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A review of the effects of pharmaceutical pollutants on humans and aquatic ecosystem

Jaya Vinny Eapen[1†], Sweety Thomas[2†], Shelmi Antony[3], Paul George[1], Jayesh Antony[4*]

[1]Department of Biotechnology, Mar Athanasius College, Kothamangalam 686666, Kerala, India
[2]Department of Biotechnology, Mar Thoma college, Thiruvalla 689111, Kerala, India
[3]Department of Zoology, Assumption College Autonomous, Changanassery 686101, Kerala, India
[4]Department of Zoology, St. Thomas College Autonomous Palai, Palai 686574, Kerala, India

[†]These authors contributed equally to this work.
***Correspondence:** Jayesh Antony, Department of Zoology, St. Thomas College Autonomous Palai, Arunapuram PO, Palai 686574, Kerala, India. jayesha.zoo@stcp.ac.in
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Abstract

The presence of high-quality water is essential not only for human survival but also for the well-being of plants and animals. This research aimed to examine studies investigating the occurrence of antibiotics, endocrine disruptors, and other pharmaceutical products in water, sediments, and organisms within aquatic ecosystems. These substances have been linked to numerous adverse health effects on both humans and aquatic life, including reproductive issues and neurotoxic effects. The pervasive utilization of antibiotics in medical and agricultural domains has precipitated their ascension as formidable environmental contaminants. Effluents discharged from pharmaceutical industries constitute significant contributors to aquatic ecosystems' contamination with antibiotics. These pharmacological agents permeate diverse environmental niches, spanning groundwater, surface water, soils, and wastewater treatment facilities, exhibiting concentrations ranging from nanograms to grams per liter. Concurrently, the indiscriminate and excessive application of antibiotics worldwide has engendered escalating apprehensions pertaining to antimicrobial resistance—a formidable global health exigency. This review also delves into the impact of pharmaceutical pollutants on aquatic environments, particularly as endocrine-disrupting compounds. Analysis of surface water in River Taff and River Ely reveals a consistent discharge of approximately 6 kilograms of pharmaceuticals per day. The study examines particular pharmaceuticals, such as diethylstilbestrol (DES), chlorotriazines, chloroquine, and antineoplastic drugs, elucidating their varied effects on reproductive cycles. Pharmaceutical pollutants in aquatic ecosystems, originating from sources like wastewater, agriculture, and improper disposal, persist and adversely affect organisms through bioaccumulation and biomagnification. These contaminants pose significant ecological and health risks, necessitating effective mitigation strategies.

Keywords

Pharmaceutical contaminants, antibiotic resistance, endocrine disruption, neurotoxic drugs, transient neurologic symptoms, anesthetics

Introduction

Pharmaceutical and Personal Care Products (PPCPs) are integral to the quotidian fabric of human existence. They represent a diverse spectrum of consumption patterns, encompassing a wide array of substances. These substances span the spectrum from medicinal compounds, such as antimicrobials, anti-inflammatories, and lipid-regulating agents, utilized by both human and veterinary medicine, to personal hygiene items including fragrances, disinfectants, and adjunctive agents [1]. PPCPs play a pivotal role in enhancing the quality of life. Following metabolism, the resultant metabolites and conjugates of pharmaceuticals predominantly undergo excretion via urine and feces. Subsequently, they are channeled into civil sewage treatment systems, where they may become integrated into sewage sludge or gradually dispersed into surface water bodies over time [2]. Humans and other organisms are unintentionally exposed to trace residues of these PPCPs from the environment by ingesting drinking water and consuming plant or animal tissue that has been similarly exposed. These exposures may be sustained indefinitely throughout life, resulting in the accumulation of these metabolites in body tissues many orders of magnitude below those recommended for therapy [3].

Antibiotic pollution stands out as a critical issue among the many PPCPs due to its significant contribution to the horizontal transfer of antibiotic resistance genes (ARGs) between both harmful and harmless bacterial strains. This process is particularly concerning because people can unknowingly ingest these resistance genes through various channels, including recreational activities in environments contaminated by such pollutants [4]. Sources of antibiotic contamination encompass effluents from wastewater treatment plants (WWTPs), effluents discharged by hospitals and pharmaceutical processing plants, and leaks emanating from waste storage containers [5]. The elevated levels of antibiotics found in marine environments, especially during colder seasons, pose considerable threats to both ecosystems and human well-being. Specific antibiotics like ciprofloxacin (CIP), ofloxacin (OFL), erythromycin (ERY), and sulfadiazine have been identified as particularly hazardous to aquatic life. This pollution originates from various sources such as untreated human and animal wastewater and direct discharge from aquaculture products, underscoring the pressing need for comprehensive strategies to address environmental contamination [6]. The presence of antibiotics in the environment at low concentrations can infiltrate human systems, accumulating therein and giving rise to a spectrum of health repercussions spanning from reproductive disorders to muscular debility [7, 8].

A myriad of drugs, spanning from recreational substances to pharmaceutical medications, although intended to alleviate ailments, harbor the potential to induce a spectrum of detrimental effects on the nervous system. Thus, a comprehensive understanding of the neurotoxic propensities inherent within drugs is imperative for facets such as drug development, clinical management, and public health initiatives. In the forthcoming review, our objective is to delineate the intricate challenges posed by pharmaceutical pollution, encompassing issues such as antibiotic resistance, endocrine disruption, and the neural ramifications thereof.

Antibiotic resistance

The etymology of the term “antibiotic” traces its roots to its literal interpretation as “against life”. Antibiotics represent a category of compounds, whether they occur naturally, are semi-synthetic, or are synthesized chemically, characterized by their antimicrobial attributes. Ubiquitously employed in the prevention and management of infectious diseases across animal and human populations, antibiotics serve as indispensable tools in the battle against microbial infections [9]. The period between 1945 and 1955 witnessed a pivotal epoch in the annals of medicine with the advent of antibiotics. Penicillin, hailing from a

fungal source, alongside other antibiotics such as streptomycin, chloramphenicol, and tetracycline, synthesized by soil bacteria, spearheaded the dawn of the antibiotic era. These compounds, crafted by microbial entities, operate as diminutive molecules that inhibit the proliferation of fellow microorganisms [10]. The advent of antibiotics has heralded a monumental revolution in the realm of medicine, heralding the salvation of innumerable lives and etching a momentous milestone in human chronicles. A list of commonly used antibiotics is represented in Table 1. Regrettably, the extensive integration of these extraordinary medications has precipitated the rapid ascent of resistant strains. Within the medical fraternity, experts voice apprehensions regarding the looming specter of regressing to the pre-antibiotic epoch. A recent repository has unearthed an excess of 20,000 potential resistance genes (R genes), spanning nearly 400 discrete categories, predominantly extrapolated from extant bacterial genome sequences [11]. The pervasive specter of antibiotic contamination within environmental domains, encompassing aquatic ecosystems and public health spheres, in tandem with the burgeoning menace of antibiotic resistance among human populations, evokes profound alarm. Investigations emanating from Croatia [12], South India [13], and across Europe [14] underscore the disconcerting prevalence of antibiotics within wastewater effluents originating from pharmaceutical manufacturing facilities. This phenomenon engenders fluctuations across seasons, incurs ecological hazards, and fosters the proliferation of antibiotic-resistant bacteria (ARB) strains. The exigencies engendered by deficient wastewater management underscore the imperative for bolstered environmental stewardship. A holistic global outlook elucidates the ubiquity, trajectories, and repercussions of antibiotics, delineating their omnipresence within water reservoirs and the attendant hazards posed to both human health and ecological equilibrium [15]. The interplay among antibiotic utilization, environmental dynamics, and the onset of antibiotic resistance underscores the imperative for heightened research endeavors, strategic regulatory interventions, and sustained evaluations of chronic toxicity to confront this burgeoning health crisis.

Development of gene resistance

The 2014 Review on Antimicrobial Resistance (AMR) highlights that antibiotic resistance is accountable for a significant portion of yearly deaths. Acknowledging the anticipated surge in antibiotic resistance, the World Health Organization (WHO) designated it as a major global health concern in 2014, emphasizing its profound repercussions for public health. Confronting the emergence and dissemination of mobile resistance elements poses a formidable challenge due to the incomplete understanding of how the environment facilitates the development of resistance and the specific conditions under which this occurs. The limited comprehension in this domain hampers efforts to effectively manage and mitigate the evolution and spread of resistance elements [26]. The discovery of antibiotics, notably penicillin, was a major medical breakthrough in the early 20th century. However, bacterial resistance has emerged due to genetic variation caused by mutations in DNA coding regions. Antibiotic use in humans and agriculture has increased the frequency of ARGs through natural selection and horizontal gene transfer (HGT). Hospitals' antibiotic rotation strategies, aimed at mitigating resistance, inadvertently select for resistance to other antibiotics. Genetic variation in bacterial colonies in the human colon contributes to an "insurance effect" against environmental changes. Conjugation, a common form of HGT, occurs in the colon, potentially transferring ARGs between species [27].

The duration of a therapeutic antibiotic regimen varies depending on the particular infection in the host, spanning from a concise 7-day course to an extended duration lasting up to a year. The efficacy of the treatment regimen is intricately linked to the robustness of the immune system. Immunocompetent individuals have the capacity to generate diverse toxins and acquire resistance genes during the course of treatment. This phenomenon arises due to the fact that antibiotics, while adept at eradicating opportunistic pathogens, may encounter formidable obstacles when confronting resilient pathogens such as *Staphylococcus aureus* [28]. Microbial genomics has unveiled widespread ARGs in bacterial genomes, forming the "antibiotic resistome". These genes are found in diverse ecological niches, suggesting coevolution with antibiotics. Metagenomic analysis of ancient DNA indicates that antibiotic resistance predates therapeutic antibiotic use [29].

Table 1. List of commonly used antibiotics

Class	Antibiotics	Main use	Ref.
Tetracyclines	Chlortetracycline	Veterinary	[16, 17]
	Doxycycline	Human, veterinary	
	Oxytetracycline	Human, veterinary, plants	
	Tetracycline	Human, veterinary	
Sulfonamides	Sulfadiazine	Veterinary	[16]
	Sulfamethazine	Human, veterinary	
	Sulfamethizole	Human	
	Sulfamethoxazole	Human	
	Sulfathiazole	Veterinary	
Macrolides	Azithromycin	Human	[18]
	Erythromycin	Human, veterinary	
	Roxithromycin	Human	
Fluoroquinolones	Ciprofloxacin	Human	[19]
	Enrofloxacin	Veterinary	
	Ofloxacin	Human	
β-Lactams	Amoxicillin	Veterinary	[20]
	Ampicillin	Veterinary	
	Cephalexin	Human	
	Cefazolin	Human	
	Penicillin	Veterinary	
Aminoglycosides	Amikacin	Human	[21–23]
	Gentamicin	Human, veterinary	
	Neomycin	Veterinary	
	Streptomycin	Human, veterinary	
	Tobramycin	Human, veterinary	
Glycopeptides	Vancomycin	Human	[24]
	Teicoplanin	Human	
	Dalbavancin	Human	
	Oritavancin	Human	
	Telavancin	Human	
	Ramoplanin	Human	
Oxazolidinones	Linezolid	Human	[25]
	Tedizolid	Human	
	Radezolid	Human	

Evolution of antibiotic resistance genes

Microorganisms utilize antibiotics as a means of self-defense, eliminating neighboring competitors and asserting dominance across varied environments. ARB and ARGs exist naturally, potentially originating tens of millions or even billions of years in the past. Evidence of ARGs linked to β-lactams, tetracyclines, and vancomycin has been unearthed in sediment cores dating back 30,000 years [30]. Over the course of evolution, most ARGs likely originated gradually from genes with different functions. Recent evolutionary events contributing to their prevalence in pathogens primarily result from transfer events from ancestral species where the overall functionality of these genes was shaped. The process leading to acquired resistance in pathogens typically involves several steps. Initially, an ARG gains the ability to move within the genome, often achieved through associations with insertion sequences or the formation of gene cassettes incorporated into integrons. Subsequently, the gene relocates to an element capable of autonomous movement between cells, such as a plasmid or integrative conjugative element. Certain environments may be more conducive to the genetic elements involved in the mobilization and transfer of ARGs, potentially due to the presence of fecal bacteria known to carry such elements or conditions favoring frequent gene exchanges [31].

The escalation of AMR presents a critical global health emergency, spurred by the widespread consumption of antibiotics surpassing 73 billion standard units as of 2010. ARGs, with origins predating human antibiotic usage, have now proliferated extensively, propelled by environmental exposure to antibiotics. Metagenomic investigations spanning ecosystems such as soil, wastewater, and the microbiota of human and animal guts unveil diverse resistomes, demonstrating clustering patterns based on ecological contexts. Non-pathogenic bacteria like *Kluyvera* sp. and environmental sources emerge as pivotal reservoirs for resistance genes, with clinically relevant variants frequently originating from these non-pathogenic sources. HGT mechanisms, notably conjugation and transformation, assume pivotal roles in disseminating resistance, exemplified by the rapid global dissemination of genes such as *blaCTX-M* extended-spectrum β-lactamases (ESBL). As environmental antibiotic levels surge, disrupting microbial equilibrium, a looming threat to public health becomes imminent. A profound comprehension of resistomes and the dynamics of gene transfer is indispensable for formulating efficacious strategies to combat antibiotic resistance [32]. The bacterial resistome, consisting of both inherent and acquired elements, governs resistance mechanisms. Inherent resistance arises from genetic mutations independent of prior antibiotic exposure, while acquired resistance is acquired through HGT, referred to as the bacterial mobilome. Transfer mechanisms include transduction, transformation, and conjugation.

The emergence of multidrug resistance (MDR) in waterborne strains of *Aeromonas* spp., facilitated by conjugation, poses significant public health concerns due to the potential for challenging infections. The resilient nature of these strains complicates efforts to eradicate them, underscoring the critical implications of HGT in *Aeromonas* spp. for public health [33].

Impact of AMR on human health

The rising threat of AMR jeopardizes global public health, causing 700,000 annual deaths from MDR bacterial infections. Projections suggest a staggering 10 million deaths by 2050, with associated costs reaching 3.8% of the GDP, pushing millions into extreme poverty. Implementing basic measures like handwashing and responsible antibiotic use could prevent three-quarters of these deaths at minimal cost. Addressing AMR is crucial to safeguard healthcare systems and global development goals [34]. Between October 2008 and June 2013, research was conducted focusing on infections resistant to multiple antibiotics in hospitalized cirrhotic patients. These infections were classified as MDR, extensively drug-resistant (XDR), or pandrug-resistant (PDR). Approved by the local ethical committee, the study examined infection characteristics, risk factors, and outcomes. It evaluated the efficacy of recommended antibiotics and categorized infections as hospital-acquired, healthcare-associated, or community-acquired, considering pathogens resistant to three or more antimicrobial classes (MDR, XDR, PDR). The results offer valuable insights into understanding bacterial resistance in advanced cirrhotic patients and its implications for treatment [35].

Excessive use of antibiotics in young children can harm their gut bacteria, which are important for breaking down complex carbohydrates, preventing harmful bacteria from taking over, and helping the immune system develop. When the good bacteria are reduced, usually because of antibiotics, it can mess up these important functions. This shows why it's crucial to keep a healthy and diverse mix of gut bacteria in babies [36].

The widespread and often indiscriminate use of antibiotics to treat urinary tract infections (UTIs) has led to a worrying surge in bacterial resistance, particularly among Enterobacteriaceae, which include common UTI-causing bacteria like *Escherichia coli* and *Klebsiella pneumoniae*. The growing prevalence of MDR Enterobacteriaceae limits the effectiveness of available treatments, highlighting the importance of exploring older options such as fosfomycin, which has demonstrated effectiveness against MDR bacteria. With the limited development of new antibiotics, it is imperative to reconsider and explore alternative treatment strategies to address the escalating antibiotic resistance in UTIs [37]. Research conducted at Muhimbili National Hospital in Tanzania during April–May 2018 investigated the bacterial origins and factors predicting mortality in bloodstream infections (BSI) among hospitalized patients. Through blood

culture and antimicrobial susceptibility testing, the study uncovered a growing prevalence of hospital-acquired BSI instigated by MDR pathogens, notably ESBL [38]. A retrospective case-control study conducted in the medical intensive care unit (MICU) at Winthrop University Hospital analyzed 313 patients, among whom 41.7% were found to be at significant risk of MDR organisms (MDRO). Factors linked with MDRO prevalence primarily involved infections occurring in the urinary tract and lungs [39]. The increasing danger of AMR, especially concerning decompensated cirrhosis, highlights the urgent necessity for innovative approaches. The global surge in resistant bacterial varieties, worsened by excessive antibiotic consumption, necessitates a multifaceted approach within hepatology. Essential aspects include new empirical antibiotic methods, cautious use of prophylaxis, investigation into non-antibiotic options, and the implementation of stewardship initiatives. Moreover, early adoption of de-escalation strategies through prompt diagnostics, stringent infection control measures, and the exploration of surveillance programs are vital measures to tackle the heightened vulnerability to resistant infections in advanced cirrhosis and alleviate related adverse health outcomes [40].

Effect of antibiotics on water bodies

On a global scale, the yearly usage of antibiotics exceeds 100,000 tons, prompting increasing concerns regarding the fate of these substances. Antibiotics are ubiquitous in the environment, with significant levels detected in freshwater reservoirs [41]. Antibiotics have been widely utilized and proven effective in human and veterinary medicine. Their beneficial impacts have been recognized across diverse fields including agriculture, aquaculture, beekeeping, and livestock farming, where they are utilized as growth promoters. Numerous antibiotics have been detected in various environmental sources worldwide, including water bodies, industrial waste, sewage, manure, soil, plants, and living organisms [42]. The existence of antibiotic contamination in aquatic environments has been noted to reduce the overall variety of microorganisms, including those essential for carbon processing and primary productivity [7].

Antibiotics present in wastewater undergo treatment in treatment facilities; however, complete removal of these compounds is not achievable using conventional systems [15]. Although WWTPs strive to reduce pollutant levels in both urban and rural wastewater, they are ineffective in significantly decreasing the concentrations of antibiotics and ARGs [43]. Antibiotics, particularly those used in human and veterinary medicine, as well as those employed in agricultural practices and discharged through wastewater, permeate the environment. These pseudo-permanent pollutants, namely antibiotics, provoke apprehension due to the emergence of ARB, thereby posing a significant hazard to human health [44]. Figure 1 shows how antibiotics as contaminants enter the ecosystem and finally affect human life negatively. Solid phase extraction (SPE) and rapid resolution liquid chromatography/tandem mass spectrometry (RRLC-MS/MS) are analytical techniques utilized to identify the presence of antibiotics in various samples, such as surface water, effluents, and sludge. Through the application of these methods, approximately 11 classifications of antibiotics have been identified [45].

High levels of antibiotic consumption in Europe, notably in Poland, not only exacerbate environmental concerns but also pose substantial risks to public health. The challenges encountered by wastewater treatment facilities and the resulting soil contamination highlight the pressing necessity for comprehensive measures to tackle antibiotic-related issues and ensure the protection of both the environment and human health [46]. Administering sub-therapeutic doses of antibiotics to farm animals and fish as a means of promoting growth presents environmental and health hazards. This practice introduces antibiotics that are not easily broken down into the environment through multiple pathways, such as the application of manure to land and airborne dispersion. Animal waste contributes to the presence of active antibiotic metabolites in the environment, leading to concerns regarding antibiotic residues in food, the proliferation of ARB, and contamination of aquatic ecosystems. Addressing these challenges requires responsible antibiotic management in agriculture to minimize adverse effects on both the environment and human health [47]. A study examining two pharmaceutical WWTPs (PWWTPs) tasked with managing fluoroquinolone production wastewater revealed impressive removal efficiencies exceeding 95%. However, residual

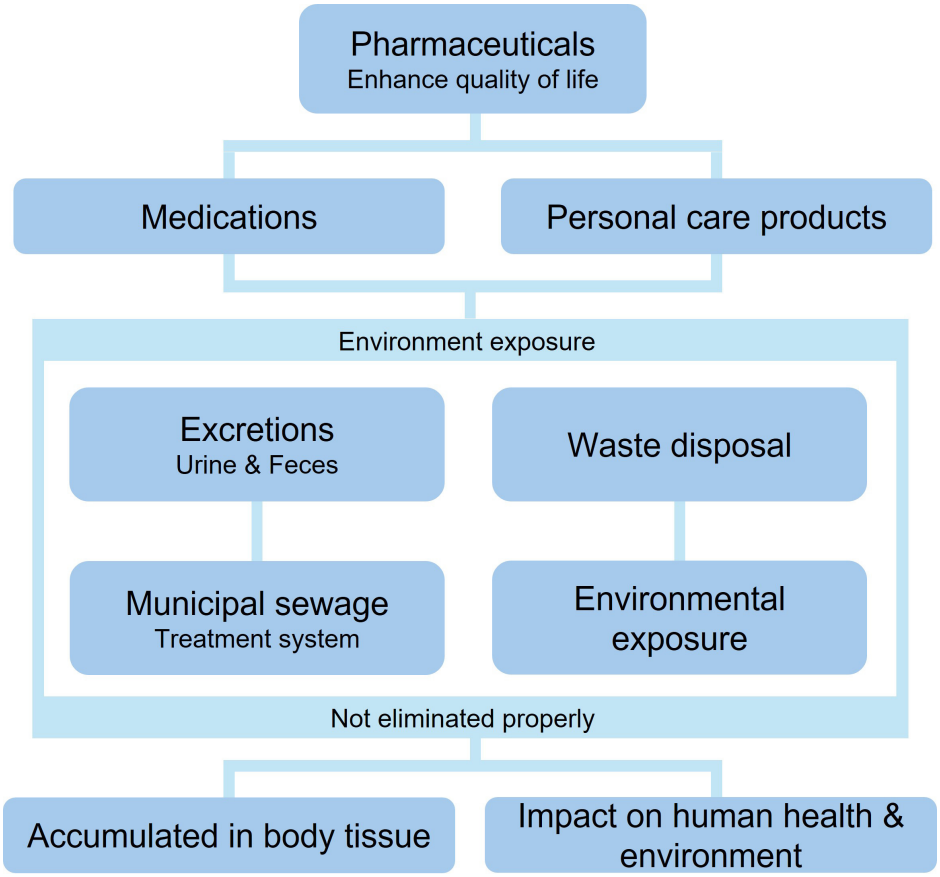

Figure 1. Representing the flow of antibiotics as pollutants in the ecosystem

antibiotics persisted, reaching levels of up to 88 μg/L. Similarly, Chinese PWWTPs demonstrated high removal rates (> 90%) for vancomycin, trimethoprim (TMP), and tetracycline; nonetheless, the final effluents retained hundreds of micrograms per liter (μg/L) of these antibiotics [48]. Transporting wastewater through sewer systems fosters the formation of biofilms on the inner surfaces of pipes, providing a habitat for microorganisms derived from wastewater. These biofilms, exposed to antibiotic residues and ARB, serve as hotspots for the dissemination and accumulation of ARGs. In a study, researchers analyzed antibiotic concentrations, integron (*intI*), resistance genes (*qnrS*, *sul1*, *sul2*, *blaTEM*, *blaKPC*, *ermB*, *tetM*, and *tetW*), and potential bacterial pathogens in wastewater and biofilm samples collected from the inlet and outlet sections of a pressurized sewer pipe. The most prevalent ARGs, *sul1* and *sul2*, were found at a ratio of approximately one resistance gene for every ten copies of the *16S rRNA* gene. Significant disparities in *intI* and resistance genes associated with fluoroquinolones (*qnrS*), sulfonamides (*sul1* and *sul2*), and β-lactams (*blaTEM*) were observed solely between biofilm samples collected at the inlet and outlet sections [49]. WWTPs receive inputs from diverse sources, exposing them to antibiotics, metals, and chemicals, which collectively foster an environment conducive to HGT. Despite mitigation efforts, research indicates that WWTPs are unable to entirely eradicate antibiotics, ARB, and ARGs. As a result, the release of WWTP effluent into environments such as surface water, groundwater, marine ecosystems, and soil introduces ARB and ARGs, potentially amplifying antibiotic resistance among indigenous environmental microorganisms [50]. Hospital wastewater from major urban areas in Vietnam, China, Malaysia, and other regions contains significant concentrations of various antibiotics such as CIP, norfloxacin (NOR), OFL, ERY, TMP/sulfamethoxazole (SMX), with levels varying from nanograms per liter (ng/L) to μg/L. These concentrations are generally comparable to those found in India and some European countries, although a few extreme values have been reported in pharmaceutical effluents in Vietnam. The presence of these contaminants is attributed to the high production rates and environmental persistence of these drugs. Such widespread contamination raises concerns about the potential for environmental and human health impacts due to the dissemination of antibiotic residues and the development of antibiotic

resistance [51]. In 2018, a study analyzed 17 different antibiotics in the aquaculture environments around the Yellow Sea, examining levels in both the wet and dry seasons. The concentration of these antibiotics in the water and sediments was found to be relatively low compared to global averages, with 11 antibiotics detected in mariculture pond surface waters at concentrations up to 995.02 ng/L. Notably, oxytetracycline (OTC) and enrofloxacin (ENR) reached high concentrations in the sediments, peaking at 1,478.29 ng/g and 895.32 ng/g, respectively. The study highlighted that the culture mode significantly influenced antibiotic levels, with greenhouse ponds showing higher concentrations during the wet season, in contrast to outdoor ponds. Particularly, turbots in greenhouse ponds exhibited the highest antibiotic accumulation, suggesting an impact of cultural practices on antibiotic presence in the aquaculture environment [52, 53]. The presence of various antibiotics in treated wastewater from scientific and military stations highlights that conventional WWTPs do not entirely remove these pharmaceuticals, leading to their release into adjacent seawater. Antibiotics were detected at low ng/L levels in seawater samples near wastewater outfalls [53].

Role of pharmaceuticals in endocrine disruption

The necessity of high-quality water for the survival of humans, as well as flora and fauna, cannot be overstated. The aquatic ecosystem faces significant challenges due to industrialization and urbanization. Anthropogenic pollutants infiltrate aquatic environments through diverse channels, including industrial and household effluents, pharmaceutical residues, and biowastes. These substances exhibit bioaccumulation in aquatic systems. Investigations into the surface water of River Taff and River Ely reveal that pharmaceutical products are discharged at an average daily load of approximately 6 kg, highlighting the extent of contamination [54].

The endocrine system regulates numerous physiological functions within our bodies, which can be disrupted by a class of chemicals known as endocrine-disrupting compounds (EDCs). These compounds which can be either natural or human-made, are predominantly of anthropogenic origin. EDCs have the capability to mimic, amplify, or hinder the actions of endocrine products. Additionally, they may also contribute to tumor formation. A significant subset of EDCs interferes with sexual hormonal activities, leading to abnormalities in reproductive processes, embryonic development, sexual differentiation, and metabolic maturation [55, 56]. FSTRA studies reported that EDCs impair reproduction and drastically decrease sperm quality and count, they also have estrogenic effects in males [57].

Gill et al.'s [58] research provides comprehensive insights into the endocrine-disrupting characteristics of diethylstilbestrol (DES), a compound initially utilized to prevent miscarriages. Their findings illuminate the adverse reproductive impacts observed in male offspring as a result of its use [58].

Effect of endocrine disruptors on female reproduction

A female reproductive cycle may be divided into fetal, prepubertal, cycling adult, pregnant, lactating, and reproductive senescent stages. Evaluation of each stage has to be done for the studies regarding the endocrine toxicity of chemicals. The estrogenic chemical decreases gonadotropin output, resulting in atrophic adult female ovaries. According to the studies, exposure to chlorotriazine caused some rat strains to remain in an estrous state for an extended period [59]. Chlorotriazines appear to have an estrogen receptor-independent mode of action [60], and the changes in estrous cycle regulation are likely to be caused by a disturbance in the hypothalamic-pituitary regulation of ovarian function [61].

Chloroquine, classified as a quinolone derivative, possesses properties such as antipyretic, antiseptic, and antibacterial effects. Originally employed as an antimalarial medication since the 1930s, it has now found applications in cancer therapy. Additionally, studies have shown a significant increase in insulin levels among individuals with type II diabetes when administered chloroquine [62–64]. Chloroquine, which has a calcium calmodulin-mediated response, disrupts estrous cyclicity as follicular steroidogenesis and pituitary hormone secretion also depend on the same response [65].

Antineoplastic drug cyclophosphamide has a negative effect on the secretion of progesterone by human granulosa cells. Reproductive toxicity can be screened by measuring the human cumulus granulosa cells [66]. Progesterone secretion by human granulosa-luteal cells is also inhibited by vinblastine [67]. According to Hansmann [68] and Jarrell et al. [69], methotrexate and cyclophosphamide target oocyte. The potential targets in oocytes are the zona pellucida, oolemma, cortical granules, yolk, chromosomes, and spindle [68, 69].

Effect of endocrine disruptors on male reproduction

Disruption of the male endocrine system can manifest at various stages and encompass a range of actions, spanning from the hypothalamus and pituitary gland to the testes. Chemicals that exhibit estrogenic, antiandrogenic, and Ah receptor-binding activity are the main culprits, as they can directly impact testosterone production or influence the regulation of gonadotropin production.

Hydroxyflutamide is used as an antiandrogen to block androgen-stimulated prostate tumor growth. It binds to the androgen receptor without activating it and also competes with actual androgens. The individuals will be genetically male and show alterations like individuals with androgen insensitivity syndrome [70]. Butylated hydroxyanisole, a frequently used antioxidant in the food and pharmaceutical industry, has estrogenic potential. The studies conducted by Paul et al. [57] showed a decline in sperm quality as the dosage increased in fishes, they also observed morphological changes in the testes of treated fishes.

Several pharmaceuticals, including nimodipine, sulindac, tranilast, flutamide, leflunomide, omeprazole, etc., are characterized as Ah receptor agonists in various cell lines and animal models [71]. A wide variety of PPCPs control endocrine activity which includes sex hormones, glucocorticoids, 17β-estradiol, etc. Currently, they are not recognized as endocrine disruptors in the environment. Substances like nonestrogenic steroids, high-volume drugs, and personal care products and additives in drugs have to be evaluated for their endocrine-disrupting properties in the environment [72].

Pharmaceutical pollution on the aquatic system

Pharmaceutical drugs play crucial roles in human, animal, agriculture, and aquaculture sectors, serving purposes like disease treatment and prevention. Their consumption has been steadily rising each year. However, the interaction of active compounds with other biological compounds can lead to unforeseen environmental consequences [73]. Therapeutic compounds find their way into the aquatic system through various sources, contaminating surface water with pharmaceutical substances and their metabolites. To preserve a healthy ecosystem and biodiversity of aquatic organisms, it's crucial to maintain the quality of surface water. Analytical techniques play a vital role in identifying and assessing emerging pollution, enabling us to take proactive measures to mitigate its impact [74, 75]. The presence of antibiotics in wastewater can lead to the evolution of ARB. This phenomenon poses significant risks to human health and the ecosystem. Antibiotic and ARGs can have far-reaching consequences, potentially compromising the effectiveness of medical treatments and disrupting the balance of microbial communities in the environment [76]. Improper disposal of pharmaceutical compounds, coupled with inadequate wastewater treatment methods, can result in the accumulation of these compounds in the environment. This accumulation can adversely affect non-targeted organisms and induce stress on the ecosystem [77]. Developing acceptable management practices is essential for controlling emerging pollutants effectively [78]. As per the records, more than 10 million women in the US are taking medicine for birth control [73]. 17-α-Ethinylestradiol, a type of estrogen commonly found in contraceptive pills, has been observed to induce feminization in male fish at concentrations as low as 5–6 ng/L. This phenomenon highlights the potential impact of steroid hormones on aquatic organisms and ecosystems. Additionally, the presence of steroid hormones can lead to reduced fertility in aquatic organisms, further emphasizing the importance of managing and mitigating their release into the environment [73, 79].

Source of pharmaceutical chemicals

Drugs like paracetamol undergo metabolism in the gut after administration, with some becoming inactive before release into the environment. However, certain drugs can exit the body in their active form through excretion, potentially altering the nature of surface water bodies when they enter aquatic systems. This highlights the need for understanding the fate of pharmaceuticals in the environment and implementing measures to minimize their impact on water quality and ecosystems [75]. Figure 2 depicts the intricate pathways of pharmaceutical products entering into the aquatic ecosystem. Toxic pharmaceutical compounds from hospitals are often directly discharged into the main sewer systems. This practice can lead to the introduction of hazardous substances into WWTPs, where conventional treatment methods may not effectively remove all pharmaceutical residues. As a result, these compounds can persist in the environment and potentially impact water quality and ecosystem health [79]. Most water resources, including rivers, sewage, groundwater, streams, seawater, and drinking water, have been reported to contain pharmaceutical pollutants within a range from ng/L to μg/L [80]. Drugs such as antibiotics, analgesics, blood lipid-lowering agents, antiepileptics, and β-blockers are consistently being detected in aquatic bodies across many countries [65, 68]. Landfill leakage is a significant contributor to aquatic pollution. When it rains, water percolates through landfills, picking up various chemicals and contaminants along the way. These leachates containing pollutants like heavy metals, organic compounds, and other harmful substances, can infiltrate groundwater, rivers, and streams, directly impacting the aquatic ecosystem [66]. In the United States, clofibric acid, a major metabolite of lipid regulator, was reported in sewage treatment plants (STPs). STPs can also act as significant sources of pollution in aquatic systems due to the incomplete removal of pharmaceutical compounds and other pollutants during the treatment process [69]. Agricultural runoff can indeed contribute to the presence of pharmaceuticals in water bodies. Antibiotics and hormones are used in livestock farming and agriculture, they can be washed off the fields or carried away by rainwater, eventually making their way into rivers, lakes, and other water sources through runoff. Once in the water, these pharmaceuticals can pose risks to aquatic organisms and even to human health if the contaminated water is used for drinking or irrigation of crops consumed by humans [66]. The presence of pharmaceuticals in water bodies can indeed alter the natural behavior and composition of microbial communities, which can have significant effects on aquatic biodiversity and ecosystem functioning [61].

Impact of pharmaceutical contaminants

Pharmaceutical contaminants enter aquatic systems through various sources, including untreated water used for drinking, irrigation, and household activities. This leads to the accumulation of antimicrobial-resistant bacteria. Pharmaceuticals are primarily developed for the benefit of humans and animals, but when they enter the aquatic system, organisms with similar biological characteristics can also be affected by the same pharmaco-dynamic effects [71]. In aquatic ecosystems, important processes like denitrification, nitrogen fixation, and organic breakdown are typically governed by specific groups of bacteria. The presence of antibiotics can disrupt all these processes. Antibiotics may inhibit or alter the activity of these bacterial groups, leading to disturbances in nitrogen cycling, organic matter decomposition, and other essential ecological processes. As a result, the overall functioning and stability of the aquatic ecosystem can be compromised, with potential implications for water quality, nutrient dynamics, and the health of aquatic organisms [72]. Sewage effluent containing pharmaceutical residues is discharged into streams or other water bodies, and humans and animals can come into direct contact with these drugs, leading to potential negative impacts on their health [73].

According to the reports, ketoprofen, fenoprofen, naproxen, mefenamic acid, diclofenac, and ibuprofen are among the anti-inflammatory drugs found in the aquatic environment [82]. Physiological factors such as pH can influence the activation and effectiveness of drugs. Ibuprofen, also known as 2-(4-isobutyl phenyl) propionic acid, is commonly used for its analgesic, anti-inflammatory, and antipyretic properties. Interestingly, at a pH below 7, ibuprofen can also act as an antimicrobial agent against *Staphylococcus aureus*. This means that in acidic environments, such as those found in certain parts of the body or in laboratory settings, ibuprofen can inhibit the growth of this gram-positive bacterium [83]. Ketoprofen is

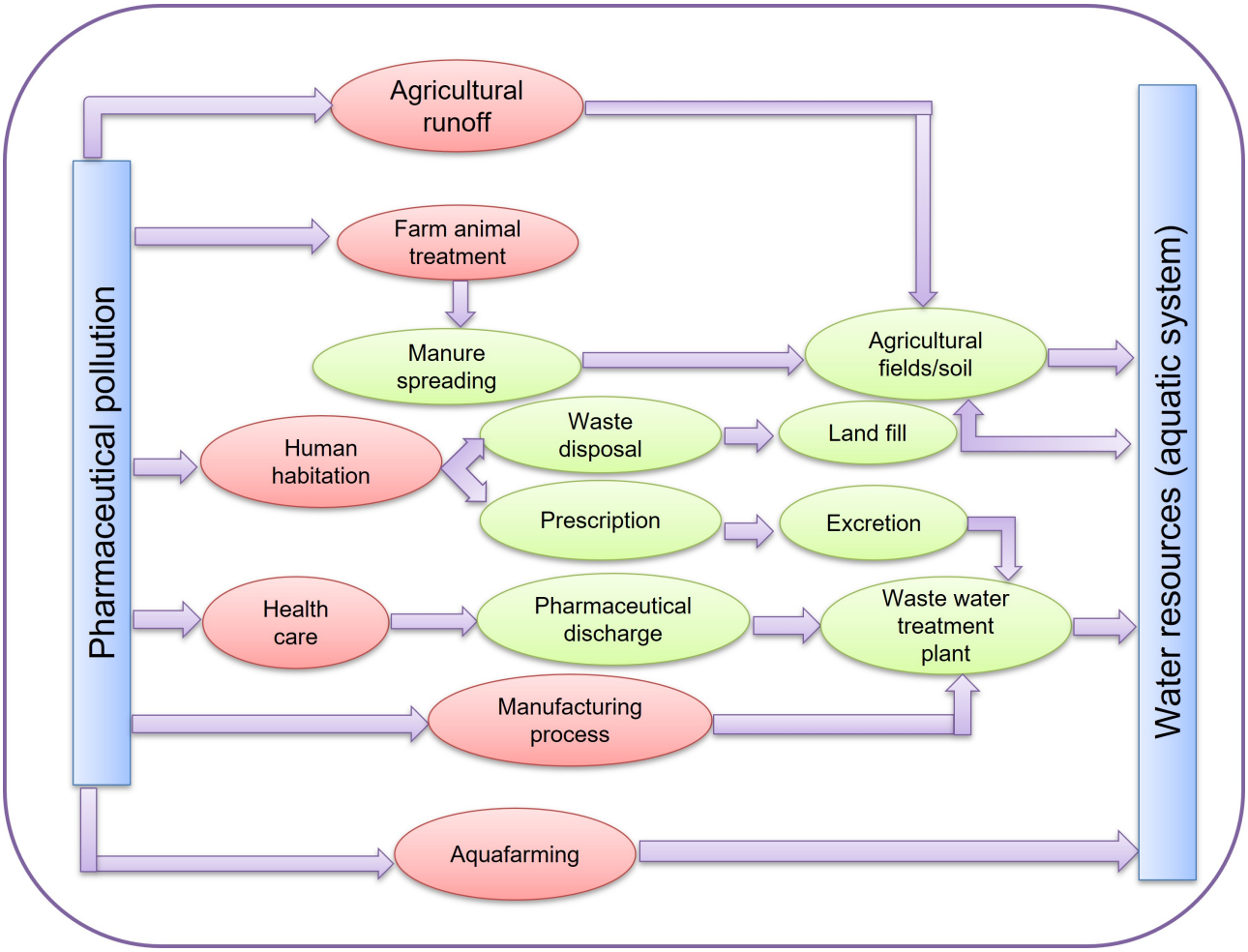

Figure 2. Source of pharmaceuticals in the aquatic system [81]

also an anti-inflammatory that has higher toxicity to *Scenedesmus obliquus* [77]. In zebrafish, hatching was delayed due to the presence of nonsteroidal anti-inflammatory drugs. Zebrafish, when exposed to diclofenac, can also infect the gill formation. Human drugs have also been reported to cause damage to the brain, liver, and ovaries of *Danio rerio* [84].

Antidepressant drugs such as fluoxetine, paroxetine, citalopram, sertraline, venlafaxine, and duloxetine contain psychoactive substances which are used for the treatment of physiological disorders, mental illness, obsessive-compulsive disorder, panic disorder, attention-deficit disorder, and eating disorders. The mechanism of action of these antidepressants involves modulating the levels of neurotransmitters in the brain, particularly serotonin, dopamine (DA), and norepinephrine [85]. Aquatic organisms possess similar neurotransmitter receptors to humans, which means that the improper use of drugs like antidepressants can also impact these species [65]. Fluoxetine, a drug used to treat depression, can interact with the 5-hydroxytryptamine (5-HT) receptor and trigger neuromuscular activity in the nematode *Caenorhabditis elegans*. According to reports, this antidepressant has also caused neuroendocrine disruption in crustaceans and molluscs [78].

Another significant source of contamination is antibiotics, and their use has progressively increased in recent years. Quinolones, tetracyclines, macrolides, sulfonamides, and β-lactams are among the types of antibiotics commonly found in the environment. The most frequently prescribed antibiotics in human medicine include fluoroquinolones, macrolides, and aminoglycosides, whereas in veterinary medicine, penicillins, tetracyclines, and macrolides are the most commonly used [77]. Antibiotics have been extensively utilized worldwide by humans, animals, and in agriculture. In Germany, ARGs have been detected in drinking water biofilm. When antibiotics and resistant bacteria enter the ecosystem, they can transform harmless pathogens into life-threatening antibiotic-resistant strains. Additionally, they can elicit

allergic responses. Some reports suggest that these drugs can impede the growth of soil bacteria, thereby inhibiting natural microbial decomposition. Moreover, pharmaceutical chemicals can alter the habitat of invertebrates, leading to reduced feeding, disruption of water balance, decreased growth rates, delayed molting, inhibition of pupation, prevention of adult emergence, and disruption of mating [79].

Neurotoxicity of pharmaceutical drugs in humans

The neurotoxicity of pharmaceutical drugs in humans is an inevitable area of investigation within both pharmacological and neurological studies. Drugs, whether prescribed for therapeutic purposes or abused recreationally, possess the capacity to induce profound effects on the central nervous system (CNS), thereby causing structural and functional alterations in neurons and associated cellular elements. An in-depth comprehension of the diverse complications and underlying mechanisms of neurotoxicity of these commonly used drugs is essential for the development of safer medications and the formulation of novel strategies aimed at mitigating neurological impairments. This segment of the review paper endeavors to explore the diverse array of drugs implicated in inducing neurological complications encompassing both pharmaceutical and therapeutic agents, while underscoring the paramount importance of ongoing research in revealing their impact on nervous system health and cognitive brain functions.

Cognitive side effects of antiepileptic drugs

Antiepileptic drugs (AEDs) engender cognitive and behavioral deficits by modulating activities of CNS. AEDs function either by suppressing neuronal excitability or by augmenting inhibitory neurotransmission. Polypharmacy, elevated blood levels of AED, patient age, type or frequency of seizures are various factors that contribute to an increased risk of cognitive deficits. The most common cognitive side effects observed in AED therapy include sedation, somnolence, distractibility, insomnia, mood variation, and dizziness [86]. Notably, adults may manifest depressant cognitive side effects, while children may exhibit aggression and hyperactivity. When compared with adult counterparts, children are highly vulnerable to cognitive complications of antiepileptic medications due to the impact of these drugs on neurodevelopment [87]. Similarly, a previous cohort study proved a higher prevalence of adverse drug events among older outpatients [88] attributable to age related decline in homeostatic mechanisms in the body, especially within the CNS, liver, and kidneys. Previous researchers proved that neuronal death, replacement with proliferating glial cells, and reduction in dendritic synapses are some of the CNS changes associated with aging. Age-related organ decline shifted elderly individuals to heightened sensitivity to the side effects of benzodiazepines (BDZs), stemming from the accumulation of BDZs and related active metabolites [89].

Side effects of anti-HIV drugs on the central nervous system

Efavirenz, a non-nucleoside reverse transcriptase inhibitor which is used as a medication in the treatment of AIDS patients is reported to be associated with various CNS side effects. These manifestations include dizziness, disrupted sleep, impaired concentration, drowsiness, abnormal dreaming, unhappiness, depression, aggression, increased anxiety, and paranoid and manic reactions [90–93].

Central nervous system toxicity after liver transplantation

Cyclosporine therapy for immunosuppression in patients undergoing liver transplantation can precipitate severe CNS side effects like confusion, cortical blindness, quadriplegia, seizures, coma, and white-matter discharges, which often manifests in patients with decreased serum cholesterol levels after transplantation. A study observed various CNS toxicity symptoms in a subset of liver transplant recipients (13 among 48 patients) following cyclosporine administration. But all these symptoms have been reversed by dosage reduction of cyclosporine [94].

Side effects of benzodiazepines on central nervous system

BDZs are a class of medications that slow down the activity of the brain and nervous system by acting as a positive allosteric modulator of gamma amino butyric acid (GABA)-A receptor. As GABA gives a soothing effect on the brain, BDZs are commonly prescribed for the management of anxiety, insomnia, epilepsy,

seizures, and related mental health conditions. When BDZs are administered orally, it is well absorbed by the gastrointestinal tract while in the case of intravenous administration, it fastly diffused to the brain and CNS. Alprazolam, clonazepam, lorazepam, midazolam, and diazepam are few BDZ medications [89].

Noteworthy side effects associated with BDZs include dose dependent manifestations such as drowsiness, lethargy and fatigue, impaired motor coordination, dizziness, vertigo, mood variations, dysarthria, blurred vision, anterograde amnesia, sedation, lack of concentration, eccentric behavior, ataxia, etc. Due to slow elimination from the body (because of their lipophilic properties) and significant accumulation in fatty tissues, the overmedication of BDZs causes disability in thinking, slurred speech, confusion, etc. Prolonged usage of BDZs further causes the development of tolerance, dependence, and withdrawal symptoms upon abrupt cessation [89, 95]. Broadly, cognitive impairment is the major BDZ mediated CNS toxicity which significantly increases the risk of falls, fractures as well as the incidence of motor vehicle accidents [96]. Patients may experience anterograde amnesia, hindering their ability to recognize loved ones and recall significant portions of their lives. Additionally, delirium (serious alteration in mental function) and disinhibition (inability to withhold an inappropriate or unwanted behavior) are the other two concerning effects of the toxic accumulation of BDZs and their metabolic byproducts [89]. Elderly patients in the intensive care unit (ICU) are especially susceptible to BDZs induced delirium, which increases the rate of morbidity and mortality [97, 98].

Neurotoxicity of methamphetamine

Methamphetamine (METH) is a strong stimulant of CNS which is mainly used as a recreational drug and rarely used as a second line treatment for obesity and attention deficit hyperactivity disorder. High dose of METH usage leads to various neuropsychiatric problems like agitation, anxiety, paranoia, psychosis, cerebral stroke, seizures, schizophrenia, and attention and memory deficits [99–103]. Some of the serious METH induced neurotoxic consequences are neuronal apoptosis, impaired dopaminergic and serotonergic functions, astrocytosis, and microgliosis [104–109]. Some previous studies reported an increased risk of Parkinson's disease among METH users [109–112]. METH-associated brain damage involves the destruction of DA and serotonin transporters (DAT and 5-HTT) that leads to decreased levels of DA [113–115]. The METH users showed a significant reduction in grey matter volume in cortical and hippocampal regions of the brain [116, 117]. The METH neurotoxicity is mediated by the generation of reactive oxygen species such as hydrogen peroxide, superoxide radicals, and hydroxyl radicals [118–120]. The microglial and astrocyte activation in METH exposures leads to increased secretion of pro-inflammatory cytokines in the brain [121–125]. Mitochondrial dysfunction and activation of endoplasmic reticulum stress are the other two key factors causing METH induced neurotoxicity [101, 126–128]. METH alters the expression of transcription factors like c-fos, fosB, Fra-2, Egr-1, Egr-2, Egr-3, etc. [129–132].

Neurotoxicity of MDA & MDMA

Amphetamine derivatives like 3,4-methylenedioxyamphetamine (MDA) and 3,4-methylenedioxy-methamphetamine (MDMA) are mainly used for recreational purposes and mood alterations in humans. Among these two drugs, MDMA is more toxic to serotonin axons in the brain of primates. Individuals exposed to MDMA demonstrate reduced levels of cerebrospinal fluid, 5-hydroxyindoleacetic acid (CSF 5-HIAA, a major metabolite of 5-HT) [133, 134].

Anesthetic neurotoxicity

Several animal and observational human studies proved the occurrence of neurotoxic changes in the developing brain resulting from exposure to general anesthetics leading to inauspicious neurodevelopmental outcomes later in life. Anesthetics like propofol, etomidate, sevoflurane, desflurane, and isoflurane accelerate inhibitory GABA receptor activity, and sedatives like ketamine block excitatory glutamate receptors and thus induce various neurotoxic effects in laboratory animals [135]. Commonly used anesthetics like injectable propofol and inhalable isoflurane induce apoptosis in the neonatal brains of primates [136, 137]. In primates, prolonged exposure to ketamine (24 h) during brain development leads to

permanent deficits in memory and attention [137]. The age of exposure and dosage of anesthetic are the two major key factors influencing the extent of damage. Studies on nonhuman primates proved that these drugs induce various histological changes like widespread apoptosis, cell death, reduced synapse numbers, morphological alterations in neurons and hindered neuron formation in the hippocampus, and impaired learning and academic performance [135, 138]. Experiencing multiple instances of anesthesia and surgery can exacerbate learning deficits [139].

Neurotoxicity of spinal drugs

Limited studies are available to record the neurotoxicity of various drugs employed for spinal anesthesia. Laboratory studies suggest that local anesthetics exhibit neurotoxicity at high concentrations, while lidocaine and tetracaine possess neurotoxic potential at clinically relevant concentrations [140]. Clinically accepted concentrations of some local anesthetics cause nerve cell injury. Direct application of 2.5–5% lidocaine resulted in a threefold increase in intracellular calcium and 20% cell death in the neuronal cell line during one hour of exposure [141]. Previous clinical and laboratory evidence reported that spinal analgesics like morphine, sufentanil, clonidine, neostigmine, and a majority of antioxidants, preservatives, and excipients used in commercial formulations appear to have minimal neurotoxicity [142].

Rabbit studies reported that there are no neurologic complications seen with clinically used concentrations of tetracaine, lidocaine, bupivacaine, or chlorprocaine while higher concentrations of tetracaine and lidocaine caused histopathologic and neurological impairments [140]. Four cases of short-lived neurological symptoms following spinal anesthesia with 5% hyperbaric lidocaine were documented by Schneider et al. [143]. About 4–33% incidence of transient neurological symptoms (TNS) following spinal anesthesia with lidocaine are documented, depending on the type of surgical procedure [144, 145]. Although laboratory models showed neurotoxicity with all local anesthetics, extensive surveys of spinal anesthesia complications indicate their relative safety in humans [142].

Some epidemiologic studies have proved the occurrence of numerous neurological complications associated with spinal anesthesia. However, the incidence of these complications among patients remains relatively low when compared with the overall patient population. Radiculopathy, cauda equina syndrome, persistent and transient paresthesia, paraplegia, paresis, exacerbation of disc disease, meningitis, foot drop, neurologic exacerbation, and TNS are various neural problems associated with spinal anesthetic drugs [144–150]. Further investigation through human studies is necessary to gain a better understanding of the precise issues associated with the neurotoxicity of spinal drugs, as this domain remains insufficiently explored.

Conclusions

In conclusion, antibiotic resistance stands as a global health and environmental crisis rooted in genetic variation, HGT, and extensive antibiotic use. Urgent strategies and responsible antibiotic practices are essential to address the escalating impact on human health and the environment. Coordinated global efforts are imperative to combat this crisis and secure a sustainable future. The study's focus on pharmaceutical contamination in aquatic ecosystems reveals alarming endocrine-disrupting effects, impacting both female and male reproductive cycles. Disturbances in estrous states and disruptions in ovarian function raise concerns about broader ecosystem health implications. The multifaceted nature of pharmaceutical-induced endocrine disruption, affecting testosterone production and sperm quality in males, emphasizes the need for immediate measures to mitigate potential risks. The diverse sources of pharmaceutical contaminants, from improper disposal to hospital discharge and agricultural runoff, necessitate comprehensive evaluations and urgent actions to mitigate adverse effects on both environmental and human health. Neurotoxicity of drugs underscores the interplay between pharmacology and neurology. Increased vigilance, comprehensive risk assessment, and innovative therapeutic strategies are essential to mitigate these harmful effects and safeguard neurological health. Through advanced research in pharmaceutical and scientific fields, we can develop safer medications and improve public health.

To effectively tackle the pressing issue of antibiotic resistance and pharmaceutical contamination, a comprehensive and multi-faceted approach is essential. Strengthening regulatory frameworks is crucial, with governments needing to enforce stricter controls over the production, distribution, and disposal of pharmaceuticals. Public and healthcare professional education campaigns can promote responsible antibiotic use and adherence to prescribed treatments. Enhancing surveillance and monitoring of pharmaceutical contaminants in ecosystems, alongside investing in research and development for new antibiotics and alternative therapies, is vital. International collaboration is also necessary to harmonize regulatory standards and share research outcomes. Improvements in waste management practices, including better infrastructure for pharmaceutical disposal and treatment, can significantly mitigate environmental contamination. Developing non-antibiotic therapies can reduce reliance on antibiotics, thus decreasing the potential for resistance. Finally, fostering public-private partnerships can pool resources and expertise, offering a robust response to these environmental and public health challenges. These strategies collectively can help manage antibiotic use and mitigate their adverse effects on health and the environment.

Abbreviations

AEDs: antiepileptic drugs

AMR: antimicrobial resistance

ARB: antibiotic-resistant bacteria

ARGs: antibiotic resistance genes

BDZs: benzodiazepines

CNS: central nervous system

DA: dopamine

EDCs: endocrine-disrupting compounds

GABA: gamma amino butyric acid

HGT: horizontal gene transfer

MDMA: 3,4-methylenedioxymethamphetamine

MDR: multidrug resistance

METH: methamphetamine

ng/L: nanograms per liter

PPCPs: Pharmaceutical and Personal Care Products

UTIs: urinary tract infections

WWTPs: wastewater treatment plants

μg/L: micrograms per liter

Declarations

Author contributions

JVE and ST equally contributed to: Conceptualization, Writing—original draft. SA and PG: Conceptualization, Writing—original draft. JA: Writing—review & editing, Validation, Supervision.

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The authors declare that they have no conflicts of interest.

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