiotic Waste

Proper waste management practices are essential to prevent harm to human health and the environment. Various approaches, such as prevention, minimizing production, reusing, recycling, energy recovery, and proper disposal, can be employed to manage pharmaceutical waste effectively [184]. There are well-established methodologies used in various research studies for removing antibiotics from different matrices, including hospital wastewater, domestic wastewater, water reclamation facilities, synthetic wastewater, laboratory wastewater, and aquaculture wastewater [12]. Conventional strategies for antibiotic removal encompass physical, chemical, and biological methods, including settling/precipitation, flocculation, membrane separation, sorption and biosorption onto activated carbon, the activated sludge process, and chemical disinfection. The chemical-physical removal methods include the removal of antibiotics by substrates like zeolite, shucks, and volcanic rock, followed by other adsorption methods. It also includes the utility of nanoparticles coated with different polymers, such as liposomes or dendrimers, for removing antibiotics [185].

Another technique is adsorption, which can remove antibiotics from environments such as soil, sediments, and naturally occurring minerals [186]. ZnCl₂-modified biochar, activated carbon, multi-walled nanotubes, and graphene oxides have been utilized in various studies for the efficient adsorption of antibiotics [187]. Likewise, hydrolysis is another technique that can be used for the degradation of organic substances, such as amides and esters. Furthermore, UV-visible irradiation from sunlight also plays a crucial role in degrading certain antibiotics in aquatic water bodies. Another method involves the Adsorption method using Activated Carbon, which has been reported to be effective for removing most antibiotics [188]. Studies have utilized fine-grain activated carbon and large-particle activated carbon for the removal of antibiotics from hospital wastewater and other wastewater sources. Other studies have utilized emerging methods like the use of zeolites [189]. Methods such as electrochemical oxidation, ozonation, and the Fenton process employ the same principle of producing free radicals for removing antibiotic residues, but through different processes [190].

Other removal methods involve membrane-based separation techniques and advanced oxidative treatments, such as ozone oxidation, ultraviolet degradation, photocatalytic oxidation, and Fenton chemistry[191]. Microbubble (MB) based multiple approaches have been developed for the elimination of diverse ecological pollutants. These microbubbles, due to their properties such as surface area and durability, were employed in ozone oxidation to eliminate pollutants [192]. Additionally, methods like UV/H₂O₂ are conventional and utilize UV to produce hydroxyl radicals via H₂O₂, which can scavenge antibiotics. Additionally, technique like membrane technology is based on reverse osmosis, which is promising as they are capable of removing a broad range of pharmaceutical compounds. Moreover, a combination of membranes with oxidation processes has the capability for efficient removal [193].

Furthermore, remediation strategies have been reported in various studies, like oxidative remediation (chlorination, advanced oxidation, ozonation, fentanyl process, photolysis, photocatalysis, electrochemical processes), adsorption, membrane filters, bioremediation (using bacterial methods, fungal methods, algal methods, phytoremediation, microbial fuel cells, bioreactors, and enzyme filters), and hybrid methods [194].

Furthermore, filtration methods such as Ultrafiltration (UF), Nanofiltration (NF), and Reverse Osmosis (RO) have also been reported for the removal of antibiotics [50]. Moreover, another suitable method is the utilization of biowaste, such as sawdust, green nano-adsorbents, biochar, and microbial fuel cells, which have also been employed for the effective removal of antibiotics from waste [195].

Other emerging studies discuss the potential of nanotechnology. Nano-photocatalytic degradation studies of antibiotics using different nano-photocatalysts have shown potential for the degradation of various antibiotics [196]. Different antibiotics have been remediated using nano-photocatalytic activities from aquatic ecosystems, such as Penicillin G, Tetracyclines, Ofloxacin, Amoxicillin, and Ciprofloxacin [196].

Another emerging area of research is biodegradation, which utilizes microbial degradation to remove antibiotics [197]. Biodegradation of antibiotics occurs due to two factors: biotic and abiotic factors. The biotic factors include the microorganisms, and the abiotic factors contribute to the hydrolysis, sorption, oxidation, photolysis, and reduction. [198]. Moreover, bioremediation can be performed either ex-situ or in-situ. The in-situ bioremediation method leads to the removal of contamination on the spot, whereas the ex-situ method involves removing the contaminants elsewhere [199]. Recently, algae have been widely used for bioremediation of antibiotics due to their cost-effectiveness, non-intrusiveness, safety, and effectiveness in removing antibiotics. Moreover, biochar is another useful adsorbent derived from the pyrolysis of biomass rich in carbon, which is used for the removal of antibiotics [200].

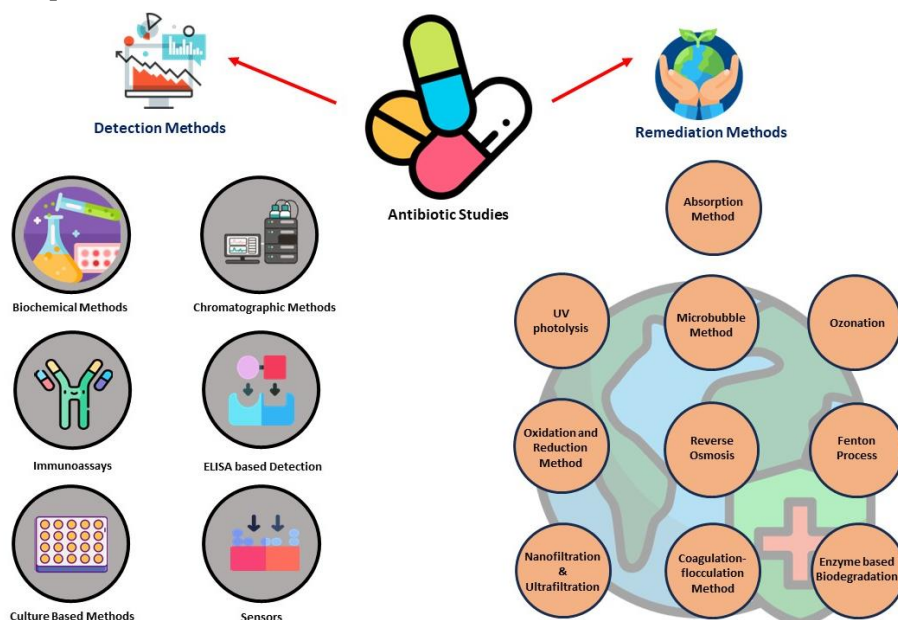


Figure 4. Different detection and remediation methods are used in antibiotic studies.

Interestingly, enzyme-based biodegradation is an environmentally friendly approach, as it offers economical and exceptionally effective strategies for removing environmental pollutants. Enzymes such as lignin-degrading peroxidases, phenoloxidases, horseradish peroxidase, manganese-activated peroxidases, and polyphenol oxidases have been developed

to achieve this [201]. A study has engineered an innovative hybrid bioreactor by integrating immobilized laccases with tyrosinase enzyme aggregates on a microfiltration membrane for the removal of pharmaceutical compounds [202]. Figure 4 below summarizes some of the common detection and remediation techniques used in antibiotic studies.

7. Discussion

Antibiotics are typically present in surface water at extremely small concentrations, typically in the nanograms per liter level or even lower. Since routine monitoring would not be practical or affordable, identifying such minute quantities requires extremely sensitive analytical methods and equipment. The detection and evaluation of antibiotics may also be hampered by the presence of several organic and inorganic components in surface water samples [203]. Surface water contains a wide range of antibiotic classes that originate from various sources, including human and animal waste, agricultural runoff, and pharmaceutical production. It can be challenging to assess the toxicity of an antibiotic and comprehend the effects of multiple antibiotics when used in combination [204].

Studies should be conducted to explore antibiotic pollution and its correlation in the aquatic environment, taking into account other environmental factors. Monitoring of point and non-point sources of antibiotic contamination is necessary to raise awareness about antibiotic pollution in aquatic water bodies. It is essential to develop a strategic plan for conducting monitoring studies at relevant locations, followed by the enhancement of the performance of existing wastewater treatment plants. More studies need to focus on the ecotoxicological research of antibiotics in the environment.

Moreover, surface water samples are complex matrices that contain various ions, dissolved organic matter, and suspended particles. These matrix components may influence the extraction, separation, and detection of antibiotics, potentially impairing the analysis's sensitivity and accuracy. Beta-lactams, fluoroquinolones, macrolides, and sulfonamides are a few examples of the numerous types of antibiotics that exist, each with distinct chemical properties. To build a comprehensive strategy for monitoring all antibiotics, it may be necessary for each class to have its unique analytical procedures for detection [205].

Antibiotics in surface water can undergo various transformation processes, such as photodegradation, hydrolysis, and microbial degradation. When compared to the parent molecules, these activities may result in the formation of metabolites or degradation products, each of which may have unique chemical properties and detection challenges [206]. Assessing the ecological relevance of antibiotic toxicity studies is crucial to understanding the potential impacts on ecosystems. However, replicating real-world scenarios in laboratory experiments is difficult, and extrapolating results from controlled environments to complex aquatic ecosystems can be challenging [206]. Current regulatory frameworks often focus on human health risks associated with antibiotics rather than their ecological impacts. Limited regulatory guidelines and monitoring programs specifically targeting antibiotics in surface water can hinder comprehensive toxicity assessments and appropriate management strategies [207]. To address antimicrobial resistance (AMR), several regulatory frameworks and initiatives have been established at the regional and global levels. The European Union's Water Framework Directive requires the monitoring and regulation of pollutants, including pharmaceuticals, to ensure the protection of water quality. Similarly, the Drinking Water Directive provides stringent standards for microbiological and chemical parameters in drinking water. Moreover, WHO's Global Action Plan on AMR outlines a strategic approach to combat AMR through a

One Health framework, addressing human, animal, and environmental health. These frameworks underscore the importance of coordinated efforts and stringent policies in mitigating the spread of AMR [208].

One reason for antibiotic pollution may be related to national income. Low-income countries often have limited access to wastewater treatment plants, resulting in a higher concentration of antibiotics in the environment [156].

Insufficient removal of emerging molecules in treatment facilities also results in the passage of polluted water into surface water systems (Lakes, Ponds, Rivers, and inland water), which could pose serious ecological and health risks to the ecosystem. The public's acceptance of the wastewater reuse guiding policies needs to be increased. For example, amoxicillin levels varied significantly, ranging from below detection limits to 0.1726 µg/L during treatment, and then decreased to below detection limits to 0.0625 µg/L after treatment, considering the development of compounds, such as antibiotics, in the water sources [47].

Furthermore, one of the major challenges is to calculate the amount of exposure per amount of antibiotics present in water used for drinking, and determining the potential risks to human health has been hindered by the dearth of data concerning the large variety of human and veterinary drugs now in use. Monitoring projects are resource-intensive with costs, people requirements, and infrastructure. In addition to the problem, there are no standardized sampling and analytical methodologies to support monitoring research. Therefore, to comprehend the impact of low levels of pharmaceuticals in drinking water on human health, future research should focus on developing practical methods for prioritizing pharmaceuticals within an overall risk assessment [209]. Research on the occurrence of antibiotics in various regions can contribute to understanding the global status of antibiotic pollution. The biotransformation and bioaccumulation mechanisms of these antibiotics in aquatic species and higher-order organisms require in-depth exploration.

Comprehensive toxicity data for many antibiotics, especially in environmental contexts, are limited. Toxicity studies have primarily focused on acute effects and a few commonly used antibiotics, while long-term and chronic effects, as well as the potential ecological impacts of exposure, are not well understood for many antibiotics. There is no standardized protocol or test specifically designed for assessing the toxicity of antibiotics in surface water [210]. Existing toxicity testing methods, such as acute and chronic toxicity tests with aquatic organisms, do not fully capture the complexities and long-term effects related to environmental exposure to antibiotics.

Molecular-level studies should be encouraged to identify pathways and biomarkers involved during antibiotic exposure from the environment, the toxic impact of antibiotics, the metabolic pathways involved, and the epigenetic alterations that occur during contamination [211]. The co-existence of antibiotics with other toxicants also needs to be evaluated to assess toxic impacts [212]. Moreover, antibiotics can function in various ways, including preventing the development of bacterial cell walls, delaying protein synthesis, and interfering with DNA replication. Hence, identifying the precise processes by which antibiotics cause harm to non-target organisms and ecosystems is a challenging endeavor that requires in-depth study and analysis [213].

Antibiotic toxicity may be influenced by several environmental factors, including pH, temperature, exposure to sunlight, and the presence of other compounds or contaminants in the water. These factors can affect the stability, bioavailability, and toxicity of antibiotics, making

it challenging to isolate and evaluate their individual effects [213]. Hence, research in this area also needs to be explored.

LC with MS is currently the most capable method for antibiotic identification, which opens further research areas to improve antibiotic detection. Various mass spectrometers are used for the analysis of antibiotic residues, such as single-quadrupole (Q), linear ion trap (LIT), time-of-flight (TOF), and quadrupole ion trap (QIT) [214]. Similarly, UV/visible spectroscopy has been widely used for antibiotic analysis, Cefazolin, Ceftazidime, Meropenem, Ceftriaxone, Dicloxacillin, Ertapenem, Cephalothin, Benzylpenicillin, Flucloxacillin, Piperacillin, Ampicillin, and Ticarcillin [215]. Hence, method development using chromatographic techniques can provide better detection limits for the detection of antibiotics in our environment.

Additionally, several studies have reported that the most popular method for detecting antibiotic residues is liquid chromatography combined with tandem mass spectrometry. Other studies have reported the use of UPLC-MS/MS for detecting daptomycin content in human plasma and breast milk [216]. Moreover, gold nanoparticles (AuNPs) possess useful optical properties and a high extinction coefficient, making them suitable for the identification of different ions and small molecules [217]. The quantity of cefixime has been measured by several researchers using an AuNP solution via SPR. Other applications of gold nanoparticles include the determination of kanamycin, which holds a promising future [218].

Moreover, a study has proposed a bifunctional, chemically customized polymer-based sensor for the rapid colorimetric and fluorescence identification of norfloxacin in water samples [219]. Additionally, scientists have developed a cellulose-supported microchip for tagging functional nucleic acids, combined with a rival fluorescent lateral-flow assay for identifying ampicillin [220]. A study has also proposed a chemiluminescence method, employing a fluorometric assay with ruthenium chloride (IV) and methoxylated Cypridina luciferin analogs (MCLA) to determine fluoroquinolone compounds in milk [221]. Another investigation introduced nanocomposites (IL/Chit@MGO) derived from biofunctionalized ionic liquids, chitosan, graphene oxide, and magnetic nanoparticles, which were applied in chemiluminescent aptamer-based sensors for tetracycline detection [222].

Moreover, ELISA is an inexpensive and rapid monitoring tool capable of detecting antibiotics and their by-products in water samples, and their use should be encouraged. Additionally, these tests require a small sample volume and are portable in the field. Other emerging techniques for detecting antibiotics include pulsed electrochemical detection (PED), charged aerosol detector (CAD) [223], and evaporative light scattering detector (ELSD) [224]. These are promising techniques that require further exploration. Future studies for antibiotic analysis should focus on the areas of green solvents and green extraction techniques. More research should also focus on photolysis, which is used for the removal of antibiotics. In many scenarios, the toxicity of photoproducts has not been explored, providing a research perspective.

Research should focus on the development of methods with high throughput, high sensitivity, and improved sample pretreatment for the rapid processing and detection of antibiotics in environmental matrices. Additionally, research is needed to investigate the integration of various detection methodologies to enhance the detectability of antibiotics in environmental samples [225]. Lastly, low and middle-income countries lack skilled medical workers and focus less on monitoring antibiotic usage, leading to their occurrence in food products and the environment [226].

8. Conclusion

The scope of antibiotic contamination is not new, but modern integrative sciences are required to bring novelty to tackle this problem. The review discussed the issue of antibiotic contamination in aquatic water bodies, on which most life depends. This review encompasses various sources that contribute to the contamination of aquatic water bodies. Furthermore, it provides recent examples of the global burden of antibiotic contamination, as well as the important model organisms used for assessing its toxicity. It discusses both traditional and modern remediation strategies. Antibiotics have been used widely in our society for years since their discovery. Regulations need to be implemented to address the overuse of antibiotics, safeguarding the environment and the health of humans and animals from antibiotic pollution in aquatic water bodies and their misuse. International Organizations need to encourage countries to reduce their antibiotic usage in humans and animals to a minimum. Additionally, emphasis needs to be placed on surveillance and research of antibiotics to strengthen the healthcare and regulatory sectors. Awareness of the public sector in this aspect needs to be explored as well. Studies should be encouraged on the monitoring of antibiotics and their byproducts in the environment to evaluate their health effects. Global guidelines need to be developed for the rational use of antibiotics. Adequate training and strict infection-control parameters need to be established to minimize and control antibiotic pollution. Specific legislation and guidelines need to be established and implemented to tackle antibiotic prescriptions at hospitals, as well as the proper disposal and collection of unused or expired drugs, which also require regulation.

Traditional extraction methods employ harmful solvents that are not environmentally friendly, raising concerns about indirect environmental pollution. Future studies on antibiotic analysis should also focus on areas of green extraction methods using environmentally friendly solvents to prevent indirect environmental contamination. Innovative studies, such as systematic surveillance for environmental monitoring at the regional level, should be encouraged to foster a comparative research environment for understanding the environmental contamination of antibiotics.

Author Contributions

Conceptualization, E.K. and P.S.; methodology, P.S.; software, E.K.; validation, R.A., and K.C.; formal analysis, E.K.; investigation, P.S.; and E.K.; resources, R.A.; data curation, E.K.; writing—original draft preparation, E.K.; and P.S.; writing—review and editing, K.C.; visualization, P.S.; supervision, R.A.; project administration, R.A.; funding acquisition, R.A. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

The authors declare no conflict of interest.

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