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Review article

Pharmaceutical compounds and their toxicity to marine organisms: Emerging contaminants and innovative strategies to reduce pharmaceutical pollution – A review and meta-analysis

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ABSTRACT

Pharmaceutical pollution in coastal and marine environments poses a serious threat to aquatic organisms. This article provides a critical overview of the toxicological impacts of commonly used classes of drugs, including antibiotics, anticancer, antidepressants, antihypertensives, and analgesics, on coastal and marine organisms. This review highlights how these pharmaceuticals affect growth, reproduction, development, physiology, behaviors, and mortality changes in coastal and marine organisms. In particular, antibiotics contribute to the emergence of antibiotic-resistant bacteria in marine ecosystems, whereas analgesics and antidepressant drugs alter normal marine animal behavior and impair reproductive patterns. Additionally, antihypertensive drugs, particularly beta-blockers, interfere with cardiovascular physiology, reducing heart rate and altering blood pressure regulation in marine fish. They also disrupt gill ion transport, osmoregulation, and metabolic performance in marine mollusks and crustaceans, resulting in reduced growth, reproduction, and resilience, ultimately threatening ecosystem stability and biodiversity. This review also summarizes the environmental concentration of those drugs found in coastal and marine waters. Beyond antibiotics, analgesics, antidepressant medicines, and anticancer agents are also acutely toxic and pose a severe health risk even at short-term exposure. Importantly, this article systematically reviews the various pharmaceutical compounds in seawater and highlights the urgent need to control pollution from these sources. Specific steps are outlined to reduce pharmaceutical pollution by improving wastewater management, strengthening regulatory processes, and promoting green chemistry solutions. This review compiles and evaluates recent findings on the occurrence, bioaccumulation, and toxicological impacts of pharmaceuticals in marine organisms, while identifying key knowledge gaps and emerging ecological concerns. This study also provides a comprehensive overview of pharmaceutical contamination in marine environments and emphasizes the urgent need for monitoring and mitigation. In addition, the review outlines future research to understand the long-term consequences of pharmaceutical pollutants better and to develop innovative strategies and management techniques to mitigate their impact on coastal and marine ecosystems.

Abbreviations: AOPs, Advanced oxidation processes; CE-MS, capillary electrophoresis–mass spectrometry; CNS, central nervous system; CAS, conventional activated sludge; COX, cyclooxygenase; DIA, data-independent acquisition; EDA, effect-directed analysis; EU, European Union; FDA, Food and Drug Administration; GC–MS, gas chromatography–mass spectrometry; HRMS, high-resolution mass spectrometry; LC-MS-MS, liquid chromatography–tandem mass spectrometry; MBRs, membrane bioreactors; MOFs, metal-organic frameworks; MAOIs, monoamine oxidase inhibitors; MRM, multiple-reaction monitoring; NSAIDs, non-steroidal anti-inflammatory drugs; POCIS, polar organic chemical integrative sampler; PRISMA, preferred reporting items for systematic reviews and meta-analysis; QuEChERS, quick, easy, cheap, effective, rugged, safe; ROS, reactive oxygen species; SSRIs, selective serotonin reuptake inhibitors; SNRIs, serotonin-norepinephrine reuptake inhibitors; SPE, solid-phase extraction; SPME, solid-phase microextraction; TOF, time-of-flight; TCAs, tricyclic antidepressants; UTIs, urinary tract infections; WWTPs, wastewater treatment plants; WHO, World Health Organization.

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1. Introduction

The use of pharmaceuticals has increased rapidly over the past few decades, providing substantial benefits to human health and well-being. Medications ranging from antibiotics to antidepressants have become indispensable in modern healthcare, contributing greatly to improved life expectancy and enhanced quality of life (Mezzelani et al., 2018; Samal et al., 2022; Yuan et al., 2023). However, the enormous global consumption (~4500 billion doses by 2020) of pharmaceuticals has led to the introduction of numerous contaminants into aquatic environments. These pollutants primarily enter water systems through human and animal excretion, improper disposal of medications, and discharges from pharmaceutical manufacturing industries (Khan et al., 2020; Mezzelani et al., 2020; Chaturvedi et al., 2021; Hasani et al., 2023; Lakdawala et al., 2023). Unlike many environmental pollutants, pharmaceuticals are specifically designed to exert biological effects at low concentrations, often resulting in persistent and widespread contamination (Tijani et al., 2013, 2016; Wilkinson et al., 2016; Dey et al., 2019). These compounds are not fully metabolized and can remain biologically active after excretion. Wastewater treatment plants, although capable of removing many contaminants, do not fully filter out pharmaceuticals, resulting in their release into ponds, lakes, rivers, and oceans (Sharma et al., 2019; Kumar et al., 2022; Morin-Crini et al., 2022). Studies have indicated that a wide range of pharmaceutical compounds, including antibiotics, antihypertensives, antidepressants, analgesics, and anticancer drugs, are commonly found in surface waters, groundwater, and even drinking water at trace levels (Deo, 2014; Seid-Mohammadi et al., 2019, 2020; Sanusi et al., 2023).

Pharmaceuticals in marine ecosystems can interfere with critical physiological functions in aquatic organisms, leading to toxic effects (Fernandes et al., 2020; Mezzelani et al., 2020; Chaturvedi et al., 2021). For example, antibiotics may disrupt microbial communities that facilitate nutrient cycling and decomposition (Lucas et al., 2021; Wang et al., 2021; Porretti et al., 2022). Additionally, synthetic hormones such as estrogens can disrupt endocrine function in fish, impairing reproduction and threatening population stability (Sumpter, 2005; Blanchfield et al., 2015; Badamasi et al., 2020). Pharmaceuticals can cause both acute and chronic toxicity effects in aquatic organisms. Acute toxicity typically arises from short-term exposure to high concentrations of contaminants, resulting in rapid and often lethal outcomes. In contrast, chronic toxicity occurs due to prolonged exposure to lower concentrations, leading to sub-lethal effects such as behavioral changes, growth inhibition, and reproductive failure (Do Amaral et al., 2019; Menon et al., 2020; Jacob et al., 2021). Chronic exposure is particularly insidious as it can result in bioaccumulation and biomagnification through the food web, causing long-term ecological disturbances (Lam et al., 2019; Alphonse et al., 2023; Borriello et al., 2023).

Bioaccumulation is the process through which toxic substances gradually accumulate in organisms over time. Biomagnification, on the other hand, refers to the increase in the concentration of these substances at each trophic level within the food web (Lagesson et al., 2016). Both processes can lead to high levels of pharmaceuticals in long-lived species and top predators, potentially causing severe toxic effects. For example, the biomagnification of pharmaceutical compounds has been observed in fish and birds, leading to physiological and behavioral changes that threaten their survival and reproductive success (Brodin et al., 2014; Shore et al., 2014). While substantial research has been conducted on the presence and effects of pharmaceuticals in the aquatic environment (Santos et al., 2010; Rzymski et al., 2017; Valdez-Carrillo et al., 2020; Bottoni et al., 2010; Kayode-Afolayan et al., 2022; Mezzelani and Regoli, 2022; Ortúzar et al., 2022), significant gaps remain in our understanding. Recent investigations have increasingly emphasized the global concern surrounding pharmaceutical residues in aquatic environments due to their persistence, continuous input, and potential ecological toxicity. With the rapid expansion of pharmaceutical consumption worldwide, trace levels of numerous active pharmaceutical ingredients have been widely detected in rivers, estuaries, and coastal waters, raising concerns regarding long-term ecological consequences and ecosystem stability (Wilkinson et al., 2022; Adedipe et al., 2024; Eapen et al., 2024). These findings highlight the urgent need for comprehensive evaluations integrating toxicity evidence, environmental occurrence, and effective mitigation strategies to better understand and manage pharmaceutical pollution in marine ecosystems (Aib et al., 2025; Naseem et al., 2025; Nugnes et al., 2025). Additionally, the interactions between various pharmaceutical compounds and their cumulative effects on marine organisms remain poorly understood. The complexity of these interactions, along with the potential for synergistic effects, makes it difficult to predict and manage their ecological impact accurately. Several approaches have been proposed to reduce the impact of pharmaceuticals on aquatic ecosystems, including improvements in wastewater treatment technologies (Xu et al., 2022), stricter regulations on pharmaceutical disposal, and the development of more environmentally sustainable pharmaceuticals. Despite these initiatives, there is still a critical need for more comprehensive regulatory frameworks and innovative strategies to address this growing environmental concern effectively. To control environmental contamination, international organizations, such as the World Health Organization (WHO), the Food and Drug Administration (FDA), and the European Union (EU), have established environmental quality standards and threshold limits of pharmaceutical residues in water (Desai et al., 2022).

This article aims to present a comprehensive overview of the toxic effects of pharmaceuticals on marine organisms. It explores the sources and pathways of pharmaceutical contamination entering aquatic systems, identifies the types of pharmaceuticals frequently detected in coastal and marine environments, and discusses their specific toxicological effects on a variety of coastal and marine organisms. By synthesizing current research, this review also emphasizes the ecological risks linked to pharmaceutical pollution and highlights key areas that require further investigation. Moreover, its primary goal is to inform scientists and policymakers and to support future efforts to reduce the adverse impacts of pharmaceuticals on aquatic ecosystems, thereby promoting the protection and long-term sustainability of these essential natural resources.

2. Methodology

This review primarily investigates the presence and impact of pharmaceuticals and their metabolites in marine organisms. Essential information for this review was gathered through literature searches, including the key words “pharmaceuticals and marine” on Web of Science from January 2000 to November 2025. Relevant articles for this review were identified using the advanced search framework of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) (Fig. 1). PRISMA provides structural guidelines for systematically identifying, screening, selecting, and assessing studies for eligibility (Page et al., 2021). It is widely applied and recognized in peer-reviewed journals (Page et al., 2021). A meta-analysis and flowchart documenting the search procedure (Fig. 1) and article selection were developed according to Page et al. (2021). A total of 7563 records were initially identified through Web of Science searches. After removing duplicates ($n = 5$), 7558 articles remained for abstract screening. Of these, 5535 were excluded as irrelevant based on title/abstract, leaving 2023 full-text records for assessment (Fig. 1).

Laboratory (e.g., controlled exposures) and field monitoring studies (marine water, marine species, and biota), and review or synthesis papers reporting on pharmaceuticals or their metabolites in marine, coastal, or estuarine environments were considered. Only English-language publications were eligible, within a date window from January 2000 to December 2025. Studies limited to freshwater systems, non-peer-reviewed sources (such as theses, conference abstracts, or preprints), commentaries lacking primary data, records without extractable information, and duplicates were excluded. For the

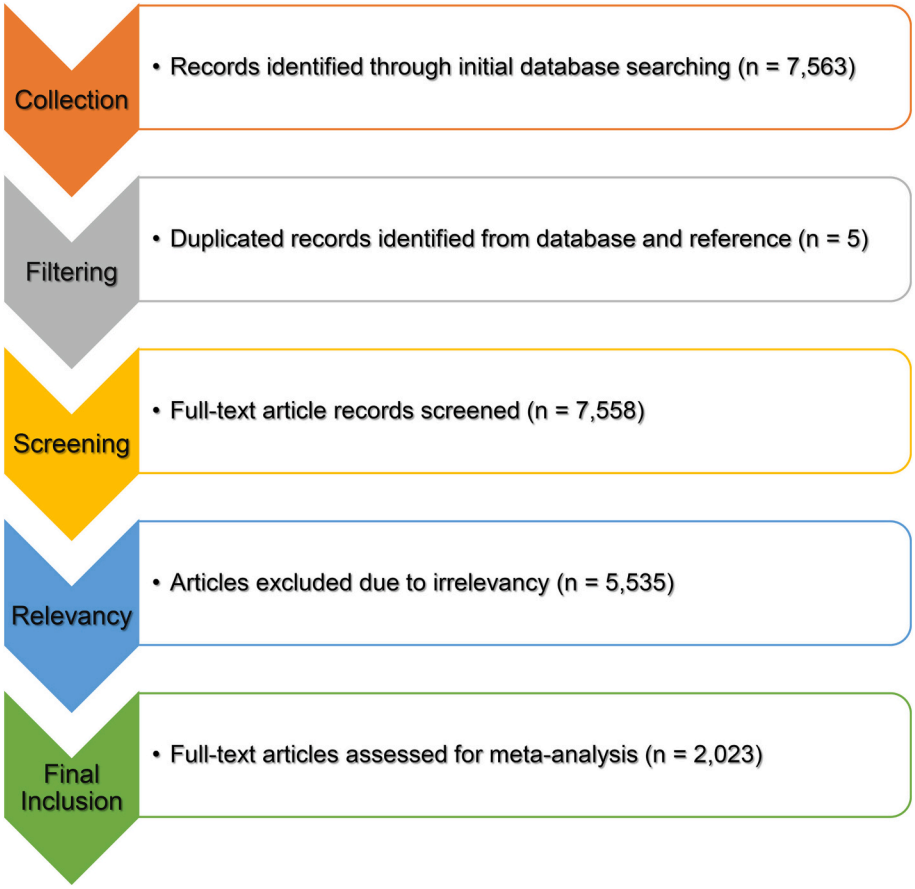


Fig. 1. The PRISMA flow diagram illustrates the literature search strategy used in this. It presents the systematic process of identifying, screening, assessing relevance, and selecting scientific articles for inclusion. The initial database search produced 7563 records, from which 5 duplicate entries were removed. The remaining 7558 articles were then screened at the full-text level, leading to the inclusion of 5535 studies due to irrelevance. Ultimately, 2023 articles met the eligibility criteria and were included in the quantitative synthesis.

systematic PRISMA review, Web of Science served as the sole citation index; however, additional databases, including PubMed, Scopus, Google Scholar, and ProQuest, were used to compile general literature for the main text. Notably, a 25-year timeframe (January 2000 to November 2025) was chosen to emphasize continuous developments. A significant number of articles addressed the presence of pharmaceuticals and their metabolites in coastal and marine environments. A year-by-year distribution of publications is presented in Fig. 2, highlighting the consistently higher volume of research, including recent increases in studies on pharmaceuticals in coastal and marine environments.

Connections and relationships among the reviewed articles were visualized using a co-citation analysis generated with VOSviewer

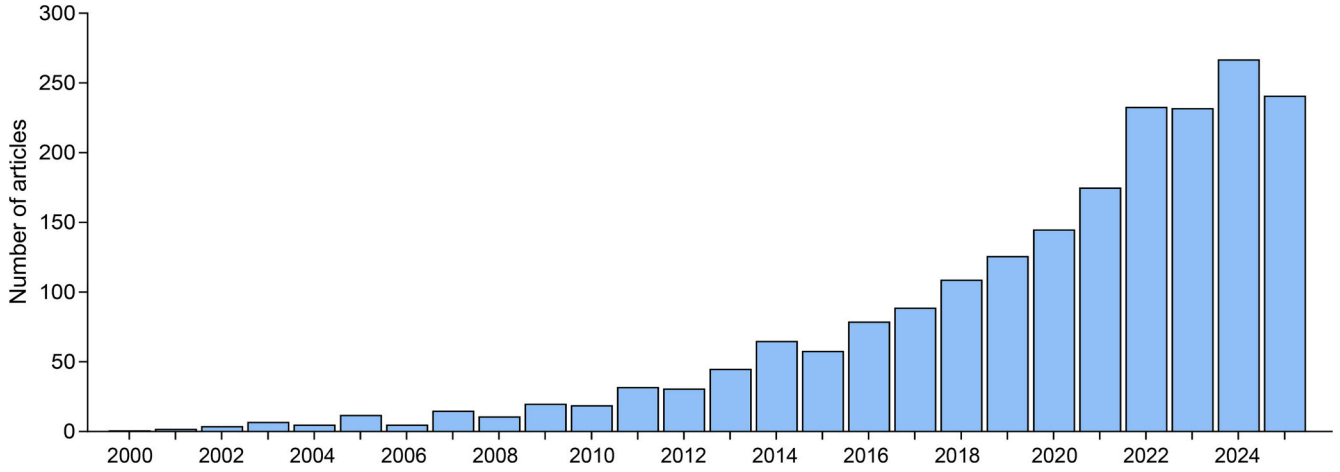


Fig. 2. Number of articles on pharmaceuticals in marine environments published from January 2000 to December 2025, as indexed in the Web of Science. This figure illustrates the publication trend, showing a growing scientific focus on pharmaceutical contamination in marine ecosystems. The increasing number of reflects heightened global awareness of environmental transport, ecological risks, and persistence of for these compounds. Additionally, the trend indicates to expanding multidisciplinary research efforts focused on environmental monitoring and the development of sustainable pharmaceutical waste management strategies.

software (version 1.6.20, Leiden University, Leiden, The Netherlands). VOSviewer identifies keywords in article titles and abstracts and groups them into clusters based on frequency co-occurrence. Fig. 3 presents the resulting co-citation map, which automatically organized the detected keywords into various clusters: exposure, effects, distribution, characterization, etc., which represent research themes related to pharmaceuticals in coastal and marine environments. Fig. 4 illustrates a timeline map of the evolution and use of these clusters. The map highlights the relatively recent emergence of characterization and identification of pharmaceuticals and their tight effects on marine organisms. Together, the co-citation and timeline maps serve as valuable tools for visualizing keywords associated with each other, how they cluster with the literature, and how their interactions have evolved, providing deeper insight into the scientific research on pharmaceuticals and marine organisms.

The review explores how these compounds and their transformed derivatives may influence the physiology, behavior, and reproductive patterns of marine organisms. Pharmaceuticals, their metabolites, and residues enter marine ecosystems through various routes. A schematic diagram illustrates the pathway of pharmaceuticals released into seawater from the pharmaceutical industry, their distribution to hospitals and clinics, and subsequent administration to humans and veterinary animals (Fig. 5). Additionally, chemicals are also released from wastewater treatment plants. Consequently, all the compounds initially enter freshwater before reaching coastal and marine environments, thereby contributing to marine pollution. Special attention is given to highlighting potential synergistic or antagonistic effects arising from the co-occurrence of pharmaceuticals and their metabolites. This review also assesses the methodologies employed in previous research, discussing the challenges and advancements in analytical techniques capable of detecting and quantifying pharmaceutical metabolites in aquatic systems. It addresses the complexities of predicting the environmental fate of these metabolites, thereby contributing to a more comprehensive understanding of their ecological impact. Furthermore, this review identifies knowledge gaps and proposes avenues for future research, emphasizing the importance of investigating the interactions between pharmaceuticals and their metabolites in realistic environmental contexts.

3. Pharmaceuticals in coastal and marine environments

3.1. Antibiotics

The contamination of the marine environment by pharmaceuticals, particularly antibiotics, has become a serious concern due to their crucial role in modern medical practice. The overuse of these drugs has led to the emergence of antibiotic-resistant bacteria, posing a threat to the health of marine animals (Hossain et al., 2022). Furthermore,

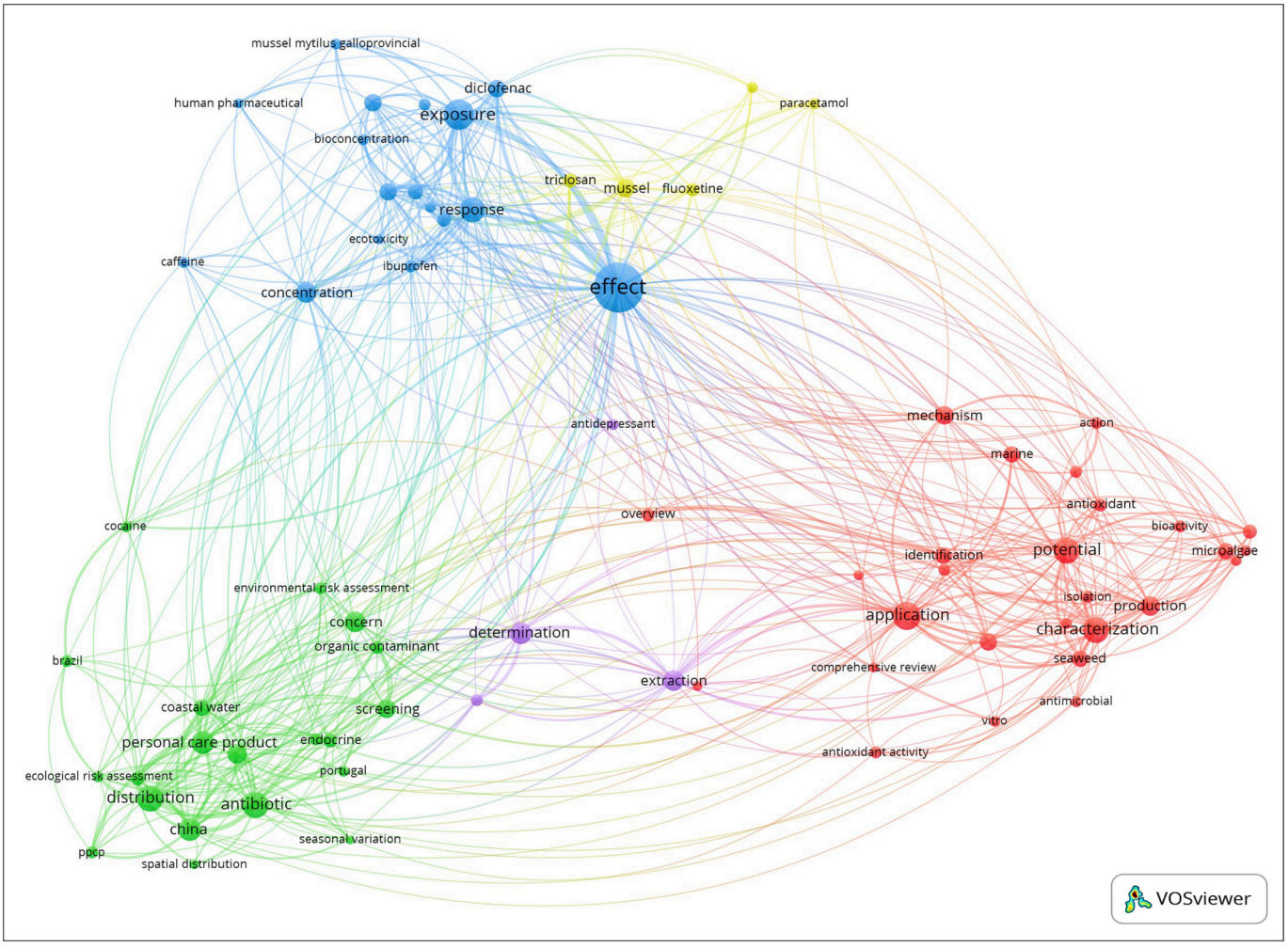


Fig. 3. The co-citation map displays scientific publications grouped into three major clusters according to keywords. The red cluster focuses on “application” and “characterization”, representing on pollution and ecotoxicological impacts. The blue cluster highlights “exposure” and “effects” in marine organisms, while the green cluster emphasizes “distribution” and “ecological risk assessments”, showcasing studies on the ecotoxicological consequences of pharmaceutical contaminations in marine and coastal environments.

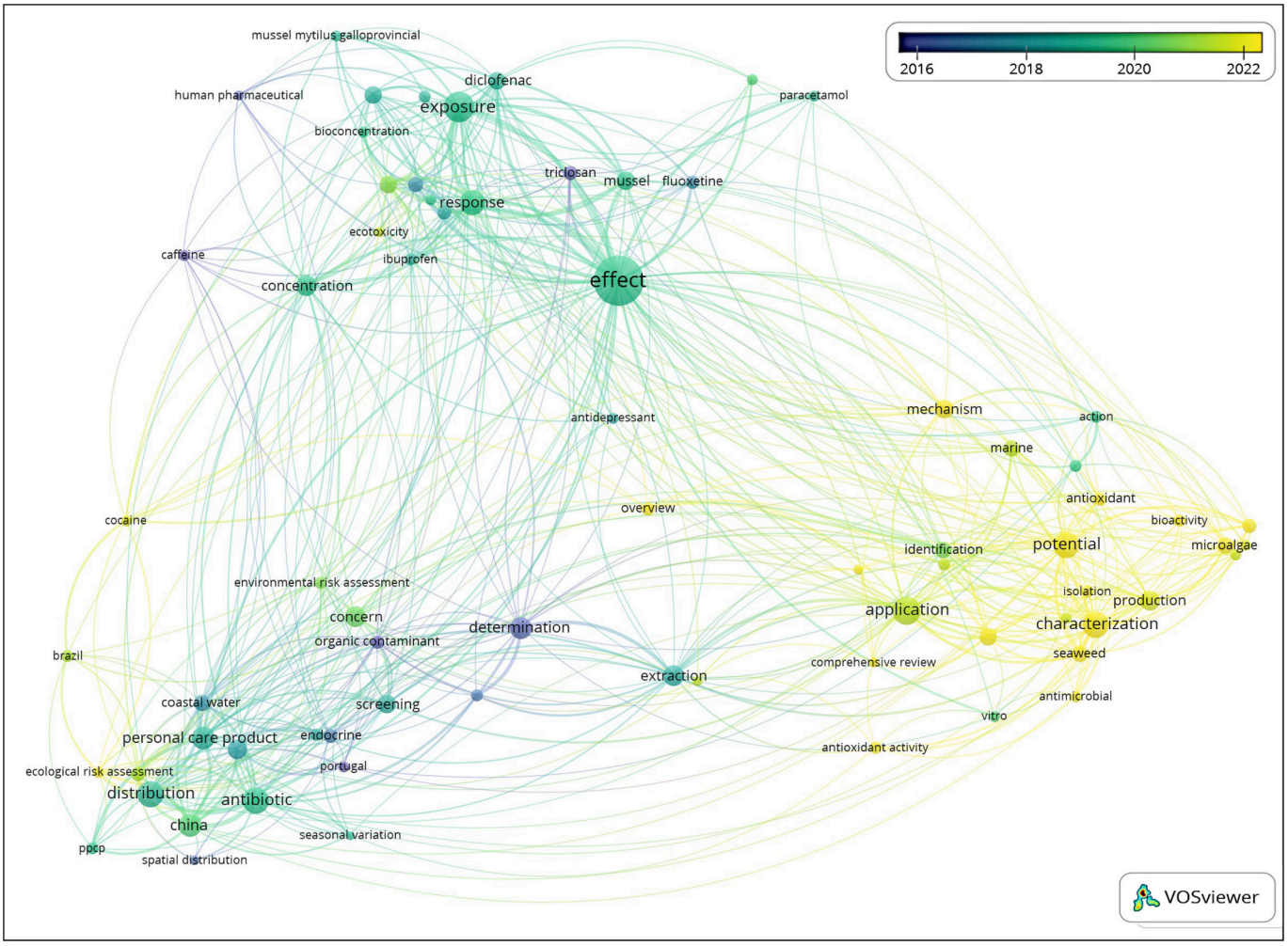


Fig. 4. A timeline map illustrates the progression of key research terms, highlighting changes in thematic focus within studies on pharmaceutical pollution. Recent research (2020–2025) has increasingly emphasized identification, characterization, and potential mechanisms, while earlier studies (2000–2018) mainly focused on determination, distribution, exposure and effects. Notably, timeline mapping and co-citation analyses provide valuable insights into research trends and conceptual relationship by revealing patterns of term usage, frequency, and evolution over time.

improper disposal of antibiotics from pharmaceutical wastewater treatment plants and hospital discharges has led to their accumulation in marine ecosystems (Zhang et al., 2019; Mahdavian et al., 2022). These compounds are not readily degradable in seawater over long periods and can therefore be ingested by marine organisms (González-Gaya et al., 2018; Seid-Mohammadi et al., 2019). The presence of antibiotics, along with their metabolites, inflicts significant harm on marine species and contributes to the proliferation of antibiotic-resistant bacteria in these environments (Hossain et al., 2022). Antibiotics enter coastal and marine ecosystems through various pathways (Fig. 3, Table 1), including waste from pharmaceutical industries, hospital effluents, and human excretions (Deo, 2014; Carvalho and Santos, 2016). Although antibiotics at low concentrations primarily target bacteria (Liu et al., 2018a, 2018b), they can also have adverse effects on non-target organisms (Table 2). This phenomenon raises concerns about potential chronic effects resulting from antibiotic-induced imbalances in natural microbial communities, which form complex food webs (Bornbusch et al., 2021).

Recent studies have highlighted the toxic effects of various antibiotics on physiological processes in marine organisms at increasing rates. For instance, β-lactam, a class of antibiotics that includes penicillin and cephalosporins, are among the most frequently used antibiotics (Elander, 2003; Lima et al., 2020). Generally, these antibiotics are thought to have limited negative impacts on non-target aquatic organisms that were not intended to be affected by human-generated compounds. However, they can disrupt cellular processes in marine organisms (Fabbri and Franzellitti, 2016; Teixeira and Granek, 2017). Some studies have detected penicillin, amoxicillin, and their metabolites in seawater (Kimiran-Erdem et al., 2007; Samarghandi et al., 2019). Exposure to these antibiotics may alter cellular membrane integrity in fish, leading to reduced immune responses and increased susceptibility to bacterial infections (Limbu et al., 2018).

The widely used antibiotic class known as fluoroquinolones, which includes ciprofloxacin and norfloxacin, is also commonly found in the marine environment (Van Doorslaer et al., 2014; Shokoohi et al., 2020). Several studies have shown that this drug acts as a gyrase inhibitor, affecting bacterial DNA replication and causing toxic effects on the DNA of both human and marine organisms. By binding to DNA gyrase and topoisomerase IV, ciprofloxacin and related fluoroquinolones prevent supercoiling and proper segregation of DNA during cell division. This inhibition results in double-strand DNA breaks, chromosomal fragmentation, and activation of stress response pathways. In marine organisms, such disruptions trigger oxidative stress, apoptosis, and impaired reproduction, ultimately compromising survival and ecosystem stability (Isidori et al., 2005; Laureti et al., 2013). Research has suggested that ciprofloxacin concentrations of 50 ng/L or higher can damage DNA in fish and mussels (Elizalde-Velázquez et al., 2022). Additionally, it leads to oxidative stress and a decrease in reproductive

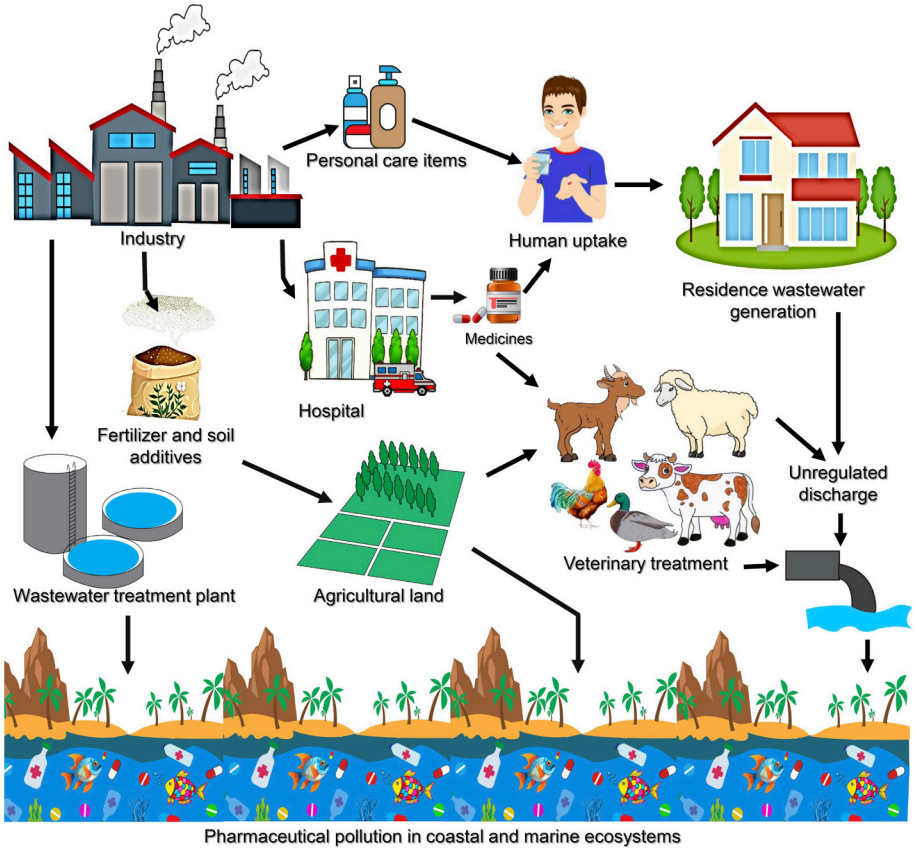


Fig. 5. Pharmaceuticals enter coastal and marine environments through various pathways, such as hospital discharges, effluents from wastewater treatment plants, and veterinary applications. This schematic illustrates the main routes through which these pharmaceutical compounds are released into marine environments.

Table 1
The origins and pathways of pharmaceutical contamination in coastal and marine environments involve multiple sources. Understanding these pathways is essential for identifying pollution hotspots and evaluating ecological risk measures to reduce the pharmaceutical contaminants in coastal and marine ecosystems.

Source Type	Primary exposure route	Pharmaceuticals	Effects on aquatic organisms	References
Municipal wastewater	Water ingestion, gill uptake	Antibiotics, pain relievers, antidepressants	Altered behavior, reduced fertility	(De Assis, 2021)
Hospital and healthcare	Bioaccumulation	Antibiotics, analgesics, hormones	Endocrine disruption, reproductive effects	(Puckowski et al., 2016)
Agricultural runoff	Runoff into water bodies	Antibiotics, veterinary drugs, herbicides	Aquatic organism mortality, growth inhibition	(Islam and Midya, 2023)
Industrial discharges	Industrial effluents	Various pharmaceuticals used in manufacturing	Organ damage, behavioral change	(Okoro et al., 2023)
Recreational activities	Direct release, skin Absorption	Sunscreen agents, analgesics	DNA damage, altered reproduction	(Pathak, 1982)
Aquatic food chain	Bioaccumulation in fish	Transfer from lower trophic levels	Biomagnification, impaired reproduction	(Griboff et al., 2018)
Microplastic interactions	Ingestion by aquatic organisms	Adsorption of pharmaceuticals on microplastics	Internal organ damage, reduced feeding	(Elgarahy et al., 2021)
Pharmaceutical manufacturing	Direct release, runoff	Residual pharmaceuticals and by-products	Genetic mutation, growth abnormalities	(Tijani et al., 2013)
Human Waste	Human urinary excretion, feces	Pain relievers, antidepressants, antimicrobials	Endocrine disruption, behavioral changes	(Vaudin et al., 2022)
Livestock and pet waste	Veterinary drug use	Antibiotics, antiparasitic, growth promoters	Aquatic organism mortality, antibiotic resistance	(Morley, 2009)
Residential areas	Companion animal waste	Pain relievers, antiparasitic, antibiotics	Altered aquatic ecosystems, fish mortality	(Bártíková et al., 2016)
Household waste	Disposal of expired drugs	Pharmaceuticals and veterinary medications	Bioaccumulation, organ dysfunction	(Karungamye et al., 2022)
Veterinary facilities	Veterinary aquatic therapies	Aquatic drugs and disinfectants	Aquatic organism toxicity, water quality impacts	(Kim et al., 2008)
Dairy farm operations	Dairy farm runoff	Veterinary drugs, hormones	Hormonal disruption, altered reproduction	(Havens et al., 2020)
Atmospheric deposition	Airborne pharmaceuticals	Precipitation, aerial deposition	Respiratory stress, organ dysfunction	(Fatima et al., 2023)
Disposal of unused medications	Improper disposal in household waste	Landfill leaching, surface runoff	Neurotoxicity, impaired immune function	(Pereira et al., 2015)

Table 2
Occurrence and accumulation of pharmaceutical compounds in coastal and marine organisms. Monitoring the types and concentrations of pharmaceutical compounds in aquatic organisms is essential for assessing ecological risks, understanding toxicological impacts, and evaluating potential threats to coastal and marine ecosystems.

Type of pharmaceuticals	Study region	Marine organisms	Name of species	Concentration (ng/g)	References
1. Antibiotics					
Amoxicillin	Malaysia	Croaker	Atlantic threadfin (*Pennahia anea*)	5.79	(Omar et al., 2019)
Azithromycin	Spain	Mussels	Mediterranean mussel (*Mytilus galloprovincialis*)	13.3	(Alvarez-Munoz et al., 2015)
	Southern France	Fish	Sole (*Solea solea*)	1	(Miossec et al., 2020)
	South Korea	Kelp	Sugar kelp (*Saccharina latissima*)	13.3	(Alvarez-Munoz et al., 2015)
			Tangleweed (*Laminaria digitata*)	1.3	
Cephalexin	Saudi Arabia	Barnacles	Lace algae (*Hydroclathrus clathratus*)	3.8	(Ali et al., 2018)
Chloramphenicol	Brazilian coasts	Mussel	Blue mussel (*Mytilus edulis*)	4	(Mello et al., 2022)
Clarithromycin	Southern France	Fish	Red mullet (*Mullus barbatus*)	1	(Miossec et al., 2020)
Dimetridazole	Europe	Bivalves	Pacific oyster (*Crassostrea gigas*)	8	(Álvarez-Muñoz et al., 2015)
Difloxacin	China	Bivalves	Dalian oyster (*Crassostera talienwhanensis*)	57	(Li et al., 2012)
Metronidazole	Saudi Arabia	macroalgae	Sea lettuce (*Ulva lactuca*)	5.9	(Ali et al., 2018)
Norfloxacin	South China Sea	Corals	Staghorn coral (*Acropora millepora*)	66	(Zhang et al., 2019)
	South China Sea	Corals	Elkhorn coral (*Acropora cervicornis*)	28	(Zhang et al., 2019)
Ofloxacin	USA	Mussels	Mediterranean mussel (*Mytilus galloprovincialis*)	18	(Dodder et al., 2014)
Ormetoprim	USA	Fish	Atlantic salmon (*Salmo salar*)	0.5	(Done and Halden, 2015)
Ronidazole	Spain	Bivalves	Pacific oyster (*Crassostrea gigas*)	2	(Alvarez-Munoz et al., 2015)
Roxithromycin	Spain	Clams	Rusty mussel (*Chamalea gallina*)	0.20	(Serra-Compte et al., 2017)
	Spain	Mussels	Mediterranean mussel (*Mytilus galloprovincialis*)	0.17	
	Netherland	Fish	European flounder (*Platichthys flesus*)	0.13	
Sulfamethoxazole	Europe	Bivalves	Queen scallop oyster (*Crassostrea gallina*)	13	(Alvarez-Munoz et al., 2015)
Sulfamethoxazole	North China	Fish	Javeline goby (*Acanthogobius hasta*)	10	(Liu et al., 2018b)
			Bartail flathead (*Platycephalus indicus*)	4.8	
			Tongue sole (*Cymoglossus robustus*)	5.4	
			Dotted gizzard shad (*Konosirus punctatus*)	22	
Sulfamethazine	South China Sea	Corals	Encrusting coral (*Favites abdita*)	7	(Chen et al., 2009; Zhang et al., 2019)
Sulfamethoxazole	Saudi Arabia	barnacles	Rough barnacle *(Balanus perforatus*)	13.1	(Ali et al., 2018)
Sulfadiazine	USA	Bivalves	Olympia oyster (*Ostrea lurida*)	0.70–0.78	(Granek et al., 2016)
Trimethoprim	Saudi Arabia	barnacles	Turban algae (*Turbinaria conoides*)	0.84–1.50	(Ali et al., 2018)
Tilmicosin	France	Mussel	Mediterranean mussel (*Mytilus galloprovincialis*)	0.4	(Serra-Compte et al., 2017)
Tylosin	Europe	Fish	Atlantic salmon (*Salmo salar*)	0.2	
Virginiamycin	USA	Fish	Atlantic salmon (*Salmo salar*)	5	(Done and Halden, 2015)
2. NSAIDs and analgesics					
Acetaminophen	Southern France	Fish	European hake (*Merluccius merluccius*)	1	(Miossec et al., 2020)
Diclofenac	Portugal	Fish	Golden mullet (*Liza aurata*)	36–171	(Álvarez-Muñoz et al., 2015)
Ibuprofen	Saudi Red Sea	Fish	Green hair algae (*Enteromorpha intestinalis*)	231	(Ali et al., 2018)
Ketoprofen	Brazilian coasts	Mussel	Blue mussel (*Mytilus edulis*)	12	(Mello et al., 2022)
Naproxen	Brazilian coasts	Bivalve	Carib pointed-venus (*Anomalocardia brasiliana*)	11	
Phenazone	Spain	Bivalve	Rusty mussel (*Chamalea gallina*)	13	(Alvarez-Munoz et al., 2015)
3. Antidepressants					
Amitriptyline	Saudi Red Sea	Fish	Golden snapper (*Lutjanus johni*)	18	(Ali et al., 2018)
Benztropine	USA	Fish	Pacific staghorn sculpin (*Leptocottus armatus*)	0.20	(Meador et al., 2016)
Carbamazepine	barnacles	Saudi Arabia	Common silver biddy (*Gerres oyena*)	5.5	(Ali et al., 2018)
Citalopram	Spain	Bivalves	Pacific oyster (*Crassostrea gigas*)	2	(Alvarez-Munoz et al., 2015)
Diazepam	Nigeria	Fish	Chinook salmon (*Oncorhynchus tshawytscha*)	0.25–0.39	(Meador et al., 2016)
Fluoxetine	Saudi Red Sea	Fish	Milk fish (*Chanos chanos*)	9	(Ali et al., 2018)
Lormetazepam	Italy	Bivalves	Mediterranean mussel (*Mytilus galloprovincialis*)	0.4–439.5	(Mezzelani et al., 2020)
Norfluoxetine	Portugal	Mussel	Mediterranean mussel (*Mytilus galloprovincialis*)	9–22	(Silva et al., 2017)
Ormetoprim	USA	Fish	Pacific staghorn sculpin (*Leptocottus armatus*)	160	(Meador et al., 2016)
Paroxetine	Italian coast	Mussel	Mediterranean mussel (*Mytilus galloprovincialis*)	50	(Mezzelani et al., 2020)
Primidone	Malaysia	Fish	Sea catfish (*Arius thalassinus*)	0.11–3.59	(Omar et al., 2019)
Sertraline	Spain	Mussel	Mediterranean mussel (*Mytilus galloprovincialis*)	1.5	(López-García et al., 2019)
Norsertraline	English coast	Oysters	Pacific oysters (*Crassostrea gigas*)	5–6	(Maskrey et al., 2021)
Venlafaxine	Spain	Bivalves	Golden mullet (*Liza aurata*)	2–3	(Alvarez-Munoz et al., 2015)
4. Anticancer					
Cyclophosphamide	Europe	Bivalves	Sea star (*Asterias rubens*)	687	(Queirós et al., 2021)
Cisplatin	Europe	Mussel	Blue mussel (*Mytilus edulis*)	250	
5-Fluorouracil	Spain	Mussel	Mediterranean mussel (*Mytilus galloprovincialis*)	10	(Gonçalves et al., 2022)
Doxorubicin	Europe	Mussel	Marine ragworm (*Nereis diversicolor*)	8.7–9.6	(Ribeiro et al., 2022)
Tamoxifen	Brazil	Oyster	Pacific oyster (*Magallana gigas*)	10–100	(Paiva et al., 2024)
5. Antihypertensives					
Atenolol	Spain	Algae	Water algae (*Desmodesmus subspicatus*)	11	(López-Serna et al., 2012).
	Belgium	Algae	Water algae (*Raphidocelis subcapitata*)	0.29	Cleuvers, 2005).
	Saudi Red Sea	Fish	Atlantic cod (*Gadus morhua*)	63	(Ali et al., 2018)
	Hong Kong	Crustaceans	Banana shrimp (*Meapenaeus ensis*)	21.1 6.10	(Ruan et al., 2020)
	Hong Kong		Green tiger prawn (*Parapenaeopsis tenella*)	3.48	

(*continued on next page*)

Table 2 (*continued*)

Type of pharmaceuticals	Study region	Marine organisms	Name of species	Concentration (ng/g)	References
	China		Red swimming crab (*Portunus sanguinolentus*)	18.0	
	China		Indian white shrimp (*Metapenaeus affinis*)	1.22	
	Europe	Bivalves	Pacific oyster (*Crassostrea gigas*)	18	(Alvarez-Munoz et al., 2015)
Propranolol	UK	Algae	Diatom (*Skeletonema pseudocostatum*)	0.11	Roberts and Thomas, 2006).
		Bacteria	Bioluminescent bacteria (*Aliivibrio fischeri*)	0.11	
		Mollusk	Mediterranean mussel (*Mytilus galloprovincialis*)	0.11	
Metoprolol	Spain	Bacteria	Bioluminescent bacteria (*Aliivibrio fischeri*)	8	
	China	Mollusk	Rusty clams (*Anadara ferruginea*)	2.21	(Ruan et al., 2020)
	Hong Kong	Fish	Flatfish (*Solea ovata*)	3.08	
	China	Crustaceans	Smashing mantis shrimp (*Harpiosquilla harpax*)	3.18	

capacity in marine organisms, such as ragworms (*Hediste diversicolor*) (Nogueira and Nunes, 2020).

Accumulating evidence indicates that aminoglycoside antibiotics, such as gentamicin and streptomycin, used to treat bacterial infections, are detectable in seawater (Hernández et al., 2019). Aminoglycoside antibiotics inhibit protein synthesis by binding to the bacterial ribosome, leading to mistranslation and premature termination of polypeptide synthesis. This leads to the accumulation of misfolded proteins and oxidative stress. In marine organisms, aminoglycosides also disrupt mitochondrial ribosomes, impairing energy metabolism, damaging cellular membranes, and ultimately inducing apoptosis and organ dysfunction across multiple tissues (Hermann, 2007; Barnhill et al., 2012). A study on fish exposed to gentamicin revealed nephrotoxicity, damaged kidneys, decreased filtration rates, and an electrolyte imbalance (Ranasinghe et al., 2023). Besides severe renal damage, other effects include developmental impairment and reduced fitness in fish larvae, which can influence their survival rates, especially in areas where water quality is already compromised (Udupa and Prakash, 2019).

Macrolides, such as erythromycin and clarithromycin, are another class of antibiotics detected in marine environments (Hirsch et al., 1999; Baranauskaite-Fedorova and Dvarioniene, 2022). These antibiotics block bacterial protein synthesis by binding to the ribosomal subunit (McCoy et al., 2011), but can also damage tissue architecture and inhibit metabolite concentrations in the tissues of marine bivalves (Lacaze et al., 2015; Zhang et al., 2024). A study on Pacific oysters (*Crassostrea gigas*) treated with erythromycin revealed that this drug severely damaged the digestive glands (Kijewska et al., 2023). Consequently, this response significantly reduced nutrient absorption by the digestive glands, thereby inhibiting the oyster growth. Due to the overall toxic effects, macrolide antibiotics in marine waters reduce reproductive fitness and affect entire populations of marine organisms (Wan et al., 2015; Kraemer et al., 2019).

Various antibiotics are found in surface water samples from East and Southeast Asia (Anh et al., 2021). Similarly, antibiotics have been detected in coastal and marine waters in the United States, particularly near sewage treatment plants and pharmaceutical industries (Na et al., 2011; Fang et al., 2012; Liu et al., 2018a, 2018b). A study in the coastal waters of Italy found amoxicillin, a penicillin antibiotic, at concentrations of 150 ng/L (El Ayari et al., 2024). This study also observed that exposure to similar concentrations of amoxicillin reduces reproductive success in sea urchins (*Paracentrotus lividus*) due to oxidative stress and disrupts normal cellular processes (El Ayari et al., 2024). Furthermore, in the South Yellow Sea in China, researchers detected trimethoprim, an antibiotic used to treat urinary tract infections (UTIs) in humans, at levels of 50 ng/L in coastal waters, causing developmental abnormalities in the larvae of marine crustaceans such as tiger prawn (*Penaeus monodon*) (Du et al., 2017; Zhang et al., 2023). High levels of antibiotic contamination have also been reported in coastal waters of various countries, including China, India, and South Korea (Yang et al., 2020a, 2020b; Anh et al., 2021). Concentrations of fluoroquinolone antibiotics, such as norfloxacin and ofloxacin, used to treat UTIs, were found at levels between 50 and 500 ng/L in the Bohai Sea in China. This concentration causes considerable alterations to fish gill tissues, resulting in respiratory impairment and disrupting osmoregulation and excretory functions (Du et al., 2019). Additionally, it leads to changes in liver microstructure that impair detoxification processes in fish. Furthermore, ciprofloxacin, a fluoroquinolone antibiotic, has been detected at concentrations of 250 ng/L in coastal waters near pharmaceutical manufacturing hubs (Bojarski et al., 2020).

Moreover, recent studies have examined the effects of antibiotics at environmentally relevant concentrations (>100 ng/L) in marine species (Carvalho and Santos, 2016). For instance, research investigating the effects of pharmaceuticals on marine species examined the toxicological consequences of sulfamethoxazole, a sulfonamide antibiotic used for various infections, on blue mussels (*Mytilus edulis*). It showed that a concentration of 100 ng/L significantly increases oxidative stress and DNA damage in the gills of mussels (Lacaze et al., 2015). Additionally, a study conducted in the Mediterranean Sea found that amoxicillin was present at a concentration of 12,640 ng/L, which caused growth inhibition, reproductive impairments, and alterations in several haemocytes in marine bivalves (*Mytilus galloprovincialis*) (Matozzo et al., 2016). Subsequently, antibiotics in marine environments can impair physiological functions in aquatic organisms and alter their normal behavior (Yang et al., 2020a, 2020b). Fluoroquinolone antibiotics, including ciprofloxacin, exhibit toxic effects and alter the swimming behavior of fish. Ciprofloxacin also affects the nervous system, leading to abnormalities in motor function and regular activity in teleost species (Nogueira et al., 2019). These physiological and behavioral changes can be more pronounced in fish and shellfish species, directly affecting their survival, increasing mortality, and creating imbalances in marine ecosystems (Medkova et al., 2022). Macrolides are another important class of antibiotic agents detected in seawater. Macrolide antibiotics, such as clarithromycin, significantly affect immune responses in marine species (Yang et al., 2020b). Specifically, mollusks exposed to clarithromycin exhibited impaired immune responses, leading to altered survival rates (Kijewska et al., 2023). A study conducted on the estuarine clams (*Ruditapes philippinarum*) found that exposure to amoxicillin, trimethoprim, and clarithromycin at a concentration of 1000 ng/L, whether individually or in combination, caused a significant decrease in immune function, including phagocytic activity, which led to reduced survival rates of clams (Nicolussi et al., 2022).

Antibiotic exposure can also indirectly affect marine ecosystems by altering microbial communities. Many marine organisms, including fish, shellfish, and invertebrates, depend on symbiotic relationships with beneficial bacteria for various physiological functions, such as digestion and nutrient absorption. Antibiotics, such as tetracycline, can disrupt these microbial communities, leading to imbalances in nutrient cycling, compromised protein synthesis, and decreased digestive efficiency (Xu et al., 2021; Wu et al., 2022). This antibiotic impairs the growth and reproduction of marine species, ultimately affecting their population dynamics and the health of their ecosystems. Other antibiotics, including sulfamethoxazole, also inhibit bacterial folic acid synthesis (Fernández-Villa et al., 2019). A scientific study demonstrated that

exposing mussels to sulfamethoxazole at concentrations of 50–150 ng/L induced oxidative stress and lipid peroxidation in gill tissues, resulting in adverse effects on respiration (Serra-Compte et al., 2019).

Although increasing evidence suggests that antibiotic pollution is toxic to marine life, there are still relatively few global safeguards to mitigate or prevent this contamination. Addressing this issue will require comprehensive strategies, including improved wastewater treatment, reduced antibiotic over-prescription, and enhanced public awareness.

3.2. Antihypertensives

Antihypertensive drugs are primarily used to treat high blood pressure or hypertension, a significant risk factor for cardiovascular diseases such as heart failure, myocardial infarction, stroke, angina pectoris, and kidney failure (Rosendorff et al., 2015; Laurent, 2017). These medications primarily target the cardiovascular and endocrine systems to control blood pressure and improve heart function (Bereda, 2021). Several groups of drugs used for antihypertensive treatment are available, with beta-blockers being one of the most prescribed classes (Mayor, 2006; Mahfoud et al., 2024). Beta-blockers selectively target the beta-adrenergic receptors in the heart, which regulate heart rate and contractile force (Ladage et al., 2013). They work by blocking the action of epinephrine on these receptors, leading to a slowed heart rate and reduced blood pressure (López-Sendó et al., 2004; Mann, 2017).

Beta-blockers are used in managing hypertension and related conditions, including heart failure, arrhythmias (irregular heart rates), and angina (chest pains). They are also prescribed to lower the risk of heart attacks in individuals with preexisting diagnoses of heart disease (Joseph et al., 2019). Common examples of beta-blockers used to treat such conditions include atenolol, metoprolol, and propranolol (Paravastu et al., 2009). While these drugs are effective in treating hypertension and other cardiovascular problems, they pose environmental threats due to their residues and metabolites, which are excreted and found in the environment, particularly in marine waters (Desbiolles et al., 2018; Branchet et al., 2021). Like many medications, beta-blockers are often discarded improperly, excreted in human waste, and released into the environment during pharmaceutical manufacturing. Beta-blockers exert toxicity in marine organisms by antagonizing β-adrenergic receptors, disrupting cardiovascular regulation, and metabolic homeostasis. In fish and mollusks, this leads to altered heart rate, impaired circulation, and reduced energy allocation. Such physiological stress cascades into reproductive failure, behavioral changes, and increased susceptibility to predation, threatening ecosystem balance (Ramil et al., 2010; Maszkowska et al., 2014). Atenolol, metoprolol, and propranolol are the most commonly detected beta-blockers in marine environments (Branchet et al., 2021). Although these medicines can effectively treat various health issues, their environmental impact is concerning, as many do not break down easily and can harm aquatic organisms even at low concentrations (Cleuvers, 2005; Kingsbury and Hartman, 2023).

Atenolol is a beta-adrenergic blocker that treats high blood pressure and angina, helps prevent heart attacks. It is one of the most prescribed beta-blockers worldwide and has been detected in several environmental studies (Küster et al., 2010; Ivantsova and Martyniuk, 2023). inhibits beta-1 adrenergic receptors in the heart, lowering heart rate and blood pressure (Smith et al., 2012). This compound is often found in aquatic environments, including rivers, lakes, and oceans, where it significantly impact on aquatic life (Fabbri and Franzellitti, 2016). A study in the Saudi Red Sea and Hong Kong has found atenolol at concentrations of 63 ng/L and 18 ng/L, respectively, causing observable changes in behavior, reproduction, and survival rates in marine fish and invertebrates (Ali et al., 2018; Ruan et al., 2020). For example, fathead minnows (*Pimephales promelas*) and Atlantic salmon (*Salmo salar*) exposed to atenolol exhibit impacts on growth, energy storage, and physiological responses. Additionally, atenolol disrupts biological pathways that regulate endocrine signaling and the handling of genetic material, affecting growth, reproduction, protein folding and sorting, and degradation, which leads to cellular stress and dysfunction. Physiological disturbances interrupt feeding and migration, and cause irregular reproductive cycles (Winter et al., 2008; Hampel et al., 2010). The bioaccumulation of atenolol in aquatic organisms poses a significant risk to biodiversity (Winter et al., 2008). The drug accumulates in the tissues of aquatic animals as they ingest contaminated water, posing a threat to their long-term ecological health.

Another common beta-blocker is metoprolol, which is used to treat hypertension, heart failure, and arrhythmias. This beta-blocker blocks the beta-1 adrenergic receptors in the heart, reducing heart rate and blood pressure similarly to atenolol (Bristow, 1997; Torp-Pedersen et al., 2005). It is widely prescribed for individuals who have suffered heart attacks or are at risk of heart disease. Despite its effectiveness in treating these conditions, various residues and metabolites of metoprolol have been detected in various aquatic habitats, potentially affecting marine species (Love et al., 2024). Metoprolol has been detected in aquatic environments and has been shown to cause developmental defects and behavioral issues in marine organisms (Godoy et al., 2015). A study has reported that metoprolol levels at concentrations of 20 ng/L cause toxicological effects such as elevated lysosomal destabilization rates in the digestive gland, growth retardation, immobilization, and abnormalities in marine species, including hard clams (*Mercenaria mercenaria*) and the American oysters (*Crassostrea virginica*) (Khan et al., 2018). Most of these effects can be attributed to the drug's impact on the endocrine systems of these animals, which are crucial for normal reproductive and developmental processes. Metoprolol also alters swimming behavior, making fish more vulnerable to predator attacks (Lorenzi et al., 2012). Changes to the structure and function of marine ecosystems can have far-reaching consequences for the survival and growth of marine species, especially at the zooplankton and top fish levels of the food chain, which are critical for maintaining balance in marine biomes. Similarly, the persistence of metoprolol in the environment can have long-term effects on marine flora and fauna, altering ecosystem health and reducing biodiversity (Love et al., 2024; Punginelli et al., 2024).

Propranolol, unlike atenolol and metoprolol, is a non-selective beta-blocker and thus can block both beta-1 and beta-2 adrenergic receptors (Hauck et al., 1994). This broad action contributes to propranolol's effectiveness across various conditions, but it also leads to more side effects. Like other beta-blockers, propranolol is excreted in urine and can enter aquatic environments through wastewater effluents (Capolupo et al., 2018). Several studies have detected varying concentrations of propranolol in aquatic environments worldwide. The concentration in the Yangtze estuary in China was 142 ng/L (Yang et al., 2011). Additionally, in the South Sea off the coast of South Korea, the concentration was recorded at 11.9 ng/L, while concentrations in the United Kingdom's estuaries were 56 ng/L (Thomas and Hilton, 2004; Kim et al., 2017; Capolupo et al., 2018). Propranolol in marine environments has been linked to behavioral and physiological effects in numerous marine species. An experimental study examined the impacts of propranolol on various marine species at different concentrations. Exposure to propranolol in mussels (*Mytilus galloprovincialis*), sea urchins (*Paracentrotus lividus*), and seabream (*Sparus aurata*) at concentrations of 500, 5000, and 50,000 ng/L showed that propranolol did not affect mussel gamete fertilization, but significantly reduced fertilization in sea urchins. However, exposure to propranolol caused morphological abnormalities in mussels and sea urchin embryos, particularly at higher concentrations (Capolupo et al., 2018). These findings highlight the potential risks of pharmaceutical contaminants, such as propranolol, to marine ecosystems. Propranolol also exhibits neurotoxic effects and inhibits the growth of Baltic Sea blue mussels (*Mytilus edulis trossulus*) (Ericson et al., 2010). Propranolol exposure can pose significant threats to these organisms, hindering their ability to swim, navigate their surroundings, and communicate specificity, potentially leading to reduced reproductive success and population decline. Like other beta-blockers,

propranolol persists in marine ecosystems, accumulating its effects over time and thereby exacerbating its impact on marine life.

Growing concerns are emerging regarding the concentrations of beta-blockers, such as atenolol, metoprolol, and propranolol, in marine environments and the associated threat to aquatic ecosystems. Additionally, a mixture of multiple beta-blockers causes morphological changes in the tissues of marine organisms. For example, metoprolol and propranolol mixtures induce nitrative stress, leading to altered tissue architecture in the American oysters (Fig. 6), and significantly affecting their physiological functions (Salinas and Rahman, 2025). While these drugs effectively treat high blood pressure and other cardiovascular conditions, they have adverse effects on marine life, leading to behavioral changes, impaired reproductive cycles, and long-term ecological damage. Addressing this issue will require developing new wastewater treatment technologies, implementing stricter regulations on pharmaceutical waste, and conducting ongoing research to understand the full extent of these drugs' impacts on the environment. Only through collaborative efforts can we tackle the problem of pharmaceutical pollution and protect our oceans and their inhabitants.

3.3. Analgesics and NSAIDs

Analgesics and non-steroidal anti-inflammatory drugs (NSAIDs) are the most common medications used to manage acute and chronic pain, as well as to reduce inflammation (Brooks, 1998; Vo et al., 2009). These pharmaceuticals also treat headaches, minor injuries, and severe conditions such as arthritis and post-surgical effects (Wehling, 2014; Gilron, 2016). Due to their widespread use, these drugs often enter seawater

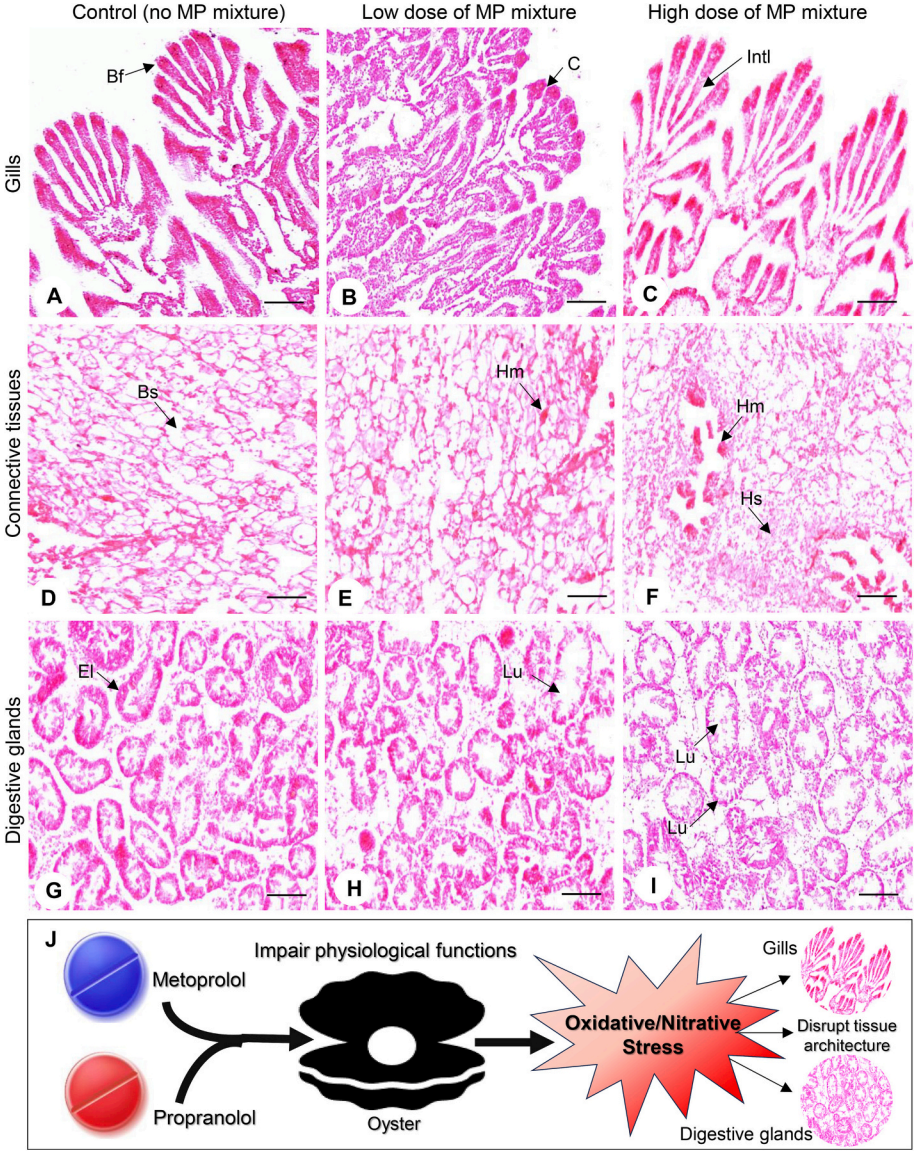


Fig. 6. Effects of metoprolol and propranolol mixtures on tissue architecture of American oysters. Representative photographs of gill (A-C), connective tissue (D—F), and digestive gland (G-I) sections (hematoxylin-eosin staining) collected from oysters exposed to control (A, D, G), low-dose (50 ng/L propranolol and 250 ng/L metoprolol) (B, E, H), and high-dose (250 ng/L propranolol and 650 ng/L metoprolol) (C, F, I) of metoprolol and propranolol mixtures for one week. Metoprolol and propranolol mixture experiments and collected tissue samples, histological and hematoxylin-eosin staining procedures were described previously by Salinas & Rahman (2024). Note: The UTRGV Institutional Animal Care and Use (IACUC) does not require protocols for aquatic invertebrates, including oysters. Arrows highlight structural changes damaged branchial filaments and widened inter-lamellar space in the gills (A-C), increased numbers of hemocytes in the connective tissues (E, F), and disrupted, enlarged epithelial tubules of the digestive glands (G-H). (J) Schematic illustrates how metoprolol-propranolol mixtures induce oxidative and nitrative stress, disrupt tissue architecture, and impair physiological functions in oysters. Branchial filament, blood sinus (bs), cilia (C), epithelial lining (El), hemocyte (Hm), intra-lamellar (Intl), lumen (Lu).

through excretion, wastewater effluent, and improper disposal by manufacturers and hospitals (Alsayadi and Arora, 2023). Once released into rivers and streams, these medications can persist and accumulate in the biosphere, posing significant threats to coastal and marine ecosystems. Analgesics and NSAIDs exert toxicity in marine organisms by inhibiting cyclooxygenase (COX) enzymes, thereby disrupting prostaglandin synthesis, which is essential for regulating inflammation, reproduction, osmoregulation, and homeostasis (Bethke et al., 2023). These disruptions trigger oxidative stress, impair cellular signaling, and damage vital tissues, including the liver, kidney, and gills. Prolonged exposure further alters immune responses and endocrine regulation, reducing growth, reproduction, and survival in marine ecosystems (Bonnefille et al., 2018). A broad range of analgesics and NSAIDs, including diclofenac, ibuprofen, paracetamol, morphine, codeine, and naproxen at varying concentrations, have been detected in nearly all types of aquatic ecosystems globally (Korkmaz et al., 2022; Szopińska et al., 2022).

In recent decades, the presence of NSAIDs and analgesics in seawater and their harmful effects on marine organisms have been investigated (Paíga et al., 2015; Mezzelani et al., 2016; Pusceddu et al., 2018; Feo et al., 2020; Świacka et al., 2020) Diclofenac, a widely studied analgesic in marine environments, is a non-steroidal anti-inflammatory drug used to treat mild to moderate pain in humans (Jafarinia et al., 2016). Research indicates that diclofenac can persist in aquatic environments ranging from 1 to 50 days and accumulate in the tissues of marine organisms (Schmitt-Jansen et al., 2007; Bonnefille et al., 2018; Batucan et al., 2022). For example, a study in the Baltic Sea reported diclofenac concentrations of 1.5 ng/L in seawater and 800 ng/L in fish tissues (Trombini et al., 2022). Diclofenac has also been found at concentrations of 2000 ng/L in regional coastal waters of South Korea (Näslund et al., 2020) and 1000 ng/L in European coastal waters, including the Mediterranean Sea (Desbiolles et al., 2018). Diclofenac exposure leads to oxidative stress and disrupts biochemical and physiological functions of marine invertebrates such as Mediterranean mussels (*Mytilus galloprovincialis*) (Arrigo et al., 2024). High population density and industrial activities have increased pollution in these regions. The toxic effects of diclofenac on aquatic animals are well documented, including damage to the liver, kidneys, and gills, which impair physiological functions in teleosts (Bonnefille et al., 2018; Maqbool et al., 2023). Moreover, exposure to diclofenac has been associated with liver toxicity in fish, characterized by alterations in enzyme activities and histopathological changes in liver tissues (Wolf, 2021). In the kidneys, diclofenac can cause tubular necrosis and glomerular damage (Ragab et al., 2022), thereby hindering the excretion of waste products in fish (Näslund et al., 2017). Gills, essential for respiration and ion exchange in fish, can sustain structural damage from diclofenac, reducing the efficiency of physiological processes (Näslund et al., 2017). Recent studies have documented the toxic effects of diclofenac on the blue mussel (*Mytilus trossulus*), resulting in histopathological changes, tissue damage, and altered immune responses. For example, diclofenac has been detected at concentrations of 4000 and 40,000 ng/L in the blue mussels (Świacka et al., 2020). This exposure led to a decrease in electrolyte balance, impaired water filtration, and induced oxidative stress in kidney tissues (Alessandretti et al., 2021; Shamsudin et al., 2022). The kidneys, vital for maintaining water balance, osmoregulation, and removing metabolic waste, are subject to severe physiological stress from morphological changes (Robson, 2014). The persistent presence of diclofenac in the marine environment poses a significant concern for the long-term health of fish populations, especially in areas with high levels of pharmaceutical pollution (Mezzelani et al., 2020). In addition to its physiological effects, diclofenac causes reproductive impairment in marine species (Godoi et al., 2024). It has been shown to affect endocrine systems and impair reproductive functions in teleost species such as the three-spined stickleback (*Gasterosteus aculeatus*) (Trombini et al., 2022). Moreover, environmentally relevant concentrations of diclofenac (100–1000 ng/L) alter mating behavior, reduce egg production, and cause abnormal embryonic development in brine shrimp (Singh and Pflugmacher, 2026). This reproductive impairment can ultimately reduce fish populations, disrupting marine food webs.

Another popular pain reliever, ibuprofen, has also been found in aquatic environments. A study in the Mediterranean Sea found ibuprofen concentrations at 10 ng/L in seawater and 5 ng/g in the tissues of marine mollusks (Mezzelani et al., 2018). Exposure to ibuprofen can induce oxidative stress, damaging cellular components such as lipids, proteins, and DNA in aquatic organisms (Ogueji et al., 2017; Mezzelani et al., 2020; Mikula et al., 2024). In fish, ibuprofen has been shown to cause tissue damage by altering osmoregulatory mechanisms that affect Na^+/K^+-ATPase activity in the gills and intestine of the Senegalese marine sole (*Solea senegalensis*) (Isidori et al., 2005). Furthermore, ibuprofen can disrupt the endocrine system, leading to reproductive and developmental abnormalities in marine mussels (*Mytilus galloprovincialis*) (Gonzalez-Rey and Bebianno, 2012; Gonzalez-Rey and Bebianno, 2014). Exposure to even the lowest concentration of ibuprofen (11,500 ng/L) downregulates many genes involved in skeletal development, aerobic respiration, and immune functions in inland silverside, *Menidia beryllina* (Jeffries et al., 2015). Other studies have shown that ibuprofen has been detected in seawater, causing oxidative stress, liver necrosis, and inhibiting cytochrome P450 enzyme activity in fish (Madesh et al., 2024). Additionally, it also disrupts normal metabolic processes and suppresses the immune system, causing disease and potentially inhibiting other physiological functions in marine teleost species (Madesh et al., 2024). In addition to ibuprofen, acetaminophen, a common analgesic, has also been found in seawater and has been shown to induce toxic effects on marine organisms (Antunes et al., 2013; González-Mira et al., 2018; Almeida and Nunes, 2019; Giménez and Nunes, 2019; Almeida et al., 2020). Studies revealed that exposure to acetaminophen at concentrations of 100–300 ng/L disrupts digestive glands and antioxidant defense systems in blue mussels and Pacific oysters (Bebianno et al., 2017; Piedade et al., 2020). Similarly, Almeida and Nunes (2019) demonstrated that exposure to acetaminophen (625–5000 ng/L) induces oxidative stress and alters antioxidant activity in the tissues of the sea snail (*Phorcus lineatus*). Notably, these bivalve mollusks filter large volumes of water to feed, suggesting increased exposure to pharmaceutical pollution. This disruption of their antioxidant defenses allows for the accumulation of reactive oxygen species (ROS) in cells and tissues. As a result, ROS damages to DNA structure and protein expression and induces lipid oxidation. This can impede growth, reproduction, and pathogen resistance, resulting in higher mortality rates in marine organisms (Park et al., 2018; Nunes, 2020; Duarte et al., 2023).

One of the most widely used analgesic compounds, naproxen, has been detected at concentrations of 300 ng/L in the Sea of Marmara (Korkmaz et al., 2022). Although the detectable concentrations of analgesics and NSAIDs in seawater are low, they have been shown to exert significant toxic effects on marine organisms. Naproxen is widely used to reduce fever and is also considered toxic to marine life (Suzuki et al., 2014). For example, investigations conducted in three-spine stickleback (*Gasterosteus aculeatus*) showed that naproxen (18, 70, 299, and 1232 μg/L for 27 days) affects kidney architecture and hepatic gene expression, and induces jaw lesions in fish in a manner similar to diclofenac (Näslund et al., 2020). Notably, molting is a crucial event in the crustacean growth, enabling them to increase in size and replace damaged cuticles. If this process is interrupted, offspring will likely experience slower development rates, increased predation, and a reduction in overall population within marine ecosystems. Furthermore, naproxen induces immunosuppression in fish and shellfish, making them more susceptible to infections and diminishing their ability to cope with environmental challenges (Gagné et al., 2006; Sehonova et al., 2017).

Morphine, a commonly used opioid painkiller and narcotic, has been detected in marine and coastal waters in Europe and Asia (Malev et al., 2020; Chen et al., 2021a, 2021b). Concentrations of morphine in seawater have been detected up to 6 ng/L, with tissues of marine

organisms such as fish and mollusks reaching concentrations up to 3000 ng/L (Zuccato et al., 2008). Morphine significantly affects heart rate, cardiac output, and respiratory frequency in winter flounder (*Pseudopleuronectes americanus*) seawater-acclimated rainbow trout (*Oncorhynchus mykiss*) (Newby et al., 2006). Additionally, in the kidneys, morphine can cause tubular necrosis and glomerular damage. Morphine can also disrupt the endocrine system, leading to central nervous system and renal abnormalities in tetrapods and teleost fishes (Nordgreen et al., 2009; Alvarez-Munoz et al., 2015; Ostrozka-Cieslik and Dolińska, 2020; Franco-Acevedo et al., 2021). Similar to morphine, codeine, an opioid analgesic medication, has been detected in marine environments at concentrations of 3.1 ng/L, including coastal waters in the United States and Europe (Newby et al., 2006; Zuccato et al., 2008; Lolic et al., 2015; Campos-Mañas et al., 2018; Franco-Acevedo et al., 2021). Studies have reported that codeine concentrations in seawater can reach 5 ng/L, while tissues of marine organisms, such as mussels and fish, can contain levels up to 2000 ng/L (Fontes et al., 2020; Madikizela and Ncube, 2022). Fish exposure to codeine alters enzymatic activities and causes histopathological changes in brain and liver tissues, increasing tubular necrosis and glomerular damage, and inducing neurotoxicity, leading to behavioral changes and impaired neurological and reproductive functions in aquatic organisms (Fent et al., 2006; Falfushynska et al., 2024).

One of the most critical issues associated with analgesics is the development of antibiotic-resistant bacteria. Analgesics in the environment exert selective pressure on bacterial communities, promoting the proliferation of resistant strains (Chaturvedi et al., 2021). These resistant bacteria can spread through water, sediments, and marine organisms, potentially transferring resistance genes to human pathogens. Analgesics and NSAIDs can also have direct toxic effects on marine life. Even at low concentrations, they may disrupt microbial communities and affect the growth, reproduction, and survival of various marine organisms (Tyumina et al., 2020; Rastogi et al., 2021; Batucan et al., 2022).

3.4. Antidepressant drugs

Antidepressant drugs are essential for treating major depressive disorder. These medications influence neurotransmitters such as serotonin, norepinephrine, and dopamine (El Mansari et al., 2010; Khushboo et al., 2022). The most commonly prescribed antidepressants include selective serotonin reuptake inhibitors (SSRIs) like fluoxetine, serotonin-norepinephrine reuptake inhibitors (SNRIs) like venlafaxine, tricyclic antidepressants (TCAs), and monoamine oxidase inhibitors (MAOIs) (Papakostas et al., 2007). SSRIs and SNRIs are generally recommended as first-line treatments due to their effectiveness and manageable side effects. In contrast, TCAs and MAOIs are typically reserved for more challenging cases, given their more pronounced adverse effects (Melaragno, 2021). Although antidepressants are effective, they have well-documented side effects such as weight gain, sexual dysfunction, and sleep disturbances (Friedman et al., 2004; Bockting et al., 2015; Cleare et al., 2015; Gould et al., 2021; Oliva et al., 2021). The widespread use of pharmaceuticals, including antidepressants, has raised concerns regarding their potential toxicity to various forms of marine life.

Antidepressants like fluoxetine, a commonly used SSRI for depression and anxiety (Silva et al., 2015), modify neurotransmitter activity in the central nervous system (CNS) by acting on serotonin pathways; however, they also appear to alter physiological functions in both tetrapods and teleost species (Sehonova et al., 2017; Sehonova et al., 2018). Additionally, exposure to fluoxetine inhibits spawning in bivalve mollusks (e.g., mussels) by increasing serotonin levels and disrupting normal reproductive processes, thereby lowering offspring survival rates (Lo, 2020; Maulvault et al., 2021). Antidepressants exert toxicity in marine organisms by altering serotonin reuptake, leading to disrupted neurotransmission, abnormal behavior, and impaired predator avoidance. Tricyclic antidepressants (TCAs) and serotonin–norepinephrine reuptake inhibitors (SNRIs) further disturb endocrine regulation, particularly thyroid hormone metabolism, causing growth and developmental abnormalities (Schmieg et al., 2022). These disruptions impair reproduction, stress responses, and survival, creating cascading ecological consequences in marine ecosystems (Słoczyńska et al., 2023). Amitriptyline exposure has been shown to alter stress response mechanisms, impacting fish survival when faced with predator threats (Sehonova et al., 2018).

In addition to TCAs, SNRIs like venlafaxine can cause fish to swim chaotically, hindering their ability to escape predation and find food (Brodin et al., 2014). Research has detected a variety of antidepressants in seawater globally, from the United States and Canada to China and the United Kingdom (Gaw et al., 2014). For instance, several SSRIs (e.g., fluoxetine, sertraline, and venlafaxine) were measured in California's coastal waters at concentrations ranging from ng/L to μg/L (Martínez et al., 2014). A similar finding was reported for coastal waters in the UK, where fluoxetine levels reached up to 100 ng/L in some areas (Fernandes et al., 2020). Wastewater treatment plants in Canada have been identified as significant sources of antidepressant contamination. A study of effluents from these plants revealed that fluoxetine and its metabolite, norfluoxetine, were among the most commonly detected contaminants, with concentrations ranging from 10 to 100 ng/L (Metcalfe et al., 2010). These effluents eventually enter the sea, posing risks to marine life. For example, a study examined the effects of fluoxetine on bivalve mollusks (e.g., Mediterranean mussels) and found that exposure at 50 ng/L altered gene expression related to stress and neural function (Silva et al., 2016). Even lower levels, such as 20 ng/L of sertraline, were shown to change the behavior of European sea bass (*Dicentrarchus labrax*), affecting aggression and social interactions (Costa et al., 2021). Another study found that these concentrations could lead to developmental abnormalities in sea urchin (*Strongylocentrotus purpuratus*) embryos, negatively impacting their growth and survival (Martino et al., 2022). Beyond effects on reproduction and development, antidepressant drugs also influence the behavior and physiological traits of marine animals (Estevez-Calvar et al., 2017; Sehonova et al., 2017). For instance, fluoxetine has been shown to reduce anti-predator responses in crustaceans (Andrésen, 2019). Such changes could create cascading effects throughout the marine food web, altering predator-prey dynamics. Antidepressants have also been demonstrated to impact locomotion and feeding behavior in mollusks (Estevez-Calvar et al., 2017; Yamindago et al., 2021); for example, exposure to fluoxetine reduced the mobility and feeding rates of various marine snails (*Chlorostoma funebralis, Nucella ostrina, Urosalpinx cinerea, Tegula fasciatus, and Lithopoma americanum*), potentially impairing their growth and reproductive efficiency (Fong and Molnar, 2013).

The most frequently detected class of antidepressants in seawater is SSRIs, including fluoxetine, sertraline, and citalopram (Vasskog et al., 2008). SNRIs, such as venlafaxine and duloxetine, are commonly detected in marine organisms (Fernandes et al., 2022). For instance, venlafaxine was detected in seawater at concentrations of up to 300 ng/L; such levels have been shown to disrupt circadian rhythms in fish, leading to a loss of coordination between sleep-wake cycles (Maulvault et al., 2018; Thompson and Vijayan, 2022).

Other antidepressants are detected less frequently compared to SSRIs and SNRIs, such as amitriptyline or nortriptyline; however, they still present significant risks (Rosenzweig-Lipson et al., 2007). Reports of antidepressant detection in coastal and marine environments span multiple regions. In the Bohai Sea, South China coast, and estuarine environments, numerous studies have reported fluoxetine concentrations ranging from 10 to 200 ng/L, along with other antidepressants, such as sertraline and paroxetine (Medkova et al., 2022). These levels have been shown to disrupt the endocrine systems of marine organisms, leading to hormone dysregulation and impaired reproduction (Moreira et al., 2022). In the Baltic Sea, analytical research has revealed the presence of pharmaceuticals, including some antidepressants, in sediment and water samples (Borecka et al., 2015). The global ubiquity of

these pharmaceuticals in seawater underscores the importance of international efforts to reduce their environmental impact. By improving wastewater treatment, raising public awareness, and continuing research into these patterns, we can help preserve the health and diversity of marine ecosystems.

3.5. Anticancer drugs

Anticancer drugs, also known as chemotherapeutic agents, are chemicals used to treat cancer by destroying or inhibiting the proliferation of malignant cells. These drugs can act in various ways, such as disrupting cancer cell DNA, halting cell division, and blocking proteins vital to tumor growth (Janssen and Medema, 2011; Sa and Das, 2008). The most common types of anticancer drugs are alkylating agents, antimetabolites, and targeted therapies, which operate through different mechanisms in cancer cell biology (Espinosa et al., 2003). While these drugs are effective, a common side effect is nausea and alopecia due to their impact on both cancerous and healthy cells (Aggarwal et al., 2021; Anand et al., 2023).

Anticancer drugs and their metabolites have become significant environmental pollutants following their administration in cancer therapy and subsequent release into waterways (Isidori et al., 2005; Booker et al., 2014; Nassour et al., 2021; Yadav et al., 2021). Anticancer pharmaceuticals and personal care products enter marine ecosystems through several pathways, including pharmaceutical manufacturing, hospital wastewater, and human excretion (Wang et al., 2021; Narayanan et al., 2022). Once in the marine environment, these compounds are likely to persist and accumulate over time, posing a significant threat to aquatic organisms. Multiple lines of evidence indicate that anticancer drugs are present in seawater and have detrimental effects on aquatic ecosystems (Gupta et al., 2013; Wang et al., 2021). We critically summarize a variety of anticancer drugs, highlighting their toxicological impacts on marine animal organs worldwide and their detection in seawater from several countries. Our discussion is based on recently published research papers that have identified these drugs in marine ecosystems.

Anticancer drugs include alkylating agents, antimetabolites, anthracyclines, alkaloids, and platinum-based drugs (Pellacani and Eleftheriou, 2020). Each category possesses unique cytotoxic properties that target dividing cells yet remain toxic to non-target organisms in the environment (Araújo et al., 2019; Raj et al., 2021). Cyclophosphamide and ifosfamide are representative examples of alkylating agents widely utilized in cancer treatment (Lutterbeck et al., 2015). Alkylating agents act on DNA by adding alkyl groups, leading to DNA cross-linking and inhibiting cell replication (Drabløs et al., 2004). Cyclophosphamide and its metabolite, ifosfamide, have been detected in seawater from various regions worldwide, including the United States and Europe, with cyclophosphamide concentrations reaching 2.5 ng/L along the Atlantic coast of the United States (Li et al., 2015; Mukherjee et al., 2021). Notably, alkylating compounds increase DNA damage in the liver, kidney, and gills of teleost fishes (Kienzler et al., 2013). For example, the administration of these drugs has been shown to induce liver toxicity in Blackbelly rock (*Helicolenus dactylopterus*) and European conger (*Conger conger*), evidenced by histopathological features like hepatocyte degeneration and necrosis (Mukherjee et al., 2021). As the primary metabolic hub for detoxifying foreign agents, the liver accumulates these toxicants over time, leading to diminished metabolic adaptive capabilities and long-term organ dysfunction (Della Torre et al., 2010; Hastings et al., 2020).

Antimetabolite anticancer drugs, such as methotrexate and 5-fluorouracil, mimic natural substrates involved in DNA or RNA synthesis, thereby disrupting nucleic acid production (Hatse et al., 1999; Sarder et al., 2015). Methotrexate, in particular, is a well-known anticancer agent commonly used in the treatment of leukemias and other cancers, and has been detected at concentrations of 1.5 ng/L in European coastal waters near industrialized or urban areas (Araújo et al., 2019). Current findings link methotrexate exposure to impaired reproductive functions, growth inhibition, and immunosuppression in marine mollusks, such as Manila clams (*Ruditapes philippinarum*) and Pacific oysters (*Crassostrea gigas*) (Silvestre and Tosti, 2009; Queirós et al., 2024). Histological and biochemical assessments reveal that tissues of marine mussels (e.g., *Mytilus galloprovincialis*) become inflamed, necrotic, and fibrous due to the presence of anticancer drugs (Fernandes et al., 2020; Gonçalves and Bebianno, 2023). Additionally, 5-fluorouracil exhibits immunotoxic effects, altering antioxidant enzyme activities in marine mussels, thereby increasing susceptibility to infections and diseases (Gonçalves et al., 2022).

Doxorubicin and daunorubicin are anthracyclines that act as potent anticancer agents by inhibiting topoisomerase II, an essential enzyme for DNA replication and repair (Hande, 2008; Kizek et al., 2012; Shandilya et al., 2021). Doxorubicin has been detected at 1.2 ng/L in the coastal waters of several countries, including the United States, Japan, and Brazil (Richardson and Kimura, 2016). In marine species, such as the white shrimp (*Litopenaeus setiferus*) and the purple sea urchin (*Paracentrotus lividus*), exposure to doxorubicin has been shown to induce cardiotoxicity, characterized by myocardial degeneration, arrhythmia, and heart failure (Ribeir et al., 2022). This exposure leads to oxidative stress, inflammation, and cell death in cardiac tissues, contributing to induced cardiac failure and decreased survival rates in marine organisms (Songbo et al., 2019; Rawat et al., 2021). Doxorubicin-mediated cardiotoxicity is primarily facilitated by reactive oxygen species (ROS) and the overall suppression of mitochondrial function, resulting in a decrease in the energetic sources available to cardiac cells (Rashid et al., 2013; Pang et al., 2024).

Plant alkaloids, such as vincristine and vinblastine, inhibit cell division by preventing microtubule formation. These anticancer drugs are commonly applied as chemotherapeutic agents for various tumors (Martino et al., 2018; Zhang and Kanakkanthara, 2020). Vincristine levels have been detected at 5 ng/L in seawater in India, mainly near sites with heavily pharmaceutical discharge (Zhang et al., 2013). Vincristine causes a spectrum of neurotoxic effects, including loss of motor coordination, abnormal behavior, and reduced reproductive success in marine invertebrates (e.g., sea urchin, *Paracentrotus lividus*) and teleost species (e.g., common clownfish, *Amphiprion ocellaris*) (Zare et al., 2022). This drug inhibits neuronal electrical activity, in part, by disrupting microtubule dynamics required for axonal transport and neurotransmitter release (Merheb et al., 2022).

Platinum-based drugs, including cisplatin and carboplatin, are widely used in chemotherapy because they form DNA cross-links, suppressing DNA synthesis (Ahmad, 2010). These drugs have also been detected in the seawater of several regions across Europe and North America (Queirós et al., 2021). The concentration of cisplatin in coastal waters has been reported to reach 1.8 ng/L in the United Kingdom (Turner and Mascorda, 2015). Cisplatin is known for its nephrotoxic effects, leading to damage in human kidneys (Farooqui et al., 2017; Hassan et al., 2014). Similar nephrotoxic effects have been observed in marine organisms Exposure to cisplatin (100 ng/L) has been shown to induce changes in antioxidant capacity, oxidative stress in target organs (e.g., gills and digestive glands), and DNA damage in hemocytes in blue mussel (*Mytilus galloprovincialis*) (Trombini et al., 2022), posing a risk to non-target marine organisms.

Numerous substances widely used in anticancer therapy, such as doxorubicin, cisplatin, and methotrexate, increase oxidative stress, damaging cells and tissues (Ozben, 2007). Chronic inflammation resulting from oxidative stress, impaired immune responses, and heightened susceptibility to diseases can lead to population declines in marine organisms (Regoli and Giuliani, 2014; Coates and Söderhäll, 2021). A study conducted along the Atlantic coast in the USA detected cyclophosphamide and ifosfamide at concentrations ranging from 0.1 to 2.5 ng/L. In comparison, similar studies in Europe reported doxorubicin concentrations in coastal waters of up to 1.2 ng/L (Regoli and Giuliani, 2014; Mukherjee et al., 2021). In Asia, particularly India, vincristine and

vinblastine were detected at concentrations of around 5 ng/L near pharmaceutical manufacturing plants (Mohinudeen et al., 2019). While these concentrations may seem low compared to many other pollutants entering aquatic ecosystems, they are deemed sufficient to induce toxic effects in marine organisms due to their bioactive properties.

Recent studies have also highlighted the potential bioaccumulation of anticancer drugs within marine food webs. Fish and shellfish can accumulate these drugs in their tissues at levels exceeding those in the surrounding water. This bioaccumulation poses significant risks to the marine ecosystem and human health, as many people consume fish and shellfish daily (Zenker et al., 2014; Martínez-Morcillo et al., 2020; Madikizela and Ncube, 2022). For instance, the common octopus (*Octopus vulgaris*) and the Atlantic mackerel (*Scomber scombrus*) were found to accumulate high concentrations of anticancer drugs, presenting potential food safety concerns (Gómez-Regalado et al., 2022). The toxicity of anticancer drugs could also negatively impact the marine environment through direct effects on predator-prey relationships, reproductive behaviors, and community dynamics (Yan et al., 2017; Kareva et al., 2021; Tan, 2023). For example, the harmful effects of methotrexate and 5-fluorouracil on the genotoxicity of Hong Kong oysters (*Crassostrea hongkongensis*) (Cai et al., 2018) and benthic marine amphipods (*Ampelisca brevicornis*) (Moreira et al., 2016) have been reported. As a result, these substances inhibit gametogenesis, reducing egg output and diminishing fertility (Nassour et al., 2021). This could trigger a cascade effect within marine ecosystems, decreasing population sizes or altering community structures across different trophic levels.

Furthermore, mixing various anticancer drugs in water may result in additive or synergistic toxicity. In marine environments, animals often encounter a combination of pharmaceutical contaminants, which may interact in complex ways to enhance toxicity (Heath et al., 2016). For instance, simultaneous exposure to bleomycin and vincristine, leads to increased toxicity in both marine algae (*Phaeodactylum tricornutum*) and brine shrimp (*Artemia franciscana*). Bleomycin is classified as highly toxic, while vincristine is regarded as moderately toxic, but together with their toxicity is enhanced (Jureczko and Przystaś, 2024). These interactions underscore the need for comprehensive risk assessments that treat pharmaceutical pollutants as mixtures and consider how combined environmental chemicals can impair growth, development, and reproductive functions in marine organisms.

The global distribution of anticancer drugs in seawater is due to their widespread use as pharmaceuticals in modern medicine. In North America, the United States has significant pharmaceutical consumption within its healthcare system (Robinson et al., 2007). Similarly, anticancer drugs have been identified in the coastal waters of several European countries, including Germany, France, and the United Kingdom (Booker et al., 2014). With large populations and extensive pharmaceutical manufacturing sectors, India and China contribute significantly to the influx of pharmaceutical pollutants into the marine environment (Rehman et al., 2015; He et al., 2016; Chaturvedi et al., 2021). Proper management of anticancer drugs, metabolites, and residues released into marine waters is crucial for safeguarding marine organisms.

4. Analytical methods used to detect or identify pharmaceutical contaminants in marine water

Detecting pharmaceuticals in marine water is difficult because these compounds are typically present at trace levels (nanograms per liter or lower) and seawater is a complex, highly saline matrix. To overcome this, scientists combine sample enrichment, chromatographic separation, and sensitive detection.

(i) Sample preparation and preconcentration: The most common approach is solid-phase extraction (SPE), where large volumes of seawater are passed through cartridges packed with polymeric or mixed-mode sorbents (such as Oasis HLB) that retain pharmaceuticals. These are later eluted with solvents, producing concentrated extracts suitable for analysis. In seawater, matrix effects caused by high salt concentrations are corrected using salt-tolerant sorbents, matrix-matched calibration, and isotope-dilution standards (Gros et al., 2012). Other extraction techniques include solid-phase microextraction (SPME) and stir-bar sportive extraction (SBSE), which are solvent-free and particularly suitable for hydrophobic drugs (Togola and Budzinski, 2008). QuEChERS (Quick, Easy, Cheap, Effective, Rugged, and Safe), first developed for pesticide analysis, has also been adapted for use in pharmaceuticals and seawater monitoring (Chen et al., 2021a, 2021b).

(ii) Chromatography and mass spectrometry: The gold-standard method for detection is liquid chromatography–tandem mass spectrometry (LC-MS/MS), usually operated in multiple-reaction monitoring (MRM) mode, which achieves very low detection limits suitable for coastal and open-ocean studies (Moreno-González et al., 2015). For broader chemical coverage, high-resolution mass spectrometry (HRMS) such as Orbitrap or TOF is increasingly used for suspect screening (checking against pharmaceutical lists) and non-target screening (discovering unknown compounds). Best practices now recommend standardized confidence levels (Levels 1–5) and transparent reporting of exact mass, retention time, and spectra (Schymanski et al., 2015). While less common, gas chromatography–mass spectrometry (GC–MS) is useful for volatile or derivatized pharmaceuticals (Nagai et al., 2018). For highly ionic drugs, capillary electrophoresis–MS (CE-MS) offers an alternative separation method.

(iii) Passive and integrative sampling: Grab samples only provide snapshots, so passive samplers like the Polar Organic Chemical Integrative Sampler (POCIS) are widely used. POCIS accumulates hydrophilic pharmaceuticals over days to weeks, giving time-weighted averages that capture episodic discharges (e.g., hospital or sewage treatment plant pulses). Field calibration with performance reference compounds improves accuracy (Martínez-Álvarez et al., 2022),

(iv) Effect-directed analysis: When chemical mixtures are complex, effect-directed analysis (EDA) links biological effects with specific compounds. Extracts are fractionated, bioassays test toxicity, and HRMS identifies candidate contaminants. This approach helps prioritize unknowns for further study (Alvarez-Mora et al., 2025).

(v) Integrated workflows and trends: Modern monitoring increasingly combines targeted LC-MS/MS, suspect lists, and non-target discovery within a single HRMS workflow. Data-independent acquisition (DIA) allows retrospective mining when new contaminants are identified (Kiefer et al., 2021). Researchers also recommend harmonized reporting, open spectral libraries, and retention-time indices to improve cross-study comparability. In parallel, biosensors and immunoassays are being developed as low-cost, rapid screening tools, though they still lack the breadth and selectivity of LC-MS/MS (Nichols and Geddes, 2021).

5. Comparative analysis and mechanistic summary

Although each pharmaceutical class exerts toxicity through distinct pharmacological pathways, several converging mechanisms are evident in marine organisms. Oxidative stress emerges as a common pathway across antibiotics, NSAIDs, antidepressants, anticancer drugs, and antihypertensives, often leading to lipid peroxidation, DNA damage, and impaired antioxidant defenses. Endocrine disruption is particularly prominent for antidepressants (e.g., serotonin and thyroid hormone pathways) and NSAIDs (reproductive impairment), while neurotoxicity is most evident in antidepressants and opioids such as morphine and codeine. Cytotoxicity and genotoxicity are hallmarks of anticancer drugs, which, despite being less frequently detected, pose disproportionally high ecological risks even at ng/L levels due to their strong

bioactivity. In contrast, antibiotics, while widespread, primarily exert selective pressure on microbial communities and symbionts, indirectly disrupting host physiology and ecosystem balance.

From a comparative perspective, anticancer drugs and antidepressants appear to be the most potent disruptors due to their strong cellular activity at low concentrations and their capacity to alter reproduction, behavior, and survival. NSAIDs and antihypertensives, although less cytotoxic, are more frequently detected and thus present higher risks of chronic, long-term exposure. Overall, these findings suggest that pharmaceutical pollution in marine ecosystems is not only widespread but also mechanistically multifaceted, with overlapping pathways that could produce additive or synergistic effects when organisms are exposed to drug mixtures.

6. Key challenges and innovative strategies

6.1. Key challenges

Pharmaceutical pollution in marine ecosystems cannot be addressed without recognizing the key challenges that hinder progress. These obstacles highlight critical scientific, regulatory, and social gaps that aggravate contamination. Understanding such barriers is essential for designing effective mitigation strategies. The major challenges associated with this issue are outlined below:

(i) Incomplete wastewater treatment: Conventional wastewater treatment plants (WWTPs) are not optimized to remove pharmaceutical residues. In many developing countries, untreated or partially treated wastewater is discharged directly into coastal waters, significantly elevating pollution loads.
(ii) Persistence and diversity of pharmaceuticals: Many drugs are chemically stable and resistant to degradation, as they are designed to remain bioactive. The presence of complex mixtures of pharmaceuticals, often with synergistic or antagonistic interactions, complicates ecological risk assessment and removal strategies.
(iii) Insufficient monitoring and detection: Although analytical tools are advancing, systematic monitoring in marine environments remains limited. Large data gaps, particularly in low- and middle-income countries, limit the global understanding of contamination levels, toxic effects, and long-term ecological consequences.
(iv) Regulatory and policy limitations: Few countries have established environmental quality standards specifically for pharmaceuticals. The absence of harmonized international policies and limited collaboration among health, industry, and environmental agencies weaken coordinated efforts to address transboundary marine pollution.
(v) Bioaccumulation and ecological complexity: Pharmaceuticals can bioaccumulate in marine organisms and move up the food chain, potentially threatening ecosystem balance and human health. Sublethal effects, such as altered reproduction, impaired growth, or behavioral changes, make ecological risks harder to quantify and predict.
(vi) Public awareness and disposal practices: Improper disposal of unused medicines, lack of take-back programs, and limited public awareness contribute to continuous contamination. Overprescription and unregulated pharmaceutical sales in some regions further intensify the problem.

6.2. Innovative strategies

To address the growing challenge of pharmaceutical pollution in marine environments, several innovative strategies have been proposed that can be implemented in the near term. These approaches focus on minimizing the release of pharmaceuticals, improving removal technologies, and promoting sustainable practices across the pharmaceutical lifecycle (Shree et al., 2023). Below, we highlight key strategies that have already been recognized as promising and actionable solutions to reduce pharmaceutical contamination.

(i) Advancement of wastewater treatment technologies: Improving the efficiency of current treatment methods is a practical strategy to minimize pharmaceutical release into the environment (Sivasuriyan et al., 2025; Lavanya and Namasivayam, 2026). Activated sludge processes, membrane bioreactors (MBRs), and advanced oxidation processes (AOPs) are already being implemented with encouraging results. For instance, a study comparing conventional activated sludge (CAS) with MBR systems found that pharmaceuticals, such as carbamazepine, were poorly removed in CAS (20–40%), whereas MBR processes achieved much higher elimination rates (80–90%) (Radjenović et al., 2008). Additionally, combining emerging technologies such as nanofiltration, reverse osmosis, and bio-electrochemical systems offers practical potential for more effective elimination of pharmaceutical residues (Petrović et al., 2008). While these strategies are promising, they can be further enhanced by integrating conventional methods with advanced approaches (e.g., combining activated sludge with advanced oxidation processes or coupling bioaugmentation with membrane systems). Such hybrid strategies may enhance efficiency and cost-effectiveness in real-world wastewater treatment plants.
(ii) Bioaugmentation and bioremediation: The use of microorganisms and plants to degrade pollutants provides an environmentally friendly and sustainable strategy. Research has demonstrated that specific microbial consortia and phytoremediation approaches can effectively degrade even the most persistent molecules. This method not only reduces pharmaceutical residues but also minimizes harmful by-products, making it a promising option for integration with wastewater treatment and environmental restoration efforts.
(iii) Public awareness and education: Promoting proper disposal practices through take-back programs and community-based initiatives is an immediate and low-cost strategy to reduce the entry of unused medications into aquatic systems. Public education campaigns can encourage households to return expired or unused drugs rather than discarding them improperly, significantly decreasing the pharmaceutical load entering wastewater systems and eventually marine environments.
(iv) Strengthened regulation and governance: Implementing stricter pharmaceutical waste regulations, establishing environmental quality standards, and considering extended producer responsibility programs are actionable strategies that can mitigate pollution in the near term. By holding pharmaceutical manufacturers accountable for the ecological lifecycle of their products, governments can incentivize the development of greener formulations while ensuring compliance with discharge standards and safe disposal practices.
(v) International collaboration and treaties: Because pharmaceutical pollution crosses borders, coordinated global action involving organizations such as the United Nations and World Health Organization is essential. International treaties or agreements could standardize goals and commitments across nations, promoting collaborative research, harmonized environmental quality standards, and stronger enforcement mechanisms. Such global partnerships ensure that mitigation efforts are consistent and impactful worldwide.
(vi) Global monitoring frameworks: Global monitoring frameworks that integrate environmental, biological, and chemical data, supported by citizen science programs, represent an innovative and scalable strategy for early detection and management of pharmaceutical pollution. Utilizing sentinel species, bioindicators, and real-time sensing technologies can enable early

warnings, while citizen participation increases coverage, awareness, and accountability at both local and global levels.

(vii) Green pharmaceutical design: Developing drugs that are less persistent and more easily degradable in the environment is an emerging strategy that can be implemented through collaboration between academia, industry, and regulators. Designing pharmaceuticals with "benign by design" principles ensures that therapeutic activity is preserved while minimizing environmental persistence, bioaccumulation, and toxicity, thereby reducing long-term impacts on marine and terrestrial ecosystems.

(viii) Advanced catalytic and nanotechnology-based approaches: Recent advances in nanotechnology and catalytic materials offer promising strategies for removing pharmaceutical pollutants. Photocatalysts such as TiO_2-based composites, graphene oxides, and metal-organic frameworks (MOFs) can achieve near-complete degradation of recalcitrant compounds under solar or visible light. These approaches are highly effective, energy-efficient, and scalable, making them valuable additions to next-generation wastewater treatment systems.

(ix) Artificial intelligence (AI) and predictive modeling: AI and machine learning tools can be applied to predict the occurrence, fate, and ecological risks of pharmaceuticals in aquatic systems. By integrating monitoring data with predictive models, it becomes possible to identify contamination hotspots, optimize treatment processes, and prioritize high-risk compounds for regulation oversight. This data-driven strategy enhances precision, efficiency, and proactive management of pharmaceutical pollution.

(x) Circular pharmaceutical economy: Establishing a circular economy for pharmaceuticals is a transformative strategy. By recycling pharmaceutical waste into usable resources, promoting green chemistry in production, and encouraging the use of refillable or biodegradable packaging, the overall environmental footprint of the pharmaceutical sector can be significantly reduced. This approach not only minimizes pollution but also ensures sustainable resource use and long-term ecological benefits.

7. Conclusion

Marine pharmaceutical pollution has emerged as a complex issue that requires immediate action in targeted areas. The increasing use of pharmaceuticals, including anti-inflammatory drugs, antibiotics, antidepressants, anticancer agents, and antihypertensives, contributes to their accumulation in seawater. The release of these products into coastal and marine ecosystems through discharge from pharmaceutical manufacturing, hospital effluent, and human waste produces numerous adverse effects on organisms inhabiting these environments. Increasing research on trace levels of potentially carcinogenic pharmaceutical compounds underscores the need to develop practical solutions to mitigate the impact of pharmaceutical pollution and preserve the marine environment. Furthermore, growing evidence demonstrates that pharmaceutical contaminants can bioaccumulate in marine organisms and biomagnify across trophic levels, particularly affecting fish and other higher predators. These processes may lead to significant biochemical and physiological perturbations, including oxidative stress, endocrine disruption, altered metabolic activity, and reproductive impairments in marine species. Therefore, comprehensive monitoring, improved wastewater treatment strategies, and interdisciplinary research are essential to better understand the ecological risks and protect marine biodiversity from long-term pharmaceutical contamination.

8. Future research directions

Future research directions are crucial for closing existing knowledge gaps, enhancing detection and mitigation strategies, and protecting marine ecosystems. Advancing scientific understanding will ensure sustainable management of pharmaceutical pollution and strengthen global efforts to protect biodiversity and human health. The following are some effective and essential future research directions:

(i) Although promising, advanced technologies such as MBRs, AOPs, nanofiltration, and bio-electrochemical systems still require further validation regarding energy use, scalability, and efficiency across diverse pharmaceutical classes.

(ii) Research should explore the efficacy of various microbial strains and plant species in degrading a broad range of pharmaceuticals, especially recalcitrant molecules. Investigations into genetically engineered microbes could lead to breakthroughs in degrading refractory pollutants.

(iii) Much less is known about the environmental fate of pharmaceuticals in marine ecosystems. Research should focus on understanding trophic transfer, vulnerable species, and ecosystem-level effects.

(iv) Additional studies are needed on long-term, low-level exposure impacts such as altered reproduction, endocrine disruption, immune function, and behavior across different trophic levels.

(v) Developing fast, cost-effective, and high-throughput analytical methods (including non-target screening using high-resolution mass spectrometry) is a future research priority to enable large-scale monitoring across seawater, sediment, and biota.

(vi) Research should assess the impacts of public education programs, consumer habits, and prescribing patterns on pharmaceutical pollution.

(vii) Future studies could investigate the effectiveness of global treaties or agreements in setting environmental quality standards and enforcing pharmaceutical waste regulations.

(viii) Research into phytotherapy, homeopathy, and individualized drug protocols could reduce pharmaceutical consumption and environmental load.

CRediT authorship contribution statement

Md Faisal Amin: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Md Saydur Rahman:** Writing – review & editing, Visualization, Validation, Supervision, Software, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Consent for publication

All authors have approved the submission of the final version of the manuscript.

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