Frontiers | Research Topics

Environmental contaminants in aquatic systems and chemical safety for environmental and human health, volume II

2nd Edition

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Published in
Frontiers in Public Health
Frontiers in Environmental Science
Frontiers in Microbiology
Frontiers in Marine Science

ISSN 1664-8714
ISBN 978-2-8325-2894-5
DOI 10.3389/978-2-8325-2894-5

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Environmental contaminants in aquatic systems and chemical safety for environmental and human health, volume II 2nd Edition

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Citation

Khan, M. M. T., Mickols, W. E., Sklar, L., eds. (2023). *Environmental contaminants in aquatic systems and chemical safety for environmental and human health, volume II 2nd Edition*. Lausanne: Frontiers Media SA.
doi: 10.3389/978-2-8325-2894-5

Publisher's note: In this 2nd edition, the following article has been added: Khan MMT and Sklar L (2023) Editorial: Environmental contaminants in aquatic systems and chemical safety for environmental and human health, volume II. Front. Public Health 11:1157834. doi: 10.3389/fpubh.2023.1157834

Table of contents

TYPE Editorial
PUBLISHED 13 June 2023
DOI 10.3389/fpubh.2023.1157834

OPEN ACCESS

EDITED AND REVIEWED BY
Argaw Ambelu,
Addis Ababa University, Ethiopia

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RECEIVED 03 February 2023
ACCEPTED 08 May 2023
PUBLISHED 13 June 2023

CITATION
Khan MMT and Sklar L (2023) Editorial: Environmental contaminants in aquatic systems and chemical safety for environmental and human health, volume II.
Front. Public Health 11:1157834.
doi: 10.3389/fpubh.2023.1157834

Editorial: Environmental contaminants in aquatic systems and chemical safety for environmental and human health, volume II

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KEYWORDS

environmental contaminants, chemical safety, aquatic system pollution, environmental and human health, carcinogenicity, mutagenicity, ambient water quality

Editorial on the Research Topic
Environmental contaminants in aquatic systems and chemical safety for environmental and human health, volume II

Given the finite supply of water available for human use, the continued chemical contamination of the aquatic environment may pose a significant human health hazard. Consequently, an effort must be made to develop ambient water quality criteria to protect human health and preserve the integrity of the aquatic environment. In developing water quality criteria based on human health effects, information on sources of exposure, pharmacokinetics, and adverse effects must be carefully evaluated and acknowledged. Information and fundamental knowledge on the sources of exposure are needed to determine the contribution of exposure from water relative to all other sources.

Human exposure to hazardous agents in our food, air, and water contributes to illness, disability, and death. Poor environmental quality has its greatest impact on people whose health may already be at risk, notably, pregnant women, young children, older adults, and people with preexisting illnesses. National efforts to ensure clean and safe food and water supplies continue to contribute significantly to improvements in public health and the prevention of disability. Currently, carcinogenicity and mutagenicity are considered to be non-threshold effects. For carcinogens and mutagens, criteria are calculated by postulating an “acceptable” increased level of risk and using extrapolation models to estimate the dose which would result in this increased level of risk. For other chemicals, thresholds are assumed, and criteria are calculated by deriving “acceptable daily intakes” for man which would presumably result in no observable adverse effects.

In recent years, antidepressants have acquired much attention because of their occurrence in water from the environment and aquatic organisms, as well as their potential harm to ecosystems and human wellbeing. The toxicological effects of antidepressants in different organisms, primarily fish, aquatic plants, and mammals included changes in weight, pathological changes in the brain, heart, and kidney, and a decrease in sperm dose (1, 2). It is also known that art materials may contain chemicals, which are associated with chronic toxicity (3, 4). Some of these chemicals include heavy metals such as nickel chloride that can potentially dysregulate mechanisms involved in genome maintenance and repair (5) and may predispose human cells to oncogenesis.

Recent scientific studies have demonstrated that insecticides have a strong collateral effect on both human and other non-target organisms and often on pests. Furthermore, the brown planthoppers (a serious rice pest) outbreak can be traced to the misuse of insecticides. Current pest management solely depends on chemical pesticides with effects on the environment, biodiversity, and human health (6). Although much progress has been made, crayons are among the most widely used products by children and

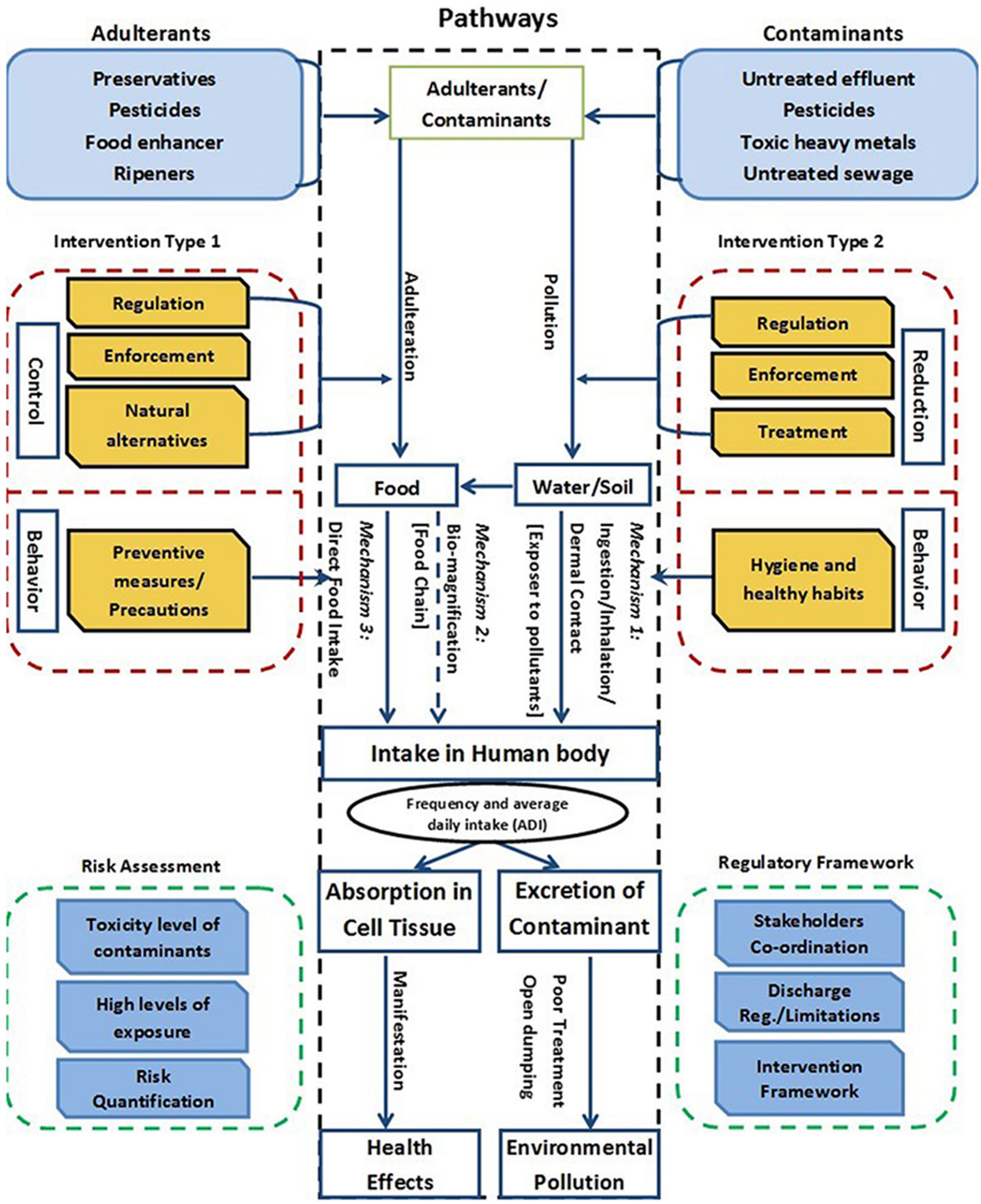

FIGURE 1
Flow chart of human exposure to contaminant pathways and associated mechanisms involved and framework for interventions (43).

can potentially be contaminated with lead, and there is a great need to further minimize the exposure to ensure the safety of consumers (7).

The risk for carcinogenic and non-carcinogenic effects associated with the exposure to contaminants through three specific mechanisms (e.g., water pollution, food adulteration, and biomagnification) can be variable depending on the types of contaminants, their respective properties, and natural attenuation or digestive mechanisms. Often, these contaminants become the part of food chain due to poor control of effluent treatment plants of textiles, tanneries, and pharmaceuticals industries as well as the open dumping of toxic/solid waste and wastewater (8, 9). Heavy metals including cadmium, mercury, lead, copper, and zinc are recognized as important marine pollutants because of their toxicity, presence in food chains, and propensity to survive in the environment for an extended period (10, 11). Leather manufacturing involves many chemical products such as chromium sulfate, tannins, bactericides, and ammonia salt (12). Moreover, protecting the shellfish aquaculture farms often requires the prevention of oyster consumption when bacterial levels are high in water (13–16).

Researchers have identified that the wastewater treatment plants were primary sources of emerging contaminants (ECs) observed in surface water samples (17). The prominent classes of ECs mostly include pharmaceuticals and personal care products (PPCPs), nanomaterials, surfactants, heavy metals, fire retardants, plasticizers, fertilizers, and pesticides (18, 19). Several classes of the ECs were recognized as endocrine disruptive compounds (EDCs) due to their deleterious effects on endocrine systems (EDCs). The impact of ECs has been reported in surface water, wastewater, and groundwater sources (18, 19). Effluents from the pharmaceutical industry are another important source, with high concentrations of pharmaceuticals being found due to discharges from factories in several parts of the world despite strict regulation of of pharmaceutical products (20–24). The ECs can effectively be eliminated by up to 99%, using the membrane bioreactor (MBR) and advanced treatment technologies such as reverse osmosis, ultrafiltration, or nanofiltration (25). The tertiary treated wastewater is discharged into the open water sources after meeting the water quality standards and is not used as a palatable source of water. Therefore, wastewater treatment plants do not use MBR technologies, which are not energy-efficient and cost-effective. Therefore, it is erroneous to assume that the traditional tertiary treated wastewater is free of these emerging contaminants (26–28). Petrie et al. (29) confirmed that wastewater treatment procedures used in the treatment plants were not effective in completely removing emerging contaminants.

Transport pathways of heavy metals and other ECs from the soil into the aquatic ecosystems are a major concern in pollution and contamination because they depend on the solubility of ECs and are influenced by aerobic or anaerobic conditions, pH, and redox potential (30). These ECs not only impair soil quality and freshwater sources but could also get into the food chain and affect human and animal health, i.e., one health. Metal type and their bio availabilities in soils determine the extent of physiological uptake and potential toxic effects of metals in living organisms (31). On the other hand, antibiotic-resistant bacteria are resistant to both natural and synthetic antibiotics (32) and thus have become a health concern worldwide. Multi-drug resistant bacteria (MDRB) with stronger resistance can be resistant to three or more antibiotics in the clinic (33, 34). Bacteria can develop intrinsic resistance to certain antibiotics but can also acquire resistance to antibiotics (35). The pathway for bacteria to acquire or develop antibiotic resistance, which is rooted in the irrational usage of antibiotics, is to prevent antibiotics from entering the target, change the antibiotic targets, and inactivate antibiotics (36, 37). The irrational usage of antibiotics can lead to the prolonged exposure of bacteria to sublethal concentrations of antibiotics, which is key to resistance selection (38).

Only a small portion of the antibiotics in aquatic products are actually absorbed, with most being discharged into the environment, resulting in antibiotic residues in aquaculture areas in discharged wastewaters and accumulated in the surrounding sediments through adsorption (39, 40). In livestock farming, antibiotics are important for the prevention of infectious diseases and their treatment as well as for promoting the growth of livestock (41). Antibiotics applied to livestock and poultry are not fully absorbed, with most being excreted into the environment through animal feces or urine (42).

Based on the above discussions, there could be strong correlations among the micropollutants, metals, harmful chemicals, ECs, antibiotics, microbes, and aquatic environmental agents, which have an effect on the public health, food chain, soil-water environments, and animals—the major parameters of one health (Figure 1). Majed et al. (43) discussed the influence of contaminant pathway to water and soil on hygiene and healthy habits, which is a behavior parameter. However, conservation habits can help conserve water, increase food supply, and provide shelter for animals, birds, and insects. These habits are consistent with actions helping to protect and manage natural resources. Many of those habits will help establish and maintain healthy habitats, which are flourishing places for animals and others to live. Furthermore, these habitats provide a strong foundation for the ecosystem toward sustainable public health policy, resilience to withstand change and stressors, and solutions for climate change. Recent evidence from European ice cores showed a strong relationship between unusual weather (low temperatures and high rainfall) and the severity of the Spanish Flu epidemic during the First World War (44). There is evidence that Hg and persistent organic pollutants (POPs) removed from the atmosphere and deposited on snow have been released to the environment at snowmelt, rapidly dispersing hazardous compounds through the atmosphere, continental, and aquatic systems and becoming bioavailable to be incorporated into food webs (45, 46).

Climate change affects the frequencies and durations of viral epidemics by altering the distribution, abundance, and activity of hosts, changing resistance to infection, the physiology of host-virus interactions, the rate of virus evolution, and host adaptation (47, 48). According to the World Health Organization (49), solid fuel includes coal as well as biomass fuels (referring to renewable plant-based materials such as wood, crop wastes, and charcoal), providing heat and light during the process of combustion. Ambient air pollutants (e.g., particulate matter and polycyclic aromatic hydrocarbons) may cause tumor formation in the breast and cervix uteri (50–52).

It has long been known that exposure to high levels of certain chemicals, such as those in some occupational settings, can cause cancer. Cancer is the second leading cause of death in the United States; it accounts for one in four deaths in the US and claims more than 1,500 lives a day. There is now growing scientific evidence that exposure to lower levels of chemicals in the general environment is contributing to society's cancer burden and health hazard. It is eminent to adapt the emerging regulations, treatment technologies, public awareness, resource management, and policy assessment to overcome the environmental contaminants-related threat and issues in the environment. Moreover, chemical safety for environmental, animal, and human health is a mandatory concern, and proper management and regulations are necessary to adopt advanced and accurate safety measures.

Author contributions

MK conceptualized the editorial article, performed the literature review, validation, and designed the article preparation. MK and LS finalized the editorial article. LS confirmed the format and requirements of this submission. Both authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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frontiers in Environmental Science

REVIEW
published: 18 June 2021
doi: 10.3389/fenvs.2021.692298

A Review of the Distribution of Antibiotics in Water in Different Regions of China and Current Antibiotic Degradation Pathways

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Specialty section:
This article was submitted to Toxicology, Pollution and the Environment, a section of the journal Frontiers in Environmental Science

Received: 08 April 2021
Accepted: 03 June 2021
Published: 18 June 2021

Citation:
Liu C, Tan L, Zhang L, Tian W and Ma L (2021) A Review of the Distribution of Antibiotics in Water in Different Regions of China and Current Antibiotic Degradation Pathways. Front. Environ. Sci. 9:692298. doi: 10.3389/fenvs.2021.692298

Antibiotic pollution is becoming an increasingly serious threat in different regions of China. The distribution of antibiotics in water sources varies significantly in time and space, corresponding to the amount of antibiotics used locally. The main source of this contamination in the aquatic environment is wastewater from antibiotic manufacturers, large scale animal farming, and hospitals. In response to the excessive antibiotic contamination in the water environment globally, environmentally friendly alternatives to antibiotics are being developed to reduce their use. Furthermore, researchers have developed various antibiotic treatment techniques for the degradation of antibiotics, such as physical adsorption, chemical oxidation, photodegradation, and biodegradation. Among them, biodegradation is receiving increasing attention because of its low cost, ease of operation, and lack of secondary pollution. Antibiotic degradation by enzymes could become the key strategy of management of antibiotics pollution in the environment in future. This review summarizes research on the distribution of antibiotics in China's aquatic environments and different techniques for the degradation of antibiotics. Special attention is paid to their degradation by various enzymes. The adverse effects of the pollutants and need for more effective monitoring and mitigating pollution are also highlighted.

Keywords: antibiotic contamination, antibiotic resistance, enzyme degradation, water environment, ecosystems

INTRODUCTION

Since Fleming discovered penicillin in 1929, hundreds of other antibiotics have been synthesized, which are being increasingly used to treat infections in humans and animals. Inexpensive and effective antibiotics have become the preferred antibacterial drugs used by pharmaceutical and farming industries to inhibit the growth of bacteria and eliminate pathogens. In the aquaculture industry, antibiotics are used extensively as drugs to prevent bacterial infections and parasitic diseases (Bitchava and Nengas, 2010). Only a small portion of the antibiotics in aquatic products are actually absorbed, with most being discharged into the environment, resulting in antibiotic residues in aquaculture areas in discharged wastewaters and accumulated in the surrounding sediments through adsorption (Kumar et al., 2005; Conkle et al., 2010; Rico et al., 2013). In livestock farming, antibiotics are important for the prevention of infectious diseases and their treatment as well as for promoting the growth of livestock (Yin et al., 2016). Antibiotics applied to livestock and poultry are not fully absorbed, with most being excreted into the environment through animal feces or urine (Briones et al., 2016). Residual antibiotics enter rivers and lakes through wastewater and accumulate in soil, where they are taken up by plants and animals (as illustrated in **Figure 1).**

As the world's most populous country and the largest consumer of antibiotics, China's antibiotic stewardship is facing significant challenges (Shao et al., 2020). Some of the antibiotics detected have been banned in clinical practice and may seriously impair human immunity (Zhou et al., 2021). In addition, exposure to veterinary antibiotics is associated with childhood obesity (Scott et al., 2016; Park et al., 2020) and liver injury (Mosedale et al., 2014), and the resulting genetic contamination of resistance poses serious threats to human health. China is vast territory with an equally diverse industrial layout. In addition, the levels of economic development vary greatly across the country, and thus the range of antibiotic concentrations in the environment is also broad across different regions. Here, first, we review the distribution of antibiotics in aquatic environments in China and the types of antibiotics, and report the distribution characteristics of antibiotics in China. Secondly, we analyze the potential impacts of antibiotics on the ecological environment in China. Lastly, we review progress in technologies for the degradation and removal of antibiotics in China and abroad, in addition to exploring the underlying principles, as well as their merits and shortcomings. This review provides a basis for risk estimation of antibiotics in ecological systems, an overview of the distribution of antibiotics in the aquatic environment in China, and the current approaches and methods used to eliminate antibiotics from ecological systems.

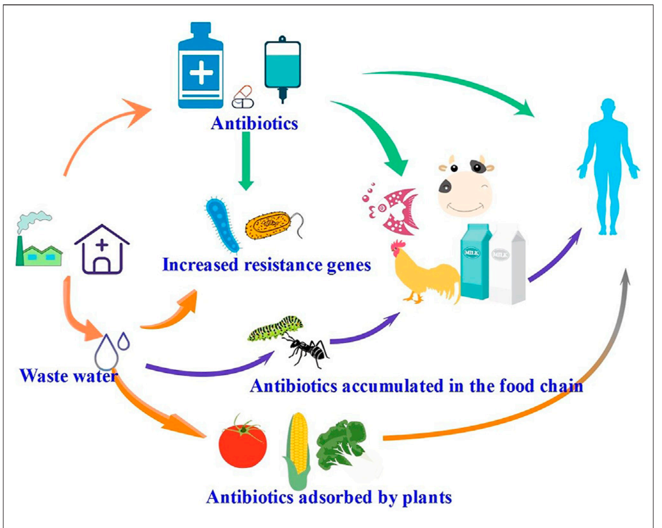


FIGURE 1 | Circulation of antibiotics in the environment.

STATUS OF ANTIBIOTIC CONTAMINATION IN AQUATIC ENVIRONMENTS IN CHINA

Types of Antibiotics in Aquatic Environments in China

The major antibiotics in aquatic environments in China are divided according to their chemical structures and include macrolides, tetracyclines, fluoroquinolones, sulfonamides, and chloramphenicol (Liu et al., 2012). Their structural formulas are listed in **Table 1.**

Antibiotics in Surface Water

In different regions of China, the spatial and temporal distribution of antibiotics in water sources varies significantly, and this difference is closely related to the local industrial structure, the mode of antibiotic disposal in the pharmaceutical industry, and the mode of antibiotic use in the livestock industry. As shown in **Table 2** by the results of a statistical analysis of data from the last five years**,** the distribution of antibiotics have been found to vary in different areas, and their contamination level also varies from region to region (Zhang et al., 2019). The antibiotic pollution is mainly concentrated in the Yangtze River Basin, and the Bohai Bay and Pearl River Delta, and Xinjiang regions. In the western region, the medical safety standards are relatively poor, and chloramphenicol, a highly effective antibiotic with relatively greater side effects, is a major problem. As a result of its continued use, the detection rate of chloramphenicol in the middle and upper reaches of the Yangtze River is significantly higher than that in the eastern region (Wang, 2020a). The pharmaceutical industry is concentrated in the economically developed eastern region, leading to the discharge of a large amount of antibiotic effluent and thus a high concentration of antibiotic pollution in this region (Bao et al., 2021). In Xinjiang, coastal areas, and other regions, the development of the livestock and aquaculture industries, which use antibiotics, has resulted in significantly higher levels of sulfonamides and tetracycline antibiotics in the environment. (**Table 3**). Quinolone antibiotics are widely used as broad-spectrum anti-infective drugs in medical treatment, and their presence has been detected in most local drinking water sources (**Table 4**). Generally, Chinese rivers and lakes have high concentrations of antibiotics. Sulfonamide and quinolone are the main pollutants in the surface waters of Chinese lakes (Liu et al., 2018).

Antibiotics in the aquatic environment may be influenced by photolysis, temperature, pH, dilution factors, bacterial populations, and hydraulic residence time, leading to inconsistencies in their concentrations (Kummerer, 2009; Kümmerer, 2009; Zhang et al., 2014; Tang et al., 2015). Based on the results of previous research (Yoshizaki and Tomida, 2000; Loftin et al., 2008; Ben et al., 2013), the concentrations and compositions of the main types of antibiotics in the abundant water period and dry water periods are shown in **Figure 2**, which show that the concentrations of antibiotics in aquatic environments vary seasonally, with detectable frequencies and average concentrations being higher in winter (dry water period) than in summer (dry water period). Industrial structure, medical level, and climate of different regions have an effect on the distribution of antibiotics in local water bodies, especially pharmaceutical and farming industries have a marked effect on antibiotic discharge. Therefore, strengthening guidance and

TABLE 1 | Major classes of antibiotics in aquatic environments in China.

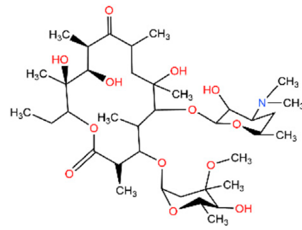
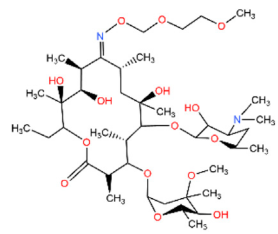
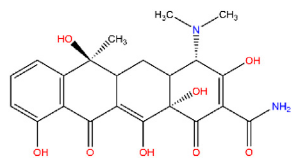
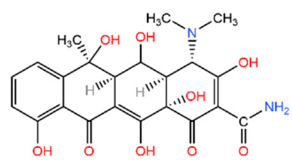
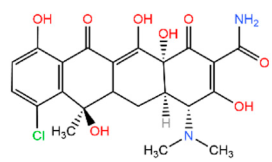
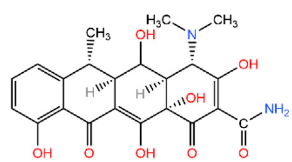
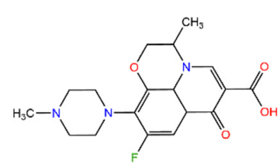
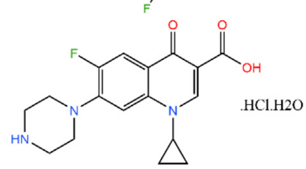
Type	Name	Abbreviation	Structure	CAS No.
Macrolides	Roxithromycin	ROX		80214-83-1
	Erythromycin	ERM		114-07-8
Tetracyclines	Tetracycline	TC		60-54-8
	Oxytetracycline	OTC		79-57-2
	Chlorotetracycli	CTC		57-62-5
	Doxycycline	DOX		209-271-1
Fluoroquinolones	Ofloxacin	OFX		82419-36-1
	Ciprofloxacin	CIP		85721-33-1

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TABLE 1 | (*Continued*) Major classes of antibiotics in aquatic environments in China.

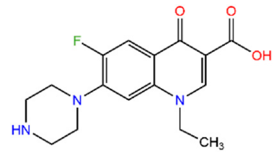
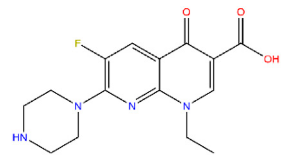
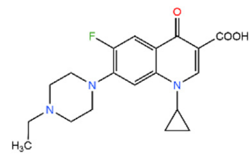
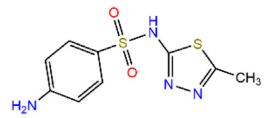
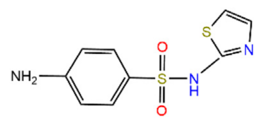
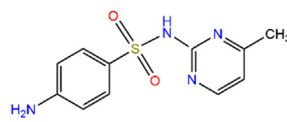
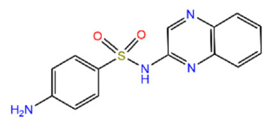
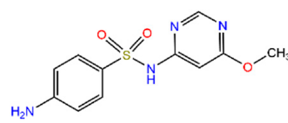
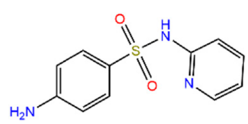
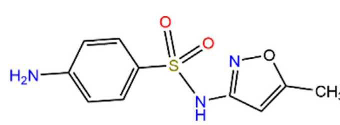
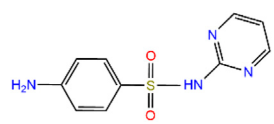
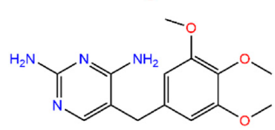
Type	Name	Abbreviation	Structure	CAS No.
	Norfloxacin	NOR		70458-96-7
	Enoxacin	ENX		74011-58-8
	Enrofloxacin	EFX		93106-60-6
Sulfonamides	Sulfamethizole	SMT		144-82-1
	Sulfathiazole	STZ		72-14-0
	Sulfamerazine	SMR		127-79-7
	Sulfaquinoxaline	SQX		59-40-5
	Sulfamonomethoxine	SMM		651-06-9
	Sulfapyridine	SPD		144-83-2
Chloramphenicols	Sulfamethoxazole	SMX		723-46-6
	Sulfadiazine	SDZ		68-35-9
	Trimethoprim	TMP		738-70-5

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TABLE 1 | (*Continued*) Major classes of antibiotics in aquatic environments in China.

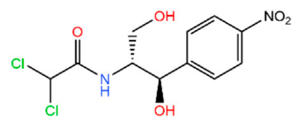
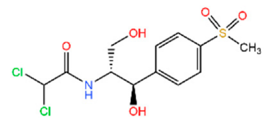
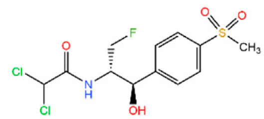
Type	Name	Abbreviation	Structure	CAS No.
	Chloramphenicol	CAP		56-75-7
	Thiamphenicol	TAP		15318-45-3
	Florfenicol	FF		73231-34-2

TABLE 2 | Distribution of antibiotics in different waters of China (From 2015 to 2020).

Waters	Regions	The amount of antibiotics detected (ng/L)					References
		Sulfonamides	Fluoroquinolones	Macrolides	Chloramphenicols	Tetracyclines	
Songhua river	Harbin	2.1~92.14	0.03~8.14	0.26~18.07	—	—	Wang et al. (2018c)
Lancang river	Lincang	1.51~37.43	0.03~1.45	0.18~4.46	—	ND~12.19	Liang (2019)
Yarlung zangbo river	Lasa	2.74~33.94	<2	0.61~33.77	—	0.70~14.07	Liang (2019)
Huangpu river	Shanghai	0~22.48	—	—	—	9.98~177.28	Fang et al. (2017)
Yangtze river (nanjing section)	Nanjing	32.42	27.25	778.49	6.46	14.55	Feng et al. (2019)
Moon lake	Ningbo	13.68~523.78	ND~267.0	5.88~552.53	—	—	Wang et al.,(2018d)
Taihu lake basin (yili-taohang section)	Changzhou-wuxi	ND~0.58	ND~0.21	0.04~0.94	—	ND~17.85	Sun et al.,(2018)
Taihu gonghu bay	Wuxi	ND~478	14~474	14~23	—	ND~4,720	Wu et al. (2016)
Tiaoxi (taihu lake basin)	Huzhou	≤326.6	≤36.5	—	—	ND	Xu et al. (2020)
Poyang lake	Nanchang	1.3~117	—	3.6~14.8	5~16.5	ND~106.5	Ding (2018)
Chaohu	Hefei	ND~189.9	ND~148.7	ND~18.48	—	ND~14	Tang et al. (2014)
South lake	Wuhan	3.52~20.48	70.70~155.52	—	—	21.41~43.43	Xiao et al. (2019)
Shahu	Wuhan	ND~0.81	37.85~75.09	—	—	20.06~29.03	Xiao et al. (2019)
East lake	Wuhan	ND~4.17	49.49~83.31	—	—	15.42~24.64	Xiao et al. (2019)
Datong lake	Yiyang	11.56~181.25	ND~83.53	—	—	ND~18.08	Liu and Lu (2018)
Yangtze river basin (three gorges Section)	Chongqing	ND~247	ND~16.4	19.1~223.7	11.9~615.8	—	Feng et al. (2017)
Nanming river	Guiyang	13.68~523.78	1.72~424.37	5.88~552.53	1.95~235.6	0.36~243.25	Wang et al. (2018e)
Weihe river (Xi'an section)	Xi'an	21.37~60	4.7~64.28	—	—	4.64~129.91	Zhu et al. (2018)
Pearl river	Guangzhou	687.90	814.1	1112.2	—	643.2	Liu et al., 2017)
Star lake	Zhaoqing	9.27~190.71	2.27~9.46	ND~0.8	—	ND	Xie et al. (2019)
Caohai karst plateau wetland	Weining	50.5	43.2	22.6	15.9	ND	Wang et al. (2020a)
Huaihe (shihe district)	Xinyang	—	—	13.1~355.6	—	ND~275.1	Wang and Wang (2020)
Xiaoqinghe (jinan section)	Jinan	DN~196.5	11.0~383.9	13.16~309.09	—	ND~8.91	Yan (2018)
Ebinur lake	Bortala Mongolian autonomous prefecture	22.50~103.72	21.61~83.78	0.56~306.75	—	ND~15.94	Wang (2020b)
Bosten lake	Bayingoleng Mongolian autonomous prefecture	ND~36.81	ND~99.32	—	—	ND~43.55	Yang (2018)
Ebinur lake	Alashankou	ND~61.01	293.78~5144.95	—	—	ND~12.01	Qianqian (2016)

TABLE 3 | Antibiotic concentrations in surface water in aquaculture areas (From 2015 to 2020).

Waters	Regions	The amount of antibiotics detected (ng/L)					References
		Sulfonamides	Fluoroquinolones	Macrolides	Chloramphenicols	Tetracyclines	
River estuary area	Dongying	0.01~11.4	0~63.3	ND~16.5	0.09~0.51	ND	Lian (2016)
Gate of yang county	Yancheng	1~2.35	3.77~9.76	0.15~2.05	2.91~3.44	ND	Han et al. (2020)
Aquaculture ecosystem in haiyang regions	Haiyang	1.41~6.72	2.14~180.14	0.32~45.66	—	ND~2.09	Chen et al. (2015)
Marine aquaculture farms	Yangjiang	1181.64	932.05	1158	—	>1536	Zhang et al. (2018b)
Maowei sea breeding pond	Guangxi province	2.6	3	71.7	8.9	—	Zheng et al. (2017)
Freshwater aquaculture area	Zhejiang province	73.6~171.1	94.1~113.2	ND	—	—	Xu et al. (2019)
Aquaculture pond	Huzhou	ND~12,623	ND~332.3	—	—	ND~5.6	Wang et al. (2019)
Tilapia farming pond	Guangxi province	44.3	14.7~22.7	—	ND	32.7~3242	Yu et al.(2020)
Procambarus clarkii breeding area	Jiangsu province	ND~198.827	ND~38.82	ND~38.471	—	ND~114.296	Zhang et al. (2019)
Aquaculture area	Shanghai	ND~83.6	ND~3.27	—	—	ND~27.53	Zhong et al. (2018)
Beijiang river and its surrounding aquafarms	Guangdong province	1016.4	480	375.8	210.5	277.5	Wang et al. (2017b)
Aquaculture ponds	Honghu	32~1096.8	18~334.3	—	—	204.1~3028.3	Yuan et al. (2019)
Hangzhou bay	Zhejiang province	16.6~44.13	41.11~115.28	—	8.41-28.57	25.98~50.2	Hao et al. (2017)
Nansha aquaculture area	Guangzhou	0.81	ND	78.01	—	—	Chen et al. (2018)
Panyu aquaculture area	Guangzhou	113~247	0~100	80~1400	—	—	Lian (2016)

TABLE 4 | Antibiotic concentrations in drinking water sources in some cities (From 2015 to 2020).

Waters	Regions	The amount of antibiotics detected (ng/L)					References
		Sulfonamides	Fluoroquinolones	Macrolides	Chloramphenicols	Tetracyclines	
Huizhou water supply plant	Huizhou	47.73	ND	11.65	—	ND	Zheng (2017)
Beijing groundwater	Beijing	ND~341.2	ND~49.5	—	—	ND~3.2	Chen et al. (2017)
Drinking water in qingyuan	Qingyuan	ND~62.63	ND~295.09	ND~9.94	ND	ND	Dai (2019)
Biliuhe reservoir	Dalian	ND~15	ND~130	ND	ND~17	—	Dong et al. (2020)
Lianhua reservoir	Xiamen	ND~11.96	ND~353.42	ND~305.19	—	ND~254.67	Liao et al. (2020)
Drinking water sources	Dongguan	24.63~38.7	11.11~82.24	27.25~206.65	—	20.08~43.02	Xie et al. (2020)
Reservoir	Chongqing	ND~40.2	—	ND~60.1	1.1~35.4	—	Feng et al. (2020)
Water plant	Suzhou	4.65	2.29	1.51	—	1.45	Di et al. (2019)
Drinking water sources	Nanjing	ND~29.58	ND~40.18	0.53~35.25	—	ND~35.61	Liu et al. (2020a)
Drinking water sources	Jiaxing	0.69~13.21	89.5~230.8	ND~56.9	121~259	—	Guo et al. (2016)
Taipu river and jinze reservoir	Shanghai	10.5~385.8	10.2~189.4	ND~56.8	—	8.1~135.5	Li et al. (2020a)
Fengshuba reservoir	Guangdong province	4.29~39.45	ND~302.76	ND~1.57	—	3.44~345	Chen et al. (2020b)

regulations of the above industries is the main approach to reduce antibiotic discharge.

Antibiotics in Sediment

Antibiotics have been detected not only in water bodies such as lakes but also in sediments, which can contain significant amounts. The level of exposure of sediments to antibiotics is usually higher than that of water because the sediment particles, which have a strong ability to adsorb antibiotics (Lee and Carlson, 2006; Kim and Carlson, 2007; ; Yang et al., 2010). Antibiotic concentrations in surface water are more susceptible to external environmental influences than those in sediment, including dilution (Cheng et al., 2014; Ding et al., 2017), adsorption of particles (Wang et al., 2017a; Yang et al., 2020), and photodegradation (Chen et al., 2016), all of which can affect the variation of the antibiotic concentrations in water. Compared to in the water column, antibiotic levels in sediments are relatively stable because their ability to strongly adsorb antibiotics leads to antibiotic accumulation in the sediments (Mangalgiri and Blaney, 2017). Different water environments lead to different adsorption properties of the sediments, resulting in a both spatially and geographically heterogeneous distribution of antibiotics in sediments, as shown in **Table 5**. Furthermore, this distribution may also be influenced by the external environment. For example, external currents may flush antibiotics-bearing sediments and thus release adsorbed antibiotics into the aquatic environment, causing secondary pollution (Radke et al., 2009). Sediments can affect the level of antibiotics in water bodies. The components of sediments are highly complex, and there are several differences in the composition of sediments in different water body

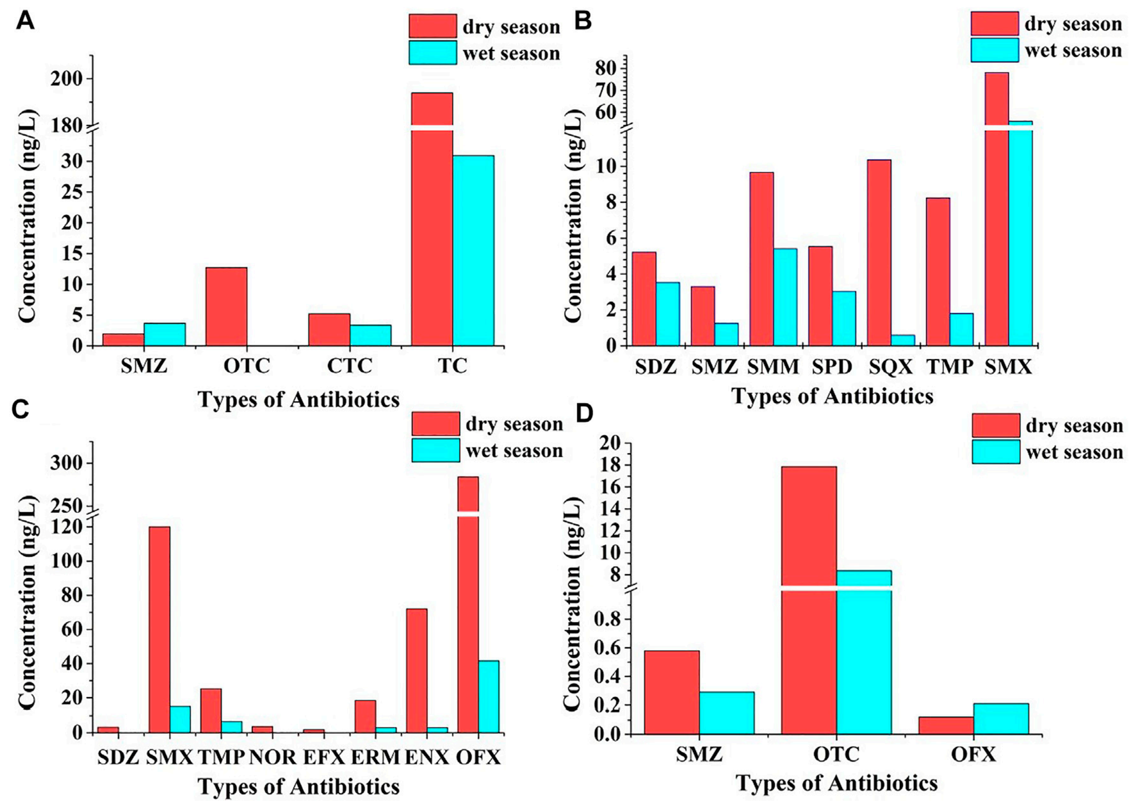


FIGURE 2 | Effect of abundant water period or dry water period on antibiotic concentrations in water bodies **(A)**: Huangpu River; **(B)**: Weihe Rive; **(C)**: Xiaoqinghe River (Shangdong); **(D)**: Taihu Lake.

TABLE 5 | Antibiotics concentrations in sediment (From 2015 to 2020).

Waters	Regions	The amount of antibiotics detected (ng/L)					References
		Sulfonamides	Fluoroquinolones	Macrolides	Chloramphenicols	Tetracyclines	
Yangtze river/Jialing river (chongqing selection)	Chongqing	2.79~23.19	22.24~33.15	7.6~14.07	—	7.02~9.76	Wang et al. (2020b)
Danjiangkou Reservoir	Danjiangkou	1.0~15	1.6~16	—	—	2.7~22	Hu et al. (2019)
Pearl river estuary	Zhuhai	ND~192	ND~157	ND~114	—	ND~206	Li et al. (2018)
Taihu lake		0.086~9.169	0.28~50.1	0.97~67.38	—	0.102~28.66	Xu et al. (2018)
Minjiang estuary	Fuzhou	ND~1.33	0.03~15.60	0.02~44.31	—	ND	Liu et al. (2020b)
Intertidal mudflat culture areas	Da'lian	0.4312~22.457	4.682~78.368	—	0.953~1.436	—	Xuan et al. (2020)
Aquaculture area		ND~71.49	ND	ND~13.19	—	—	Qian et al. (2019)
Yangtze estuary (wusongkou)	Shanghai	2.63	48.98	8.54	0.93	19.71	Guo et al. (2020)
Yangtze estuary	Xupu	ND	16.28	2.74	ND	0.96	Guo et al. (2018)
Nanfei river	Hefei	ND~2.7	ND~311	ND~15.8	—	—	Lyu et al. (2019)
Songhua river	Jilin	ND~26.9	ND~7.1	3.0–28.3	Nd–15.4	5.9~32.9	He et al. (2018)
Liao river	Jilin	ND~5.2	ND~640	ND~512	—	ND~78.8	Dong et al. (2016)
Mangrove nature reserves	Hainan	57	48.8	26.4	5.6	24.5	Liu et al. (2020c)
Mangrove nature reserves	Hongkong	39.1	28	126.6	7.7	95.6	Liu et al. (2020c)
Fengshuba reservoir	Heyuan	2.91~46.22	15.81~172.9	18.98~180.6	—	ND	Chen et al. (2020b)
Chaobai river	Beijing	7.7	432.9	12.13	—	225.8	Zhang et al. (2020b)
East China sea bay	Zhengjiang	0~25.3	0.4~45.1	0.6~60.3	—	0~108	Li et al. (2020b)
Xiangjiang river	Hunan	ND~0.98	3.77~487	0.33~9.44	ND~9.03	1.56–1115	Chen et al. (2019)

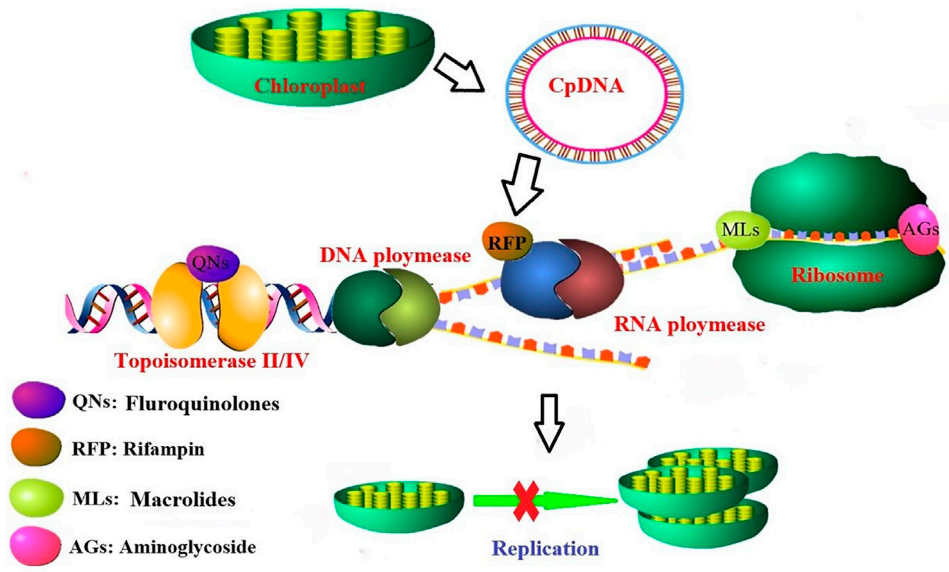


FIGURE3 | Tetracycline and sulfonamide inhibit algal growth by affecting their chloroplast replication and transcription/translation.

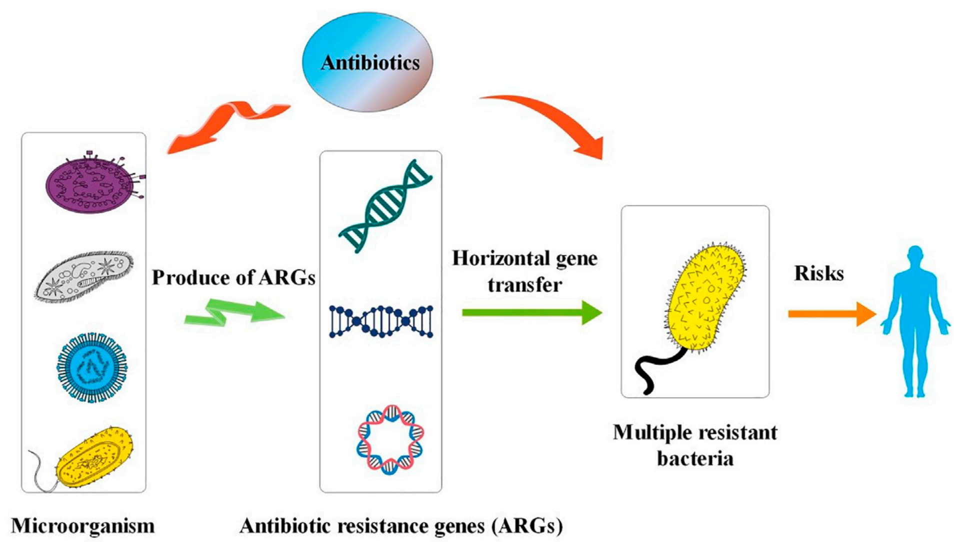


FIGURE 4 | Antibiotic resistance genes induced by antibiotics and horizontal gene transfer.

environments. The enrichment of antibiotics in sediments and how antibiotics in sediments are released into the water body still need systematic and in-depth research.

EFFECT OF ANTIBIOTICS ON PEOPLE AND ECOSYSTEMS

Antibiotic Hazards to Human Health

Antibiotics have been found in fish from some farming areas and in some cooked foods and crops, and the antibiotics can be enriched in humans after consumption. Antibiotics have a strong inhibitory effect on the entire intestinal bacterial community (He et al., 2014). Antibiotics have a strong inhibitory effect on the entire bacterial community of intestinal microorganisms. The transfer of resistance genes between intestinal endophytes and pathogenic bacteria such as *Escherichia coli*, *Klebsiella*, and *Enterococcus faecalis* leads to an imbalance in intestinal microorganisms, and this in turn causes a variety of bacterial diseases (McInnes et al., 2020) and even intestinal cancer (Sobhani et al., 2019) and experiments have shown that even a small amount of antibiotics rapidly

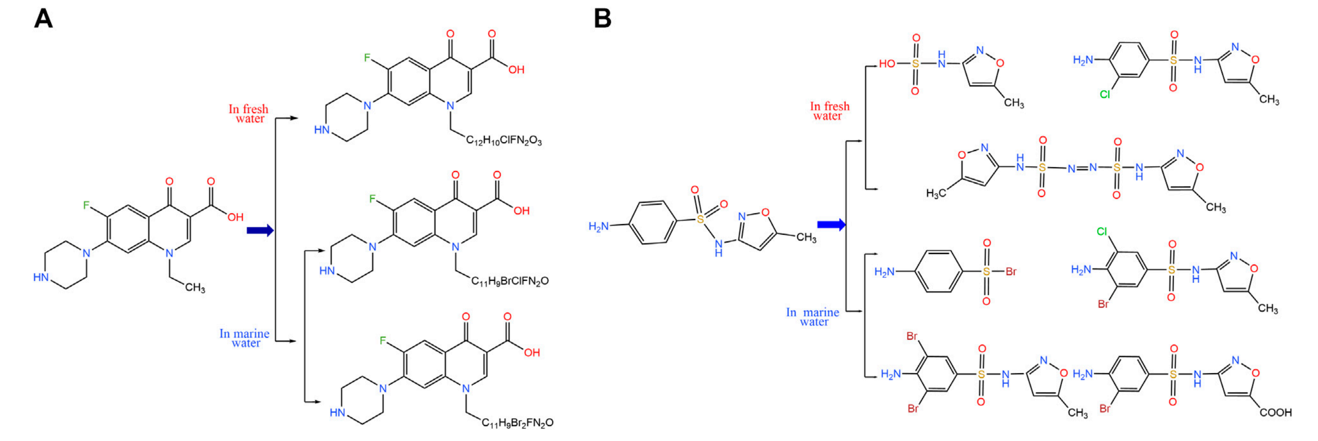


FIGURE 5 | Conversion of antibiotics to disinfection byproducts. End products of Norfloxacin or Sulfamethoxazole (McInnes et al.) reacts with NaClO in different water environments.

TABLE 6 | Characteristics of different methods of degrading antibiotics.

Methods of degrading antibiotics	Stages of application	Advantages	Disadvantages	References
Physical adsorption	Scaled up applications in industry	Low cost, simple design, and high flexibility	Low efficiency and causes secondary pollution	Dutta and Mala (2020)
Membrane filtration	Applications in drinking water production	Removal of many contaminants	High cost	Yin et al. (2021)
Chemical oxidative degradation	Scaled up applications in industry	Easy to operate, requires short time, and efficient	Environmentally unfriendly and low recycling rate	(Advanced oxidation technology engineering.)
Photolysis	In the laboratory research stage	Eco-friendly	High cost	Bo (2017)
Plant adsorption	Scaled up applications in industry	Economical, with high efficiency	Selective and diffusion of resistance genes	Liu et al. (2019)
Activated sludge and microbial strains	Scaled up applications in industry	Efficient and easy to operate	Susceptible to microbial resistance gene production	Liu et al. (2016)
Enzymatic degradation	In the laboratory research stage	Eco-friendly, efficient, and requires short time	Highly influenced by environment	Bilal et al. (2019)

changes the diversity of the intestinal flora in a short period of time (Dethlefsen et al., 2007; Fouhy et al., 2012), which may lead to a variety of diseases, especially in newborns. Antibiotic use during pregnancy or in newborns may adversely affect the neonatal gut microbiome and adversely affect the development of the infant's immune system, leading to childhood atopy, asthma, allergies, and obesity. It increases the probability of epilepsy in children (Kenyon et al., 2008; Neu and Walker, 2011; Madan et al., 2012; Mette et al., 2012; Dik et al., 2016; Koebnick et al., 2019; Milliken et al., 2019; Pronovost and Hsiao, 2019; Tadeusz et al., 2019; Zimmermann and Curtis, 2020; Zhang et al., 2021). Excessive intake of antibiotics can cause damage to the nervous system, kidneys, and other organs (Ramirez et al., 2007). At the same time, germs are prone to develop drug resistance and become super germs that are difficult to cure (Goldman, 2004; Xu et al., 2010). The dose of antibiotics used to treat a disease is controllable, but the enrichment of antibiotics from food into the body is not measurable and assessable. As food is consumed every day, determining the content of antibiotics contained in food is difficult. Therefore, the regulation of antibiotic content in food in the market is important.

Antibiotic Accumulation in the Ecological Chain

Algae are the basis of the food chain, and even a slight decrease in algal populations may affect the balance of the aquatic system (Lanzky and Halling-Sørensen, 1998). Researchers performed relevant cytotoxicity experiments to verify that the presence of antibiotics affects the genetic and normal growth of the genome (Yamaguchi et al., 2003; Yamaguchi and Subramanian, 2003). As shown in **Figure 3**, tetracycline and sulfonamide antibiotics have been found to inhibit algal growth by affecting their chloroplast

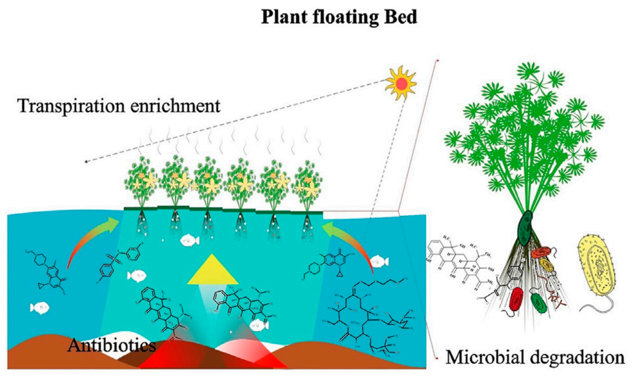


FIGURE 6 | Schematic diagram of plant floating bed adsorption of antibiotics. Plant roots adsorb antibiotics in the aquatic environment and sediment, and then antibiotics are degraded by microorganisms enriched by the roots.

replication, transcription/translation, and metabolic pathways (Brain et al., 2004; Brain et al., 2008; Baran et al., 2011). Fish appear to be less sensitive to antibiotics than algae (Li et al., 2012a). Feeding habits can affect the accumulation of antibiotics in fish, and some studies have shown that carnivorous fish have higher levels of antibiotic enrichment than other fish because they are the top consumers in the food chain in the aquatic environment (He et al., 2014). Zhao et al. showed that the accumulation of antibiotics in different tissues of animals is different, and the accumulated antibiotic levels in different tissues of fish are also different. For example, the accumulation levels of antibiotics in fish bile, plasma, and liver are relatively higher than those in other organs. (Zhao et al., 2016a). Invertebrates and fish that are chronically exposed to antibiotics are enriched in antibiotics, and people who consume these aquatic organisms face a high health risk (Metsälä et al., 2015; Wang et al., 2015; Möhle et al., 2016; Siswanto et al., 2016; Winek et al., 2016). The toxicity of antibiotics in water is influenced by their concentration, duration of exposure, aquatic species, and the coexistence of other antibiotics and/or other contaminants (Grenni et al., 2017). Plants can take up multiple antibiotics from soil and water, and while the toxicities of these multiple antibiotics are not superimposed on a single toxicity, they can induce combined toxicity (Brain et al., 2004). Antibiotics are passed up the food chain, resulting in human exposure to antibiotics *via* the consumption of food containing antibiotics; eventually, the accumulated antibiotics will have negative effects on the human body.

Increase of Potential Novel Antibiotic Resistant Gene Induction by Antibiotics

Genes are mutated and inherited in nature, and antibiotic resistance genes (ARGs) are present in the natural environment. Thus, antibiotics released into the environment exert selective pressure on the microbial community, thereby inducing drug-resistant bacteria and causing widespread bacterial resistance (Wei et al., 2019). Residual antibiotics and ARGs that enter the environment can be taken up by plants and enter the food chain through the migration distribution of the soil-water plant system (Forsberg et al., 2012), where they migrate and accumulate, and eventually enter the human body. There are two main sources of ARGs in the environment (Zhang et al., 2019a): ARGs are present in the environment itself–Antibiotics are mainly derived from secondary metabolites of microorganisms, plants, and animals, and these microorganisms are resistant to the antibiotics they produce (Russell and Yost, 2020); 2) Another source of ARGs is exogenous input (Zhang et al., 2018a). The metabolism rate of antibiotics in animals is very low, and about 25–75% of the antibiotics enter the environment through excreta without having been metabolized, thus inducing the production of resistance genes in the environment. As illustrated in **Figure 4**, ARGs can be transmitted between microorganisms and vertically between generations through horizontal gene transfer (HGT). As microorganisms evolve, new ARGs may also be produced (Ji et al., 2012; Shi et al., 2015). A wide variety of microorganisms in the environment may even lead to the creation of multidrug resistance genes or superbugs, while also increasing the potential for the induction of novel ARGs. The food chain can enhance the spread of resistance genes (Hu et al., 2016; Johnson et al., 2016). The transfer of ARGs acquired by humans from the environment or from food to gut microbes leads to an increase in gut microbial resistance (Huddleston, 2014), Studies have identified β-lactamase genes in the metabolic genome of human gut flora (Cao et al., 2021), suggesting that human gut microbes can acquire resistance genes from the environment, thereby leading to drug-resistant infections in human (Bengtsson-Palme, 2017).

Antibiotics and Disinfection Byproducts

In addition to their own toxicological effects and the genetic problem of resistance, antibiotics that remain in the aquatic environment have been found by researchers to be precursors of disinfection byproducts (DBPs) that can react with disinfectants such as chlorine and chlorine dioxide to produce halogenated carbon or nitrogen-containing disinfection byproducts (Wang and Helbling 2016; Zhang et al., 2017; Chuan et al., 2018) (**Figure 5**). DBPs are the result of the reaction between disinfectants and a special class of organics produced by the reaction of organic precursors in water. Since many antibiotics are nitrogen-containing organics, they contribute significantly to some of the more toxic N-DBPs. These disinfection byproducts, in turn, can be instrumental in inducing antibiotic resistance and resistance genes. DBPs have been shown to significantly increase bacterial resistance to antibiotics (Lü et al., 2015) and the mutagenesis rate of resistance genes (Li et al., 2016) as well as the concentration of resistant bacteria (Lv et al., 2015). The level of DBPs is often overlooked when testing for antibiotics in water, and we need to pay equal attention to the level of DBPs, which can also lead to the development of resistance genes in bacteria.

Antibiotics in Aquatic Organisms

Low concentrations of antibiotics are present in fish; however, they are mainly detected in laboratory studies. The

TABLE 7 | Antibiotic adsorption by plants reported in the literature.

Antibiotics		*Plant*	Removal (%)	References
Sulfonamides	Sulfadiazine	*Thalia*	72 ± 6	Dan et al. (2013)
	Sulfadiazine	*Arundo*	74 ± 6	Dan et al. (2013)
	Sulfadiazine	*Waseyutaka*	98.7	Xian et al. (2010)
	Sulfadiazine	*Acorus calamus*	26.42–64.93	Chen et al. (2020a)
	Sulfamethoxazole	*Cyperus alternifolius*	76.77 ± 4.13	Kumar et al. (2005)
	Sulfamethoxazole	*Dryan*	91.8	Xian et al. (2010)
	Sulfamethoxazole	*T. angustifolia/P. australis*	60 ± 26	Hijosa-Valsero et al. (2011a)
	Sulfamethoxazole	*Acorus/Typha*	29–52	Park et al. (2009)
	Sulfamethoxazole	*Thalia Dealbata Fraser*	56.9 ± 7.36	Jun et al. (2016)
	Sulfamethoxazole	*Iris tectorum Maxim*	69.2 ± 2.24	Jun et al. (2016)
	Sulfamethoxazole	*T. angustifolia*	80 ± 42	Hijosa-Valsero et al. (2011b)
	Sulfamethoxazole	*Acorus calamus*	37.81-84.05	Chen et al. (2020a)
	Sulfamethazine	*Waseyutaka*	88.8	Xian et al. (2010)
	Sulfamethazine	*Tachimasari*	89.4	Xian et al. (2010)
	Sulfamethazine	*H. pennisetum*	91–95	Liu et al. (2013)
	Sulfamethazine	*Thalia Dealbata Fraser*	100 ± 0.00	Jun et al. (2016)
	Sulfamethazine	*Iris tectorum Maxim*	100 ± 0.00	Jun et al. (2016)
	Sulfamethazine	*Acorus calamus*	18.98–65.06	Chen et al. (2020a)
	Sulfadimethoxine	*T. angustifolia*	99 ± 2	Hijosa-Valsero et al. (2011b)
	Sulfadimethoxine	*P. australis*	99 ± 2	Hijosa-Valsero et al. (2011b)
	Trimethoprim	*Thalia*	31 ± 37	Dan et al. (2013)
	Trimethoprim	*Arundo*	38 ± 10	Dan et al. (2013)
	Trimethoprim	*Thalia Dealbata Fraser*	84.6 ± 2.26	Jun et al. (2016)
	Trimethoprim	*Iris tectorum Maxim*	84.4 ± 2.28	Jun et al. (2016)
Lincosamides	Roxithromycin	*Cyperus alternifolius*	85.35 ± 2.47	Kumar et al. (2005)
	Leucomycin	*Thalia Dealbata Fraser*	100 ± 0.00	Jun et al. (2016)
	Leucomycin	*Iris tectorum Maxim*	100 ± 0.00	Jun et al. (2016)
	Clarithromycin	*Thalia Dealbata Fraser*	74.2 ± 5.63	Jun et al. (2016)
	Clarithromycin	*Iris tectorum Maxim*	87.3 ± 0.86	Jun et al. (2016)
	Erythromycin	*P. australis*	64 ± 30	Hijosa-Valsero et al. (2011b)
Tetracyclines	Oxytetracycline HCl	*H. pennisetum*	68–73	Liu et al. (2013)
	Oxytetracycline	*P. australis*	92.7–99.9	Huang et al. (2015)
	Oxytetracycline	*H. annuus*	100	Gujarathi et al. (2005)
	Oxytetracycline	*Typha orientalis*	72.43	Zhao et al. (2016b)
	Chlorotetracycli	*P. australis*	69.0–99.7	Huang et al. (2015)
	Chlorotetracycli	*Typha orientalis*	73.84	Zhao et al. (2016b)
	Tetracycline	*P. australis*	88.4-98.3	Huang et al. (2015)
	Tetracycline	*P. australis*	99.3 ± 0.4	Fernandes et al. (2015)
	Tetracycline	*Typha orientalis*	70.85	Zhao et al. (2016b)
	Tetracycline	*H. annuus*	100	Gujarathi et al. (2005)
	Doxycycline	*T. angustifolia*	75 ± 40	Hijosa-Valsero et al. (2011b)
Fluroquinolones	Ciprofloxacin HCl	*H. pennisetum*	78–84	Liu et al. (2013)
	Enrofloxacin	*P. australis*	98.7 ± 0.3	Fernandes et al. (2015)
	Difloxacin	*Phragmites australis*	>84	Jun et al. (2016)
Other PPCPs	Naproxen	*Acorus/Typha*	52–92	Park et al. (2009)
	Naproxen	*Phragmites australis*	80 ± 9	Matamoros and Bayona (2006)
	Ibuprofen	*Phragmites australis*	62 ± 2	Matamoros and Bayona (2006)
	Diclofenac	*Acorus/Typha*	73–96	Park et al. (2009)
	Carbamazepine	*Acorus/Typha*	30–47	Park et al. (2009)
	Methyl dihydrojasmonate	*Phragmites australis*	99 ± 1	Matamoros and Bayona (2006)

concentrations of antibiotics in aquatic organisms are correlated with their habits, their position in the food chain, and vary in fish and shrimp from different pelagic layers, depending on their location in the aquatic environment (Li et al., 2012b). In a previous study, sediments adsorbed with antibiotics were collected and used to construct an ecosystem to cultivate zebrafish (Chen et al., 2017a). The presence of antibiotics was detected in the zebrafish, suggesting bioconcentration of antibiotics in aquatic organisms Fish in wild water environments were tested for antibiotic levels and antibiotic levels increased progressively from herbivorous to omnivorous to carnivorous, possibly *via* food chain enrichment (Tang et al., 2020). Antibiotics with different properties showed tissue specificity in aquatic products, suggesting significant differences in bioaccumulation factors between antibiotics (Liu et al., 2014; Zhao et al., 2015; Zhao et al., 2016a). Bioaccumulation and the different metabolic pathways of different aquatic organisms lead to a more complex accumulation of antibiotics in aquatic organisms. With the improvement in living standards, there is an increasing demand for aquatic products. The

TABLE 8 | Antibiotic-degrading bacterial strains reported in the recent three years.

Antibiotics		Bacterial species	Concentration (mg/L)	Removal rate (%)	Sources	References
β-lactam	Cephalosporin	*Achromobacter sp.* YF-1	30	92.71 (7 days)	Waste medicine residue	Zhang et al. (2019a)
Sulfonamides	Sulfamethoxazole	*Shewanella oneidensis* MR-1	10	97.9 (3 days)	Laboratory	Mao et al. (2018)
	Sulfamethoxazole	*Shewanella sp.* MR-4	10	100 (3 days)	Laboratory	Mao et al. (2018)
	Sulfamethoxazole	*Pseudomonas mandelii* McBPA4	50	73 (15 days)	Laboratory	Reis et al. (2018)
	Sulfamethoxazole	*Acinetobacter sp.* W1	5~240	100 (10 h)	Activated sludge	Wang and Wang (2018)
	Sulfamethoxazole	*Ochrobactrum sp.* SMX-PM1-SA1	5	45.2 (8 days)	Wastewater	Zhang et al. (2019c)
	Sulfamethoxazole	*Labrys sp.* SMX-W11	5	62.2 (8 days)	Activated sludge	Mulla et al. (2018)
	Sulfamethoxazole	*Gordonia sp.* SMX-W2-SCD14	5	51.4 (8 days)	Pig manure	Mulla et al. (2018)
	Sulfamethoxazole	*Achromobacter sp*. JL9	50	79.45 (120 h)	Pharmaceutical wastewater	Liang et al. (2019)
	Sulfamethoxazole	*Acinetobacter sp*	30	100 (5 h)	Microbiological culture collection	Wang et al. (2018a)
	Sulfadimidine	*Bacillus cereus* J2	50	100 (36 h)	Municipal sewage	Zhang et al. (2019c)
	Sulfamethazine	*Acinetobacter sp*	30	100 (10 h)	Microbiological culture collection	Wang et al. (2018a)
	Sulfadiazine	*Acinetobacter sp*	30	100 (10 h)	Microbiological culture collection	Wang et al. (2018a)
Tetracyclines	Tetracycline	*Raoultella sp.* XY-1	20	70.68 (8 days)	Pig farm sediment	Wu et al. (2018)
	Tetracycline	*Klebsiella sp.* SQY5	10~30	67.32 (92 h)	Municipal sludge	Shao et al. (2018a)
	Tetracycline	*Achromobacter sp.* TJ-2#	50	63.9 (3 days)	Contaminated soil	Cheng et al. (2017b)
	Oxytetracycline	*Pseudomonas sp.* T4	100	26.88 (7 days)	Livestock manure	Meng et al. (2018)
	Oxytetracycline	*Achromobacter sp.* TJ-2#	50	58.3 (3 days)	Contaminated soil	Cheng et al. (2017b)
	Oxytetracycline	*Ochrobactrum sp.* KSS10	30	63.33 (4 days)	Municipal sludge	Shao et al. (2018b)
	Aureomycin	*Achromobacter sp.* TJ-2#	50	65.5 (3 days)	Contaminated soil	Cheng et al. (2017b)
Fluoroquinolones	Norfloxacin	*Staphylococcus caprae* NOR-36	5	92.6 (10 days)	Pharmaceutical wastewater	Fu et al. (2017)
	Ofloxain	*Labrys portucalensis* F11	0.45	34.6 (28 days)	Fluorobenzene	(Maia et al., 2018)
	Ofloxain	*Rhodococcus sp.* FR1	0.45	39.3 (28 days)	Fluorobenzene	(Maia et al., 2018)
	Ciprofloxacin	*Thermus thermophiles* C419	5	57 (5 days)	Pharmaceutical sludge	(Pan et al., 2017)
	Ciprofloxacin	*Enterobacter sp.* (KM504128)	5	96 (14 days)	Hospital effluent water	Liyanage and Manage (2018)
	Ciprofloxacin	*Lactobacillus gesseri.* (KM4055978)	5	100 (14 days)	Hospital effluent water	Liyanage and Manage (2018)
	Ciprofloxacin	*Bacillus sp.* (KM504129)	5	74 (14 days)	Hospital effluent water	Liyanage and Manage (2018)
	Ciprofloxacin	*Bradyrhizobium sp.* GLC_01	0.05	70.4 ± 7.4 (8 days)	Wastewater	Nguyen et al. (2018)
Macrolides	Tylosin	*Achromobacter*	50	96.08 (56 days)	Spinach soil	Zhang et al. (2018c)

government should strengthen the regulation of antibiotic content in aquatic products. There is also a need to strengthen the regulation of fishery drugs and scientific use of drugs and improve the code of practice and standards.

DEGRADATION OF ANTIBIOTICS

Antibiotic pollution is becoming increasingly serious globally. Although countries with severe antibiotic pollution have introduced corresponding policies, they have come too late and/or are inadequate to solve the problem (Kara, 2019). Currently, researchers are in the process of developing environmentally friendly alternatives to antibiotics to reduce the use of antibiotics. At the same time, owing to the excessive antibiotic content in the aquatic environment, researchers have developed various antibiotic treatment techniques to degrade antibiotics. These methods can be roughly divided into the following categories: physical adsorption, chemical oxidation, photodegradation, and biodegradation. The general characteristics of various methods of removing antibiotics from water bodies are shown in **Table 6**.

Physical Removal of Antibiotics

The removal of antibiotics from the aquatic environment can be achieved by adsorbing the antibiotics on an adsorbent and then recovering the adsorbent loaded with antibiotics. Existing physical methods include physical adsorption, membrane filtration, and precipitation. However, the physical methods can only separate the antibiotics from the environment but not degrade them, and subsequent treatment is necessary.

TABLE 9 | Antibiotic-degrading fungi reported in the recent 5 years.

Antibiotics		Fungus	Concentration (mg/L)	Removal rate (%)	Degradation enzyme	References
Sulfonamides	Sulfadiazine	*Fusarium solani* KS256	1.5	18.53 (7 days)	—	Wang et al. (2018b)
	Sulfamethoxazole	*Pycnoporus sanguineus*	10	100 (2 days)	Lac P450	Gao et al. (2017a)
	Sulfamethoxazole	*Phanerochaete Chrysosporium*	10	63.3 (8 days)	MnP and LiP P450	Gao et al. (2017a)
	Sulfamethoxazole	*Phoma sp.* UHH5-1-03	10	57 (168 h)	Lac	Hofmann and Schlosser (2016)
	Sulfamethoxazole	*Trametes versicolor* ATCC 42530	10	90–94 (30 days)	—	Aydin (2016)
	Sulfamethoxazole	*Bjerkandera adusta* ATCC 28314	10	90-94 (30 days)	—	Aydin (2016)
	Sulfamethoxazole	*Achromobacter denitrificans* strain PR1	150	91(51 h)	—	Nguyen et al. (2018)
Fluoroquinolones	Ciprofloxacin	*Pleurotus ostreatus*	500	95.07	MnP	Singh et al. (2017)
	Norfloxacin	*Penicillium janthinellum* KS272	1.5	10.59 (8 days)	—	Wang et al. (2018b)
	Ciprofloxacin	*Pycnoporus sanguineus*	10	98.5 (2 days)	Lac P450	Gao et al. (2017a)
	Norfloxacin	*Pycnoporus sanguineus*	10	96.4 (2 days)	Lac P450	Gao et al. (2017a)
	Ciprofloxacin	*Phanerochaete Chrysosporium*	10	64.5 (8 days)	MnP and LiP P450	Gao et al. (2017a)
	Norfloxacin	*Phanerochaete Chrysosporium*	10	73.2 (8 days)	MnP and LiP P450	Gao et al. (2017a)
	Norfloxacin	*Irpex lacteus*	10	100 (10 days)	Lac P450	Čvančarová et al. (2015)
	Norfloxacin	*Trametes versicolor*	10	85 (14 days)	MnP and MIP	Čvančarová et al. (2015)
	Ofloxacin	*Irpex lacteus*	10	100 (10 days)	MnP and MIP	Čvančarová et al. (2015)
	Ciprofloxacin	*Irpex lacteus*	10	100 (10 days)	Lac and MnP and MIP	Čvančarová et al. (2015)
	Ciprofloxacin	*Pleurotus ostreatus*	10	60 (14 days)	Lac	Čvančarová et al. (2015)
Tetracyclines	Oxytetracycline	*Fusarium verticillioides* KS248	1.5	34.63 (7 days)	—	Wang et al. (2018b)
	Oxytetracycline	*Penicillium janthinellum* KS272	1.5	40.29 (7 days)	—	Wang et al. (2018b)
	Oxytetracycline	*T. harzianum*	250	92 (21 days)	—	Ahumada-Rudolph et al. (2016)
	Oxytetracycline	*T. deliquescens*	250	85 (21 days)	—	Ahumada-Rudolph et al. (2016)
	Oxytetracycline	*P. crustosum*	250	83 (21 days)	—	Ahumada-Rudolph et al. (2016)
	Tetracycline	*Phanerochaete chrysosporium*	10	80 (3 days)	Lip, mnp	Qing et al. (2018)
	Tetracycline	*Trichoderma harzianum*	250	92 (21 days)	—	Ahumada-Rudolph et al. (2016)
	Tetracycline	*Trichoderma deliquescens*	250	85 (21 days)	—	Ahumada-Rudolph et al. (2016)
	Tetracycline	*Penicillium crustosum*	250	83 (21 days)	—	Ahumada-Rudolph et al. (2016)
	Tetracycline	*Rhodotorula mucilaginosa*	250	73 (21 days)	— —	Ahumada-Rudolph et al. (2016)
	Tetracycline	*Talaromyces atroroseus*	250	72 (21 days)	—	Ahumada-Rudolph et al. (2016)
Beta-lactam	Oxacillin	*Leptosphaerulina sp*	16	100 (6 days)	Lac and mnp and lip	Copete-Pertuz et al. (2018)
	Cloxacillin	*Leptosphaerulina sp*	17.5	100 (6 days)	Lac and mnp and lip	Copete-Pertuz et al. (2018)
	Dicloxacillin	*Leptosphaerulina sp*	19	100 (6 days)	Lac and mnp and lip	Copete-Pertuz et al. (2018)
	Cephadroxyl	*Leptosphaerulina sp.* CECT20913	15.2	100 (15 days)	Lac and mnp	Pérez Grisales et al. (2019)
	Cephadroxyl	*Trametes versicolor* ATCC 42530	6	100 (15 days)	Lac and mnp	Pérez Grisales et al. (2019)

Notes: Lac: laccase; LiP: lignin peroxidase; MnP: manganese peroxidase; MIP: manganese-independent peroxidase; CGMCC: China General Microbiological Culture Collection Center.

Physical Adsorption

Physical adsorption is the adsorption of antibiotic molecules on the adsorbent through intermolecular forces. Commonly used adsorbents include activated carbon, modified activated carbon, and other molecular sieve pore structure substances. Ahmed and Theydan (2014) used microwave technology to prepare activated carbon and had high adsorption rates for both ciprofloxacin (CIP) and norfloxacin. Choi et al. (2008) successfully used granular activated carbon. In a different study, Chen and Huang (2010) analyzed the strong adsorption of alumina to three tetracycline antibiotics (chlortetracycline, oxytetracycline, and tetracycline). The efficiency of an adsorbent is related to the pH of the solution. Adsorbents are widely used in wastewater management because they not only adsorb small molecules, such as antibiotics, but also some heavy metal ions and toxic substances such as dyes. Physical adsorption is a low cost method characterized by simple preparation of the adsorbent, no high technical requirements, simple operation, large specific

TABLE 10 | Antibiotic enzyme systems.

Antibiotics		Enzyme	pH	Temperature (°C)	Time	Removal rate (%)	References
Sulfonamides	Sulfamethoxazole	Laccase-syringaldehyde	6	25	<1 h	100	Kumar et al. (2005)
	Sulfamethoxazole	Laccase-acetosyringone	6	25	<1 h	100	Kumar et al. (2005)
	Sulfonamide*	Laccase-syringaldehyde	6	25	180 min	>97	Ding et al. (2016)
	Sulfadimethoxine	Laccase-2-2′-azino-bis-(3-ethylbenzothiazoline-6-sulfonic acid) diammonium salt	4.1	30	30 min	85	Weng et al. (2011)
	Sulfadimethoxine	Laccase-violuric acid	4.1	30	30 min	81	Weng et al. (2011)
	Sulfamonomethoxine	Laccase-2-2′-azino-bis-(3-ethylbenzothiazoline-7-sulfonic acid) diammonium salt	4.1	30	30 min	67	Weng et al. (2011)
	Sulfamonomethoxine	Laccase-violuric acid	4.1	30	30 min	82	Weng et al. (2011)
	Sulfadimethoxine	Laccase-4-hydroxybenzyl alcohol	4.1	30	330 min	67	Weng et al. (2011)
	Sulfadimethoxine	Laccase-syringaldehyde	4.1	30	330 min	89–90	Weng et al. (2011)
	Sulfamonomethoxine	Laccase-5-hydroxybenzyl alcohol	4.1	30	330 min	70	Weng et al. (2011)
	Sulfamonomethoxine	Laccase-syringaldehyde	4.1	30	330 min	83	Weng et al. (2011)
	Sulfamethoxazole	Laccase	4.5	30	24 h	50	Guo et al. (2014)
Fluoroquinolones	Norfloxacin	Chloroperoxidase (CPO)-H_2O_2	5	25	25 min	82.18	Zhao et al. (2017)
	Ciprofloxacin	Combi-CLEA (laccase and versatile peroxidase and glucose oxidase)	3	30	72 h	80/90	Touahar et al. (2014)
	Fluoroquinolone*	Laccase-syringaldehyde + soil	6	25	180 min	>95	Ding et al. (2016)
Tetracyclines	Trimethoprim	Combi-CLEA (laccase and versatile peroxidase and glucose oxidase)	3	30	72 h	50–70	Touahar et al. (2014)
	Tetracycline*	Laccase-syringaldehyde + soil	6	25	180 min	>95	Ding et al. (2016)
	Tetracycline	Laccase	7	20	18 h	78	Llorca et al. (2014)
	Tetracycline	Crude lignin peroxidase-veratryl alcohol	4.2	37	30 min	99	Wen et al. (2009)
	Tetracycline	Crude lignin peroxidase	3	37	30 min	92	Xingxing et al., (2016)
Macrolides	Erythromycin	EreB esterase	7	37	16 h	52	Llorca et al. (2014)

surface area, and strong capacity for antibiotic adsorption. However, due to weak intermolecular interaction, the adsorbed antibiotics can easily escape under the influence of the external environment and cause secondary pollution, and is thus limited in its use to cases with low antibiotic concentrations.

Membrane Filtration

Membrane separation technology uses micro- and nano-porous membranes to intercept or reverse osmosis of antibiotics in water for purification purposes. In practice, membrane separation is commonly used in conjunction with other methods to remove antibiotics from the aquatic environment. Wang et al. (2017a) studied the removal efficiency and influencing factors of tetracycline in water using a magnetic flocculation-membrane separation technique. Yang et al. (2020) made membrane bioreactors (MBRs) more effective for antibiotic treatment by adding rice straw to improve denitrification. In a study by Pérez and Barceló (2008), a laboratory-scale membrane bioreactor achieved a 56% elimination of diclofenac metabolite 4′-hydroxydiclofenac. The use of membrane filtration is a physical process that does not add any chemical reagents, is green, and has good selective filtration. However, because of the small size of the antibiotic molecule and the tendency of other contaminants to clog the pore size, the membrane module needs to be replaced frequently, which is costly.

Degradation of Antibiotics by Photolysis

The separation of electrons and holes generated by semiconductor photocatalysts under light excitation leads to the generation of a large number of oxygen radicals in aquatic environments, thus oxidizing any present antibiotics. Titanium oxide has a high degradation rate for antibiotics in water, however, owing to the narrow spectral absorption of pure TiO_2, researchers often modify it to efficiently degrade antibiotics in wastewater. Mushtaq et al. (2020) used titanium isopropoxide as a titanium precursor to synthesize peptide-based nanoparticles to study the degradation of NOR. Mountassir et al. (2020) constructed recyclable LDH-TiO_2 nanocomposites to degrade sulfamethyisoxazole under UV radiation, where TiO_2 can be reused, to reduce the threat to water resources. Furthermore, researchers are developing new photoelectric systems and explore the use of other metal mineral salts as catalysts to degrade antibiotics. Chang et al. (2017a) constructed a new photoelectric catalytic (PEC) coupled electroenzyme-catalyzed (EEC) oxidation system that degraded up to 98.7% chloramphenicol within 10 h. Eswar et al. (2017) investigated the performance of reticulated CuO photocatalytic degradation of tetracycline in water. Cao et al. (2018) loaded $AgPO_4$-modified $BiVO_4$ on a photoanode on conductive glass, which effectively degraded levofloxacin in water. Photodegradation, a widely used method for the degradation of antibiotics, is green and environmentally friendly, relying on water molecules to provide hydroxyl radicals and oxygen radicals to degrade antibiotics, thus avoiding the possibility of secondary pollution. However, because of the high construction cost of photoelectrodes, it can only be used short-range, which comes with certain limitations. At the same time, some suspended solids and deep pigments in the wastewater obstruct the passage of light and negatively affect the photocatalytic effect.

Chemical Oxidative Degradation of Antibiotics

Chemical oxidation is the degradation of antibiotics through free radicals produced by a chemical reaction that react directly with the antibiotic, causing its chemical bonds to break or decompose. However, this type of method produces a large amount of secondary pollution.

Ji et al. (2015), Yan et al. (2015) used thermal activation of peroxynitrite to produce sulfate radicals to effectively degrade sulfonamide antibiotics, but the effect is not very stable. Gaffney et al. (2015), Nassar et al. (2018) found that chlorination and oxidation selectively removed sulfonamide antibiotics from water, but the degradation effect was greatly influenced by the concentration of the antibiotics and pH.

Compared with earlier oxidative degradation by strong oxidants, Fenton oxidation has greatly reduced the chemical pollution of the environment (Tunç et al., 2012; Tunç et al., 2013; Le et al., 2016; Weng et al., 2020). It can effectively oxidize and remove the difficult-to-degrade organic substances that cannot be removed by traditional wastewater treatment technology. Ioannou-Ttofa et al. (2018) used light illumination combined with the Fenton oxidation technique to degrade ampicillin in water, and showed that the pH had a great influence on the degradation result. The degradation rate of ampicillin increased with an increase in solution pH under acidic conditions.

Biodegradation of Antibiotics

Biodegradation of antibiotics is the use of microorganisms, microbes, and enzymes to break down antibiotics in the environment. It generally does not cause secondary pollution, can be used in a variety of environments, and is an environmentally friendly disposal method.

Plant Adsorption

Plants take up antibiotics from river water and bottom sediments through roots, stems, and leaves, and then transport them through transpiration or degradation by microorganisms enriched by the roots (Susarla et al., 2002), thus reducing the content of pollutants in the aqueous environment. Plant removal of antibiotics is currently performed mainly by the construction of plant floating beds, artificial wetlands, and other environmental management technologies. Because of their low cost and ease of operation, artificial floating beds are more common than artificial wetlands (**Figure 6**), even though artificial wetlands can simultaneously deal with a variety of environmental pollution problems and have self-healing functions that can be used for long periods. As shown in **Table 7**, the type of antibiotic that can be removed from the water column and the antibiotic removal efficiency vary for different plants.

Degradation of Antibiotics Using Activated Sludge

Activated sludge is a collective term for communities of microorganisms and the organic and inorganic materials to which they are attached, and is used for biosorption of antibiotics, biodegradation of antibiotics, and flocculation. The complex microorganisms in the activated sludge form a complex food chain with organic nutrients in the wastewater, and the degradation of antibiotics is achieved through the action of the microbial community. Composting with activated sludge removes contaminants through adsorption and microbial biodegradation. Studies have shown (Zhang et al., 2019b; Zhu et al., 2020) that antibiotics can be removed either by microbial nitrification (autotrophic biodegradation) or by microbial chemical oxygen demand (COD) degradation (heterotrophic biodegradation) in activated sludge.

Terzic et al. (2018) found that activated sludge from a municipal wastewater treatment plant was able to degrade three major macrolides (erythromycin, clarithromycin, and azithromycin) and evaluated their toxicity. Their results showed that the harmful effects of the treated effluent were greatly reduced. Radjenovic et al. (2009) found that charged activated sludge influenced the adsorption of environmental quinolone antibiotics. However, while the adsorption was improved, the effect was not stable. Activated sludge for the degradation of antibiotics is generally derived from biopharmaceutical or hospital wastewater and significantly reduces post-degradation toxicity after activated sludge treatment. However, this method is highly dependent on environmental factors such as pH, temperature, dissolved oxygen, nutrients, and toxic substances, as well as the composition and proportion of the microorganisms, which influence the degradation time. Under low dissolved oxygen conditions, irritating gases such as ammonia or sulfur dioxide are easily produced, and the proportion of nutrients in the wastewater needs to be adjusted frequently; otherwise, the degradation efficiency is low.

The use of activated sludge to decompose antibiotics could have some disadvantages. For example, bacterial fermentation in activated sludge may occur to complete the decomposition of antibiotics. The exposure of bacteria to antibiotics may then lead to the production and proliferation of ARGs, resulting in the emergence of novel types of genetic pollutants (Zeng et al., 2019)

Degradation by Microbial Strains

As a result of prolonged exposure to antibiotics, strains of bacteria become resistant to antibiotics and may even break them down. The biodegradation of antibiotics is dominated by microbial decomposition. However, the antibiotic degradation ability of strains is influenced by many factors such as the antibiotic species, strain type, carbon source, nitrogen source, temperature, and wastewater components (heavy metal ions, COD, etc.,). In recent years, many bacterial strains with antibiotic degradation abilities have been isolated through screening, enrichment, and domestication, and mainly degrade sulfonamides and tetracyclines. This is most likely due to the fact that these two types of antibiotics are more likely to be adsorbed onto sediment and thus remain in a stationary environment for longer periods (Mulla et al., 2018). **Table 8** lists the antibiotic-degrading bacterial strains reported in the literature over the last three years.

The microorganisms that degrade antibiotics can be divided into single and mixed strains, some of which are listed in Martins et al. (2018) demonstrated for the first time that sulfate-reducing flora could remove CIP, and Cordova-Kreylos and Scow (2007) observed that exposing anaerobic sediments to the antibiotic CIP sulfate-reducing bacteria (SRB) is advantageous. In addition, there have been reports that bacteria can degrade antibiotics under sulfate-reducing conditions (Jia et al., 2017) and that nitrate reduction has been used successfully in microbial remediation, where denitrifying bacteria can effectively degrade enrofloxacin and ceftiofur (Alexandrino et al., 2017) as well as CIP. Antibiotic-degrading flora are also present in many estuarine sediments enriched in antibiotics; Chang and Ren (2015) isolated tetracycline antibiotic-degrading flora in sediments of the Eren River estuary, and Harrabi et al. (2018) enriched the flora of the Douro River estuary and achieved a greater than 95% degradation for oxytetracycline and enrofloxacin.

Fungi are more tolerant to high concentrations of pollutants than bacteria and, therefore, are more advantageous in the degradation of antibiotics. Numerous studies have shown that it is feasible to use fungi to degrade antibiotics present in the environment. In **Table 9**, the antibiotic-degrading fungi reported in the literature during the last 5 years are listed.

Enzymatic Degradation

Microorganisms can produce enzymes that degrade antibiotics, such as β-lactamases, which can cleave the β-lactam rings of cyanotoxins and cephalosporins. Based on the substrate specificity of β-lactamases, they can be roughly divided into three categories: penicillinases, cephalosporinases, and oxime-type cephalosporinases. Penicillin enzymes easily decompose penicillin antibiotics, while cephalosporin enzymes have a higher activity in decomposing cephalosporin antibiotics, and the oxime cephalosporin enzymes have a decomposing effect on both penicillin and cephalosporin, but are especially good at decomposing oxime cephalosporin. To efficiently degrade antibiotics, enzyme systems can be constructed. **Table 10** lists the enzyme systems that have been used to degrade antibiotics in recent years.

The construction of various enzyme systems and the use of immobilized enzymes to degrade antibiotics, considered a breakthrough in the field of environmental management, was motivated by the fact that enzymes are easily inactivated in the environment and cannot be used in large quantities in practical applications. Gao et al. (2017b) using magnetic nanoparticles Fe_3O_4 to immobilize β-lactamase to degrade penicillin, the efficiency remained above 95% after 35 times of repeated use; Zhang et al. (2020a) used *in situ* immobilized laccase to degrade tetracycline and ampicillin and achieved a degradation efficiency in water close to 100%. Simón-Herrero et al. (2019) found that laccase immobilized on polyimide erogels used to remove carbamazepine yielded a degradation efficiency of 74%. In a different study, Zdarta et al. (2019) successfully degraded tetracycline by laccase immobilized with electrospun materials using 1-hydroxybenzotriazole as a medium. For degradation experiments, Becker et al. (2017) constructed an enzyme membrane reactor using a mixture of immobilized laccase and eugenol for the degradation of 38 antibiotics. Their results showed that after 24 h the reactor degraded 32 types of antibiotics with a degradation rate of greater than 50%.

At present, the existing enzymes are mainly β-lactamase types for the degradation of lactam antibiotics, laccase, and other strong oxidative enzymes for the nonselective oxidative degradation of antibiotics. Due to the rapid development of immobilized materials, an increasing number of enzymes are immobilized and are already used in actual sites to manage antibiotics pollution (Shao et al., 2019; Liang and Hu, 2020; Shakerian et al., 2020; Zhang et al., 2020a), resulting in an improvement of the stability of the enzymes and the recycling and reuse of them, thus reducing the cost. Over the past two years, immobilized lacquer enzymes have been applied to the degradation of antibiotics, and some other strongly oxidizing enzymes have gradually entered the view of the general researcher and are applied to oxidative degradation of antibiotics by immobilization.

SUMMARY AND OUTLOOK

Antibiotics have greatly polluted the environment globally. Among the prevalent antibiotic pollution treatments, physical adsorption cannot degrade antibiotics, chemical oxidation is likely to cause secondary pollution, photodegradation is expensive. Biodegradation of antibiotics, however, is attracting increasing attention because of its low cost, easy operation, and lack of secondary pollution. Nevertheless, both microbial degradation and activated sludge degradation will inevitably lead to the proliferation of ARGs. Therefore, using purified antibiotic-degrading enzymes for the degradation of antibiotics poses a good alternative. Synthesizing related enzymes *in vitro* or constructing engineered bacteria to produce enzymes would reduce the cost of this approach, making it even more attractive. Therefore, enzyme degradation is becoming the future mainstream of environmental management. The main remaining problem is whether the antibiotic degradation products have toxicity. Although the degradation products of antibiotics are tested for bacterial toxicity, whether there may be a long-term toxicity problem has yet to be determined. However, it is undeniable that the toxicity of enzymatic antibiotics will be greatly reduced. Once the toxicity problem is solved, antibiotic-degrading enzymes may be used in a variety of wastewater treatments.

Antibiotics in the environment can be enriched in humans through the food chain, and they can be very harmful to young children and pregnant women. In addition, antibiotic contamination increases the development of superbugs. However, there is a lack of mandatory standards for the limits of antibiotic fugitive levels in the surface water. Thus, there is an urgent need to control antibiotics in water bodies. China's vast territory has a diverse climate, a diverse industrial layout, and unbalanced economic development. All the factors above influence the distribution of antibiotics in China, and these factors make it challenging for governments to control antibiotics. In recent years, China has attached great importance to the issue of antibiotic contamination, and the government has made significant improvements in antibiotic stewardship; however, there are still some shortcomings, such as, the antibiotic regulatory system and antibiotic management-related standards are inadequate to effectively combat antibiotics pollution. In addition, factory emissions do not meet safety standards. Furthermore, there are no institutions specializing in antibiotic use and management to monitor the use of antibiotics and subsequent pollution management. Finally, scientific guidance on drug use is still required to discourage and prevent antibiotic abuse.

AUTHOR CONTRIBUTIONS

WT and LM conceived the idea of the review, LZ collected literature, CL and LT wrote the manuscript. All authors contributed to the article.

FUNDING

This work was supported by the Beijing Collaborative innovation center for eco-environmental improvement with forestry and fruit trees, Beijing University of Agriculture; Beijing Natural Science Foundation (Grant No. 7174283). Beijing Advanced Innovation Center for Tree Breeding by Molecular Design, Beijing University of Agriculture.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Public Health

ORIGINAL RESEARCH
published: 04 August 2021
doi: 10.3389/fpubh.2021.677851

Household Air Pollution From Solid Cooking Fuel Combustion and Female Breast Cancer

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Background: Women bear a large share of disease burden caused by household air pollution due to their great involvement in domestic activities. Pollutant emissions are believed to vary by exposure patterns such as cooking and space heating. Little is known about the independent effect of solid cooking fuel combustion on breast cancer risk. We aimed to examine the association of indoor coal and wood combustion for cooking with breast cancer risk.

Methods: During June 2004–July 2008, participants aged 30–79 from 10 diverse regions across China were enrolled in the China Kadoorie Biobank. Primary cooking fuel use information in up to three residences was self-reported at baseline. Multivariable logistic regression models yielded adjusted odds ratios (ORs) and 95% confidence intervals (CIs).

Results: A total of 290,396 female participants aged 30–79 were included in the main analysis. Compared with long-term clean fuel users, the fully adjusted ORs were 2.07 (95%CI: 1.37–3.13) for long-term coal users, 1.12 (95% CI: 0.72–1.76) for long-term wood users, and 0.98 (95% CI: 0.55–1.74) for those who used mixed solid fuels to cook. Those who had switched from solid to clean fuels did not have an excess risk of breast cancer (OR: 0.88, 95%CI 0.71–1.10).

Conclusion: Long-term solid fuel combustion for cooking may increase the risk of breast cancer. The strength of association is stronger among coal users than wood users. Targeted interventions are needed to accelerate the access to clean and affordable energy.

Keywords: household air pollution, breast cancer, cooking fuel, indoor air pollution, solid fuel

OPEN ACCESS

Edited by:
Mohiuddin Md. Taimur Khan, Washington State University Tri-Cities, United States

Reviewed by:
Behzad Heibati, University of Oulu, Finland
Keith Dana Thomsen, United States Department of Energy (DOE), United States

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Specialty section:
This article was submitted to Environmental health and Exposome, a section of the journal Frontiers in Public Health

Received: *25 March 2021*
Accepted: *01 July 2021*
Published: *04 August 2021*

Citation:
Liu T, Chen R, Zheng R, Li L and Wang S (2021) Household Air Pollution From Solid Cooking Fuel Combustion and Female Breast Cancer. Front. Public Health 9:677851. doi: 10.3389/fpubh.2021.677851

INTRODUCTION

Household air pollution (HAP) causes immense disease burden throughout the world. Around 3.8 million people died prematurely from illness attributed to HAP (1). Globally, "by far the most important direct health risk is the pollution caused by incomplete combustion of solid fuels for cooking, heating and lighting" (2). The adverse impacts from HAP are largely caused by energy poverty, especially in rural regions of the low-and middle-income countries (LMICs) where some residents lack access to affordable, clean energy such as electricity, biogas and gas (3).

Instead, they rely on solid fuel collected from agricultural residues, hauled from kilometers away, or purchased at a low price to meet daily energy demand (3). According to the World Health Organization (3), solid fuel includes coal as well as biomass fuels (referring to renewable plant-based material such as wood, crop wastes and charcoal), providing heat and light during the process of combustion (4). Incomplete combustion of solid fuels produces high levels of HAP with a range of harmful pollutants, including particulate matter, sulfur oxides, nitrogen oxides, carbon monoxide, polycyclic aromatic hydrocarbons, formaldehyde, and dioxins, to name a few (5–9). In contrast, clean fuel mainly includes "electricity, liquefied petroleum gas (LPG), piped natural gas (PNG), biogas, solar and alcohol fuels", which produces low levels of emissions of particulate matter, sulfur dioxide and other by-products of incomplete combustion when properly used (9). Although the past few years have witnessed a surge in technological innovation in the household energy sector, progress remains too slow to displace the polluting fuel combustion systems and thereby mitigate their health impacts. Based on the most recent global estimates, more than 2.7 billion people heavily relied on domestic solid fuels in 2015, including 450 million people in China (10).

Household air pollution from solid cooking fuel (notably coal and wood) has been categorized as a Group 2A carcinogen (11). Special attention should be placed to females who spend considerable amount of time in proximity to polluting sources due to their great involvement in daily cooking activity (4). Ambient air pollutants (e.g., particulate matter, polycyclic aromatic hydrocarbons) may cause tumor formation in breast and cervix uteri (12–14). Evidence for the relationship with household air pollutants remains scarce. Three previous studies have examined the indoor solid fuel combustion as a risk factor for breast cancer and yielded inconsistent result (15–17). Previous studies on this topic have mainly conducted in high-income countries and focused on wood burning (15, 16). However, in some coal-producing countries such as China and India, coal is considered as a domestic source of energy (11). There is a paucity of studies on the potential impact from indoor coal combustion for cooking. Furthermore, HAP from cooking and space heating are two different exposure patterns, which may have different influences on carcinogenesis. A stove might be kept going all day for heating in winter months (3). By contrast, cooking produces HAP several times per day with a shorter period (3, 18). Field measurement reported significantly lower emissions of pollutants from domestic solid fuel combustion during heating compared to those from cooking (19). Epidemiological evidence on HAP exposure from cooking and heating reported different associations with lung cancer (20). One previous CKB study on HAP from heating fuel use and breast cancer mortality did not find any evident relationship with breast cancer mortality (17). Little is known about the independent effect of cooking fuel use on female breast cancer risk. This study reported findings on the solid cooking fuel combustion with breast cancer risk among 290,396 females.

Abbreviations: HAP, household air pollution; PAHs, Polycyclic aromatic hydrocarbons; 95%CI, confidence interval; HRs, hazard ratios; IQR, interquartile range; SD, standard deviation.

METHODS

Study Population

We used the baseline data from China Kadoorie Biobank (CKB) (21). It was initially set up to recruit 500,000 permanent residents aged 35–74 years without a known disability in five rural and five urban regions (100,000 for each region) (**Supplementary Figure 1**). From June 2004 to July 2008, 512,891 participants aged 30–79 years (302,510 females, 59.0%) completed the baseline survey. To encourage participation, we included 10,715 participants whose age was slightly outside the target range, resulting in the baseline age range 30–79 years. In 2008, ∼4% of participants were randomly selected to attend the resurvey with repeated interviews. Details of this biobank have been described elsewhere (21, 22).

Registered participants went to the local assessment stations after signing the informed consent. Trained health staffs conducted a computer-assisted interview with participants to collect a set of information, including demographics, lifestyle behaviors, and medical history via a standard electronic questionnaire. All participants also underwent physical measurements and a 10 ml blood sample collection. Ethical approval of CKB was obtained from the Ethical Review Committee of the Chinese Center for Disease Control and Prevention and the Oxford Tropical Research Ethics Committee.

Assessment of Exposure and Outcome

Participants were asked to recall their cooking frequency, type of cooking fuels and ownership of ventilated stoves for up to three most recent residences (each lived at least 1 year), and duration (in years) in each residence. Participants were asked, "In your present & two previous houses, how often did you cook at home?" Participants chose from the options of daily, weekly, monthly, rarely/never, no cooking facility (23). For those who cooked at least monthly, we further asked their primary cooking fuel which they used most frequently at each residence (coal, wood, gas, electricity, other unspecified). Solid fuels included coal and wood, whereas clean fuels included gas and electricity. Participants who reported having cooking facilities were asked the presence of chimney or extractor related to cooking stove(s) used (23). Participants cooking daily or weekly were considered as cooking regularly (23–25). Long-term exposure pattern was examined by classifying participants who cooked regularly into three groups: those who always used the same fuel in all residences (always solid, always clean), and those who used solid fuels in previous residence(s) and then used clean fuels in the present residence. Participants who always used solid fuels were further divided into three groups (always wood, always coal, a mixture of coal and wood). All participants were asked if a doctor told them that they had had cancers and the site of cancers. If participants suffered from more than one cancer, the one that occurred first was recorded. The cancer status was also confirmed by the hospital admission in the resurvey. We considered breast cancer (ICD-10: C50.42) as our primary outcome.

Covariates

Covariates of potential interest comprised of demographic characteristics, lifestyle factors, household air pollution, reproductive history and family history, which were selected based on previous literature on this topic (15, 16, 26). The demographic variables included age (continuous variable), study region (urban, rural), education (no education, primary school, middle school, high school and above), occupation (unemployed/retired, agricultural worker, factory worker, non-manual worker), annual family income (<10,000, 10,000–34,999, ≥35,000 yuan), marital status (married, never married/widowed/separated/divorced). Lifestyle and HAP variables included current smoking status (not smoke/occasionally, daily/on most days), alcohol drinking (never/rarely, occasionally/at certain season, monthly/weekly), body mass index (BMI) (continuous variable), environmental tobacco smoke exposure (ETS) (never/occasionally, 1–5 days a week, daily) and ownership of stove ventilation (all stoves, not all, none). Reproductive history included age at menopause (premenopausal, menopause age <50, menopause age ≥50), parity (0, 1, 2, ≥3), use of oral contraceptive pills (never, ever). We included physical activity levels (metabolic equivalent of task, hours/day), family history of cancer (presence or absence) and consumption of preserved vegetables (daily/4–6 days per week, 1–3 days per week, monthly, never/rarely) in our sensitivity analysis.

Statistical Analyses

We restricted our analyses to females ($n = 302,510$) and excluded 2,238 participants who did not report cooking information at three residences or used other unspecified fuels, leaving 300,272 for baseline characteristics estimation. We further excluded participants who did not cook regularly at three residences ($n = 8,839$, 2.9%) and those with fluctuating exposure condition (using clean fuel at the first residence, solid fuel at the second residence and clean fuel again at the third residence) ($n = 1,037$, 0.03%). Finally, a total of 290,396 participants were included in the main analyses.

Adjusted values of baseline characteristics by cooking fuel category were presented, with adjustment for age and region where appropriate. We adopted multivariable logistic regressions to estimate odds ratios (ORs) of breast cancer. Model 1 was adjusted for age and study region (18). Model 2 adjustment included all demographic variables (age, study region, education, occupation, annual family income, marital status) and lifestyle variables (smoking, alcohol consumption, BMI, ETS, and ownership of stove ventilation) (15). Model 3 adjustment included all above variables and reproductive history (age at menopause, parity, contraceptive use) (15). We considered clean fuel group as our reference (defined as using gas and/or electricity in all recalled residences) (18, 23, 25). We also calculated the duration of solid fuel exposure during the recall period by summing the number of years at three residences where solid fuel (coal or wood) was reported as the primary cooking fuel. Duration of exposure was classified into three groups: never, duration <25, duration ≥25. Linear trend was tested by modeling a continuous variable that was assigned the median year of duration for each participants' exposure category (27). Considering the biology of female breast cancer and HAP, we stratified the analysis by environmental tobacco smoke exposure, menopause status and contraceptive use, controlling for the same set of covariates as appropriate. The tests for interaction were performed using likelihood ratio test comparing models with and without the cross-product term.

Several sensitivity analyses were further performed. First, we additionally adjusted for potential covariates, including physical activity, family history of cancer and consumption of preserved vegetables. Second, we excluded participants who smoked daily/on most days; those who were exposed to environmental tobacco smoke daily or almost every day; those who were nulliparous; those who had ever used oral contraceptive pills. Third, we selected the lag period of 5 years and 10 years, discounting the exposure during this period. Finally, we explored the association of HAP from solid cooking fuel use with breast cancer mortality, using time in study as the time scale. All analyses were performed using Stata software 15.1 (StataCorp, TX, USA).

RESULTS

Of the 300,272 females [mean (SD) age 51.46 (10.48) years], 51.1 % always used solid cooking fuel and 18.0% always used clean fuel in all residences. Females who always used solid fuels tended to be older, more likely to live in rural region, less educated, more exposed to passive smoking, less likely to use oral contraceptive pills and had lower household income in comparison with clean fuel users (**Table 1**).

We documented 551 participants diagnosed with breast cancer. Compared with long-term clean cooking fuel use, long-term coal combustion was associated with a higher risk of breast cancer (fully adjusted OR:2.07, 95%CI: 1.37–3.13) (**Table 2**). Fully adjusted ORs of breast cancer were 1.12 (95%CI: 0.72–1.76) for those who always used wood, and 0.98 (95% CI: 0.55–1.74) for those who used mixed solid fuels to cook [mean duration of exposure: 16 years]. Long-term solid cooking fuel combustion [mean duration of exposure: 30 years] appeared to confer a higher risk of breast cancer, albeit not significant (fully adjusted OR,1.19 (95%CI: 0.84–1.67). There was no elevated cancer risk among women who had switched into clean fuels [mean duration of exposure: 18 years]. No evident relationship was observed between solid fuel use and breast cancer risk.

There was no statistical effect measure modification by environmental tobacco smoking (ETS), cooking stove ventilation, menopausal status or contraceptive use (**Figure 1**). The strength of observed associations remained largely unchanged after excluding the mixed fuel users. The adjusted OR was somewhat stronger in females with daily ETS exposure (OR: 3.26, 95% CI: 1.83–5.81) than in those who got exposed to ETS 1–5 days per week (OR 0.98, 95% CI: 0.38–2.48) and in those who never/occasionally got exposed to ETS (OR 0.73, 95%CI: 0.38–1.38).

In the sensitivity analyses, the association of solid fuel exposure and breast cancer risk was unaltered after adjusting

TABLE 1 | Baseline characteristics by cooking fuel use (n = 300,272[a]).

Characteristics	Cooking fuel exposure			
	Solid fuel	Clean fuel	Solid to clean fuel[b]	No cooking
No. of participants, n (%)	152802 (51.1)	53875 (18.0)	83719 (27.9)	8839 (3.0)
Age at baseline (y)	53.0	46.2	52.8	45.5
BMI (kg/m^2)	23.5	24.0	24.3	24.4
Physical activity (MET-h/d)	20.3	19.4	21.0	23.4
Rural (%)	91.4	10.2	20.8	46.5
Married (%)	89.3	87.1	89.4	88.7
Primary school and lower (%)	6.8	3.6	5.6	5.5
Income <10,000 (Yuan[c]/y) (%)	41.0	11.7	18.8	8.4
No occupation (%)	22.6	39.7	40.6	21.2
Tobacco smoking[d] (%)	3.9	4.5	4.6	4.5
Alcohol drinking[e] (%)	1.7	2.9	1.9	3.1
Family history of cancer (%)	16.2	16.9	17.8	16.1
Passive smoking[f] (%)	87.1	74.9	83.9	75.3
Good ventilation[g] (%)	11.7	27.2	8.2	15.5
Postmenopause[h] (%)	82.9	78.8	82.6	78.5
Having live birth (%)	98.8	98.5	99.1	97.1
Contraceptive use[h] (%)	5.5	12.6	16.6	20.6

We used linear models (for continuous variables) or logistic models (for categorical variables) to estimate predicted probabilities adjusted for age and region as appropriate.
BMI, body mass index; MET-h/d, metabolic equivalent task-hours per day.
[a] Participants were classified as clean or solid fuel users if they reported only using clean or solid fuel as primary cooking fuel at all three residences. The no cooking group included people who did not cook, or rarely cooked, or did not have cooking facility at three residences. Few participants reported fluctuating exposure condition (using clean fuel at first residence, solid fuel at second residence, and then clean fuel again at the third residence) (n = 1,037, 0.3%), thus this group were not presented.
[b] "Solid to clean fuel" exposure was defined as using solid fuel (coal, wood) as the primary cooking fuel at previous residences and then used clean fuel at the current residence.
[c] 10,000 Yuan = 1412.6688 US dollar.
[d] Tobacco smoking was defined as smoking tobacco daily or on most days.
[e] Alcohol drinking was defined as drinking any alcohol usually at least once a week.
[f] Passive smoking was defined as ever lived with smoker in the same house for at least 6 months.
[g] Good ventilation was defined as all stoves for cooking with a chimney or extractor, or had no stoves at three residences.
[h] Variables had forty-three missing values.

for potential confounders and excluding regular smokers, nulliparous women and those who had ever used oral contraceptive drugs (**Supplementary Table 1**). When 5-year or 10-year lag period was adopted, the strength of observed associations of two cancers appeared to be increased among long-term wood users and overall long-term solid fuel users, yielding significant results (**Supplementary Tables 2, 3**). We did not observe excess risk of breast cancer mortality, probably due to insufficient number of deaths (**Supplementary Table 4**).

DISCUSSION

In this study, we observed inconsistent associations of solid cooking fuel exposure with breast cancer risk. The adjusted ORs of breast cancer were not statistically significant among persistent solid fuel users in general (OR: 1.19, 0.84–1.67). In line with our finding, a case-control study of women on Long Island demonstrated no increased risk of breast cancer incidence in females who frequently burned wood in their home (16). However, when stratifying by type of solid fuel use, we observed a higher risk of breast cancer in persistent coal users (OR 2.07, 2.37–3.13) but not in persistent wood users. Apart from that, a prospective cohort study in the United States or Puerto Rico suggested that having indoor wood-burning stove/fireplace appeared to confer higher breast cancer risk (HR=1.11, 95%CI: 1.01–1.22) (15). Reports are inconsistent on which type of wood (synthetic or wood logs) can produce more polycyclic aromatic hydrocarbon (PAH) during domestic combustion (5, 6, 28). Previous association studies and risk assessment mainly focused on household wood combustion. The present study examined both wood and coal exposure and yielded inconsistent associations with breast cancer. Further prospective evidence is needed to elucidate the relationship of individual and combined effect of wood and coal exposure with breast cancer risk. Moreover, previous CKB study on heating fuel use did not observe excess risk of breast cancer mortality in any solid fuel groups (10). In contrast, this study focused on cooking fuel use and firstly suggested a positive association of long-term coal combustion for cooking with breast cancer risk. The strength of association remained largely unchanged in sensitivity analyses (**Supplementary Tables 1–3**). A possible explanation is that solid fuel combustion for cooking has a longer lifetime duration and thus provides higher cumulative inhaled pollutants compared to solid fuel combustion for heating (18). HAP from heating is a seasonal exposure during winter months while HAP from cooking is a regular exposure in this study since we included

TABLE 2 | Association of cooking fuel use with breast cancer risk among 290,396 participants[a].

	No. of participants at baseline, *n*	Cases, *n*	Model 1	Model 2	Model 3
Pattern of fuel use					
Always clean fuel (reference)	53875	148	ref	ref	ref
Solid to clean fuel	83719	243	0.92 (0.74–1.14)	0.98 (0.79–1.22)	0.88 (0.71–1.10)
Always solid fuel	152802	160	0.80 (0.59–1.07)	1.19 (0.86–1.66)	1.19 (0.84–1.67)
Solid cooking fuel type[b]					
Always coal	56835	83	1.48 (1.01–2.17)	1.81 (1.22–2.67)	2.07 (1.37–3.13)
Always wood	65956	56	0.60 (0.42–0.87)	1.12 (0.72–1.74)	1.12 (0.72–1.76)
A mixture of coal and wood	30011	21	0.69 (0.40–1.19)	0.94 (0.53–1.65)	0.98 (0.55–1.74)
Duration of solid fuel exposure (y)[c]					
Never[d]	53875	148	ref	ref	ref
Duration <25	115971	252	1.01 (0.82–1.25)	1.07 (0.87–1.33)	1.02 (0.82–1.27)
Duration ≥25	120550	151	0.65 (0.50–0.85)	0.82 (0.63–1.08)	0.78 (0.59–1.03)
P for trend			0.0013	0.1561	0.0849

Model 1 was adjusted for age and region. Model 2 was additionally adjusted for education, occupation, marital status, household income, body mass index (BMI), smoking status and alcohol consumption, environmental tobacco smoke and stoves with ventilation. Model 3 was further adjusted for age at menopause, parity and use of oral contraceptive pills.
OR, odds ratio; CI, confidence interval.
[a] *Few people did not cook at three residences (n = 8,839, 2.9 %) or had switched from solid to clean fuels (n = 1,037, 0.3%), thus were excluded from the models. Clean fuel group was considered as common reference group.*
[b] *Solid fuel group did not include those who had switched from solid to clean fuels (n = 83,719).*
[c] *Duration was calculated by summing the number of years in each residence where solid fuel (coal, wood) were reported as the primary cooking fuel.*
[d] *The never group included those who used clean fuel at three residences.*

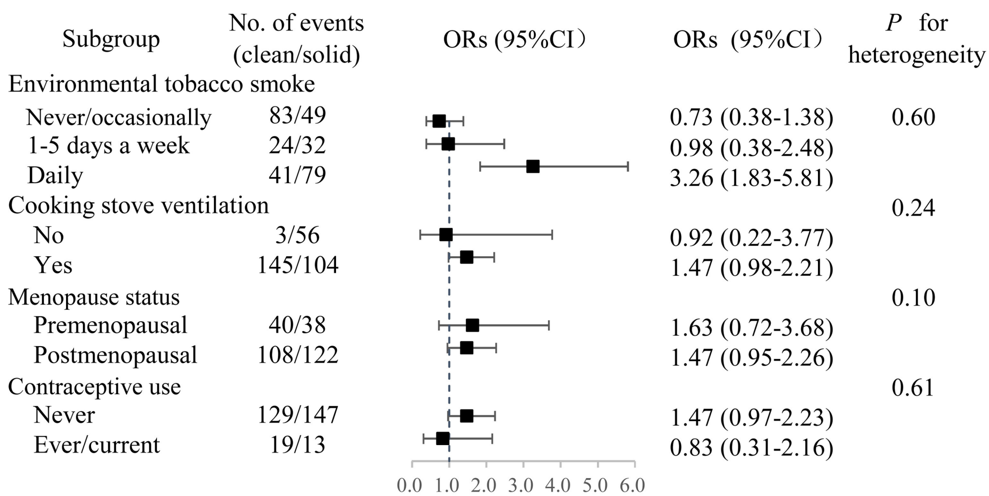

FIGURE 1 | Adjusted ORs of breast cancer associated with long-term solid fuel use. Participants who had switched from solid to clean fuels or used a mixture of coal and wood were excluded. OR, odds ratio. CI, confidence interval.

long-term solid fuel users who cooked daily or weekly in each residence lived at least 1 year. Differences in study design and covariates adjustment may also lead to different findings in two CKB studies. The association of HAP from different domestic activities (e.g., cooking and heating) with breast cancer risk needs future research to elucidate.

We observed no elevated breast cancer risk among women who had ceased using solid fuels. The point estimate of risk was lower in those who had switched from solid to clean fuels than long-term solid fuel users [OR]. Those who had ceased using solid fuels may get less exposed to solid fuel burning than long-term solid fuel users [duration in years: median (IQR): 16 (9–25) vs. 30 (21–41)]. Previous CKB study has demonstrated that the excess risk of all-cause mortality decreased by more than 60% in 5 years after cessation of indoor solid fuel burning (29). The present study further reported the health impact of cession from solid fuels on breast cancer risk. On the global basis, females bear a large share of disease burden caused by HAP due to their domestic roles (3). Our findings may have unique implications on females and suggest the reduction of solid fuel use for cooking. Targeted efforts are needed to accelerate the promotion of clean fuel production facilities and distribution networks.

The association between household air pollution and breast cancer is biologically plausible. Incomplete combustion of solid fuels releases many pollutants to the indoor and outdoor air, such as carbon monoxide, particulate matter, carcinogenic polycyclic aromatic hydrocarbons (PAHs) (5–9). Of all these pollutants, PAHs have been widely investigated and classified as carcinogenic to humans (IARC Group1) (30). About 60.5% of the global total PAH emissions were from combustion of biomass fuels including wood and crop residues (31). In China, coal and biomass fuel combustion are two major emission activates of PAHs, accounting for roughly 20 and 60%, respectively (32). The field measurements showed that the total emission factors (EFs) of 28 PAHs from solid fuel combustion during a regular cooking period ranged from 20.7 to 535 mg/kg (33). EFs of PAHs varied from several mg/kg for wood fuels to about 200mg/kg for bituminous coal, a dirty fuel burned in domestic stoves in rural China due to low cost (34). Different emission profiles between coal and biomass combustion were also observed for predominant individual PAHs including benzo[a]pyrene(BaP), pyrene (PYR), perylene (PER), Benzo[e]pyrene(BeP) and dibenzo[a,l]pyrene (DBalP) (33). Experimental evidence has confirmed that PAH metabolites can react with DNA and form PAH-DNA adducts, which leads to mutations of cancer related-genes and cell death (35–37). Potential carcinogenic pathways include sister chromatid exchange, mutations in TP53 as well as DNA methylation (26, 38, 39). BaP, a marker of carcinogenic potency of PAH mixture and an endocrine-disrupting pollutant, was associated with increased risk of breast cancer in a French cohort (13, 40).

Persistent coal users had a higher risk of breast cancer than persistent wood users. We cannot directly compare our estimate for coal exposure with prior studies. To our knowledge, this is the first study which reports the association of breast cancer with coal combustion for cooking. Our results should be interpreted with caution due to relatively small number of cases. Given the sample sizes in the subgroups, we have sufficient power for coal combustion analysis (approximately 100%) but not for wood combustion (<50%). Although the play of chance cannot be ruled out, our analysis may suggest that pollutants from coal combustion could have more hazardous effect on breast cancer development than those from wood combustion. Different fuel properties and environmental condition contributes to the different formation and changes of trace organics emitted from combustion which may have adverse effects on breast carcinogenesis (41). Results from a previous field emission test study revealed that there was a statistically positive relationship between PAH derivatives and corresponding parent PAHs in emissions from coal combustion, but insignificant relationships for those from wood burning (41). PAHs exposure could be ubiquitous and concurrent multiple indoor sources of PAHs were associated with a 30–50% increase in breast cancer risk (28). Similarly, PAH profiles from inhalation and digestion could be modifiable risk factors (28). Further studies are warranted to monitor the multiple sources of PAH emissions between coal and wood combustion for cooking and elucidate their association with breast cancer.

The chief strengths of this study include the large number of cooking fuel users (in particular for coal users), geographical diversity and completeness of data collection. Moreover, to discount the exposure that is thought irrelevant to the outcome, we conducted sensitivity analyses and selected 5-year or 10-year lag period. Our study has several limitations as well. First, the cross-sectional design of this study precludes a causal inference between solid fuel exposure and risk of breast cancer. Further prospective studies are needed to confirm the causal relationship. Second, like other CKB studies, recall-bias is possible because of the self-reported nature of the baseline survey. Nevertheless, about 78% of the participants in the resurvey reported the same type of cooking fuel as in the baseline survey, and the kappa value for cooking information was acceptable (0.6) (42). The physician-diagnosed cancer history was also confirmed by hospital admission information in the resurvey. Third, although self-reported primary cooking fuel has been adopted as a practical proxy of HAP in many studies, it remains an inherently limited indicator (3). It is possible that secondary fuel exposure and pollutants from neighborhood also contribute to the HAP. Primary fuel use represents a compromise which balances imperative of capturing detailed information on HAP with the pragmatic considerations such as feasibility of conducting surveys and eliciting reliable information from participants. Fourth, we did not account for ambient air pollution that might contribute to breast cancer risk. Since CKB public database did not disclose home address due to privacy protection, GIS method (grid-based method) cannot be used to locate and control for ambient air pollutants. However, CKB disclosed the province where study participants were resided in, and in each province the study participants were all located in the same community or village. Although we could not obtain ambient air pollution data, we adjusted for study region in all models and assumed a similar pattern of ambient air pollution exposure from the same region (29). We expected this strategy could somehow account for residual confounding from ambient air pollution (29). Finally, CKB project does not include histotype or genetic information.

CONCLUSION

Household air pollution from solid cooking fuel combustion may elevate the risk of female breast cancer. The strength of the association is higher in long-term coal users than in long-term wood users. This study may have global implications as many countries are in the transition to clean energy. Efforts to disseminate clean and affordable alternatives (electricity and gas) are gaining momentum in LMICs (3). Adoption of sustainable clean energy solutions hinges on improved understanding of gender dynamics of household energy use and sex-specific health impacts (3). Gender-responsive interventions which taking into account the gender roles in household energy acquisition and uses are required. More evidence on health impacts on females is needed for implementation of policies to promote health, as females are often the primary cooking fuel users and the ones who benefit most from transition to clean cooking fuels (3).

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethical Review Committee of the Chinese Center for Disease Control and Prevention and the Oxford Tropical Research Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

TL and SW designed the study. SW acquired the data. TL analyzed and drafted the manuscript. All authors contributed to the interpretation of data and revised the article. All authors read and approved the final article.

FUNDING

The CKB baseline survey and first resurvey was supported by grants (2016YFC0900500, 2016YFC0900501, and 2016YFC0900504) from the National Key Research and Development Program of China, grants from the Kadoorie Charitable Foundation in Hong Kong and grants (088158/Z/09/Z, 104085/Z/14/Z, and 104085/Z/14/Z) from Wellcome Trust in the UK. The funders had no role in the study design, data collection, data analysis and interpretation, writing of the report or decision to submit the article for publication. The present study was supported by the National Natural Science Foundation (Grant No. 81502884) and the National Key Research and Development Program of China [2018YFC1311704].

ACKNOWLEDGMENTS

We thank Chinese Center for Disease Control and Prevention, Chinese Ministry of Health, National Health and Family Planning Commission of China, and 10 provincial/regional Health Administrative Departments. The most important acknowledgment is to the participants in the study and the members of the survey teams in each of the 10 regional centers, as well as to the project development and management teams based at Beijing, Oxford and the 10 regional centers.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2021.677851/full#supplementary-material

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frontiers in Public Health

ORIGINAL RESEARCH
published: 21 February 2022
doi: 10.3389/fpubh.2022.821892

Presence and Plant Uptake of Heavy Metals in Tidal Marsh Wetland Soils

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Marsh grasses have been used as efficient tools for phytoremediation and are known to play key roles in maintaining ecosystem functions by reducing the contamination of coastlines. This study was initiated to understand how human activities in wetlands can impact ion-heavy metal concentrations in relation to native and invasive marsh grasses. The study site, Blackbird Creek (BBC) is a tidal wetland that experiences agricultural, fishing, recreational, residential and other anthropogenic activities throughout the year. Heavy metals cadmium, arsenic, and lead in the soils and marsh grasses were monitored along with the ion compositions of soils. The main objective of this study was to understand if the marsh soils containing monotypic stands of native (*Spartina*) and non-native (*Phragmites*) vegetation display similar levels of heavy metals. Differences were observed in the concentrations of heavy metals at study sites with varying marsh vegetation types, and in soils containing vegetation and no vegetation. The soils with dense *Spartina* and *Phragmites* stands were anaerobic whereas soil at the boat ramp site was comparatively less anaerobic and also had increased levels of cadmium. Heavy metal concentrations in soil and *Phragmites* leaves were inversely correlated whereas they were positively correlated in *Spartina* sites. Electrical conductivity and pH levels in soil also showed increased cadmium and arsenic concentrations. These findings collectively infer that human activities and seasonal changes can increase soil complexities affecting the bioavailability of metals.

Keywords: heavy metals, arsenic, cadmium, lead, marsh grass, *Spartina alterniflora*, *Phragmites australis*

OPEN ACCESS

Edited by:
Mohiuddin Md. Taimur Khan,
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Specialty section:
This article was submitted to Environmental health and Exposome, a section of the journal Frontiers in Public Health

Received: *24 November 2021*
Accepted: *24 January 2022*
Published: *21 February 2022*

Citation:
Chintapenta LK, Ommanney KI and Ozbay G (2022) Presence and Plant Uptake of Heavy Metals in Tidal Marsh Wetland Soils. Front. Public Health 10:821892. doi: 10.3389/fpubh.2022.821892

INTRODUCTION

Mid-Atlantic estuarine wetlands are vital habitats for numerous aquatic organisms including plants, fishes, birds, and mammals. Two hydrophytic plants, the native cordgrass (*Spartina alterniflora*) and the non-native common reed (*Phragmites australis*) predominate these wetlands (1, 2). The aggressive invasion of common reed in the Delaware Bay estuaries has raised concerns on the ecosystem health and the productivity of the affected areas (3–6). It has been reported that anthropogenic activities exacerbate the spread of common reed, and while invasive species are generally considered to have negative impacts on the ecosystems they inhabit. In contrast some studies indicate that the common reed has illustrated the ability to play a key role in ecosystem functions with regards to heavy metal mitigation (6). Reports also indicate that aquatic plants are regularly exposed to pollutants thereby their roots, rhizomes, and other organs could uptake higher concentrations of pollutants and heavy metals (7). This ability of plants, specifically cord grass and the common reed, makes them ideal bio-indicators and focal subjects for pollution mitigation studies (7, 8).

Wetland plants constantly live under inundated conditions increasing the rate of microbial anaerobic respiration (9). This alters the processes of adsorption and desorption of ions in the soil (10) which can affect the bio availability of metals (11). Soils in wetlands are mostly anaerobic and are often reported to have increased concentrations of heavy metals (4). The extent of metal uptake by plants from the soils largely depends on their bioavailability, redox potential, pH and hydrological conditions including the water content (12, 13). Physico-chemical changes in marsh soils can increase the solubility of heavy metals and promote their discharge into aquatic systems and may significantly harm the aquatic life and thus impact the ecology of the system (14). Transport of heavy metals from soil into the aquatic ecosystems therefore depends on the solubility of metals, which is influenced by aerobic or anaerobic conditions, pH, and redox potential (15).

According to United States Environmental Protection Agency (USEPA), mercury, cadmium, lead, nickel, copper, zinc, chromium, and arsenic are the common metal contaminants in soils affected by anthropogenic activities (15, 16). Metal type and their bio availabilities in soils determine the extent of physiological uptake and potential toxic effects of metals in living organisms (17). For example, precipitates and insoluble metal complexes in soils are largely unavailable to plants (18). In brackish wetland ecosystems, the presence of salt ions may reduce the root uptake of metals (11) and impact plant removal efficiency. Overall health of tidal wetlands is heavily reliant on the microorganisms and other organisms that dwell within the ecosystem including crustaceans, fish, and mammals. The concern is that these metal contaminants, even present at low concentrations in the sediments, can bio accumulate in the lower trophic level organisms and could become harmful to consumers at the apex of ecosystem food webs (19). In fact, heavy metal concentrations can reach critical levels in low trophic level organisms such as detritivores. For example, the Atlantic blue crab (*Callinectes sapidus*) is a detritivore that is recreationally and commercially important in the Mid-Atlantic region (20).

Several heavy metals are naturally present in low concentrations in soils and thus could be considered harmless. However, human interferences in natural ecosystems can increase the levels of these metals. Common sources of heavy metals in the study site, Blackbird Creek (BBC) tidal marsh originate from agricultural, residential, transportation and recreational activities (4, 21–23). Metals chosen for this study have known anthropogenic sources: lead (Pb) has residential and recreational sources from drinking water lines, oil, and ammunition, and arsenic (As) from pesticides and fertilizers, and cadmium (Cd) from phosphorous-based fertilizers (24, 25). This is the reason we chose to focus on Arsenic, lead, and mercury in our study. However, these metals have geological (non-anthropogenic) sources as well. This study was conducted to understand how various activities at the study sites can impact ion-heavy metal concentrations and their relations. The focus of this research was to explore if we can find differences in the heavy metal concentrations within the soils of native and non-native vegetation. Results from this research will illustrate environmental significance on how vegetation type can influence the soil quality and ecosystem health.

METHODS

Study Site

The study site Blackbird Creek (BBC) Estuarine Wetland is located within the Appoquinimink watershed in New Castle County, Delaware. Blackbird Creek is tidally fed from the Delaware Bay to a major extent and flows into the Delaware River. The wetland area has been receiving considerable anthropogenic impacts from residential, agricultural, and recreational activities yet still maintains a relatively pristine classification (26). The site is currently managed and monitored by Delaware National Estuarine Research Reserve (DNERR). This is a unique site that has Major vegetations in the tidal marsh area were identified as cordgrass and common reed.

Sample Collection

Six sampling sites were randomly selected in the BBC tidal marsh area from the mouth of the creek to the Delaware Bay with varying cordgrass and common reed plant densities: *Phragmites* (P), mixed grass site (M) containing both *Phragmites* and *Spartina*, Agriculture (Ag-B) site with buffer, Boat ramp (BR), *Spartina* (S), and Agriculture site without buffer (Ag-NB) (**Figure 1**).

Soil

The surface plant litter was removed and soil samples from the top 2.5 cm at the six sampling locations were collected monthly from May to November in 2014 and 2015. Soil samples were collected using a clean shovel and placed in labeled one-quart plastic zip-lock bags and kept on ice in a cooler for transportation from the field to the laboratory. Samples were collected monthly and for 2 years to observe the trends in soil nutrients and heavy metal concentrations with relation to human activities. The soil samples were dried at 110°C and grounded to <0.1 mm using a ceramic mortar and pestle.

Pore Water

Soil pore water samples were also collected. At each of the six soil sampling sites, a custom-built 30 × 30 cm quadrat was laid next to the soil sampling spots and wet soils were collected from the center and the four corners of the quadrat-outlined area to prepare a composite sample. triplicate samples were collected from each site. The samples in zip-lock bags were stored in a cooler on ice and transported to the laboratory. Pore water samples were collected monthly for 2 years. At the time of analysis aliquots (50 g) of the wet soil sample was transferred into a 50 mL centrifuge tube and centrifuged at 13,000 revolutions per minute (rpm) using a Sorvall high speed centrifuge (Thermofisher Scientific, RC 6+, PA) for 20 minutes to separate pore water from the soil solids according to Guo et al. (27). The isolated pore water was passed through a 0.45-micron nylon filter and analyzed for concentrations of As, Pb, and Cd using inductively coupled plasma-atomic emission spectroscopy

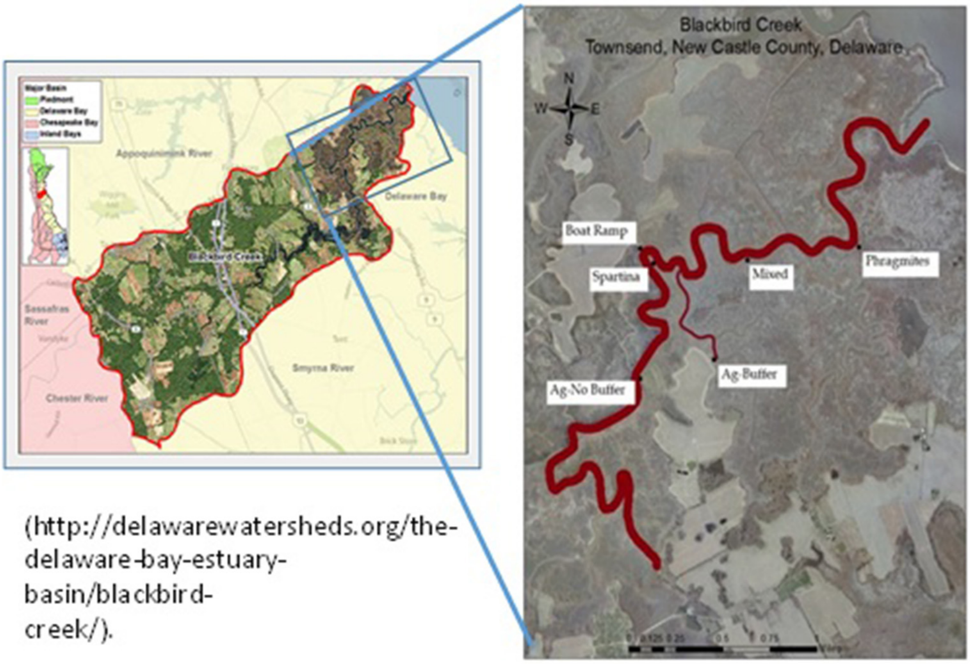

FIGURE 1 | Soil and water sampling sites in the Blackbird Creek, Townsend, Delaware *Phragmites*- (P); mixed site (M); agriculture (Ag-B); boat ramp (BR); *Spartina* (S); agriculture site without buffer (Ag-NB). First map is from DNREC website.

(ICP-AES) techniques (IRIS Intrepid II XSP Duo View, Thermo Electron, Franklin, MA).

Plants

Common reed and cordgrass leaves were collected from June through September 2014 from several individual plants at each site monthly using clean scissors. The leaves were then placed in labeled plastic bags and stored on ice and transported to the laboratory. After bringing them to the laboratory, the plant samples were frozen in liquid nitrogen and then stored at −80°C to prevent bacterial growth. Leaf samples were cut with scissors into small pieces (20–23 cm) and placed in aluminum foil boats, then dried in the oven at 80°C for 24 h. The dried samples were then ground to <0.1 mm using a motor and pestle. Three grams of the ground sample were weighed in a crucible and then heated at 460°C for 24 h in a Thermo Scientific Thermolyne Muffle Furnace (27). The ashes were cooled to the room temperature, wrapped in Bemis parafilm, and stored in a fume hood until further analysis.

Acid Digestion of the Processed Samples for Heavy Metals Analysis: All tools used for acid digestion were washed with 5% nitric acid, rinsed with deionized water, and air dried.

Soils

Soil samples were digested using Parr Microwave Acid Digestion Vessel (PMADV) following the methods of Guo et al. (27). In brief, 1,000 mg of soil sample was weighed into a Polytetrafluoroethylene (PTFE) vial, followed by addition of 3 mL concentrated trace-metal-grade nitric acid and 3 mL High Performance Liquid Chromatography (HPLC)-grade deionized water. The PTFE vial was then loaded into a digestion bomb and heated in a conventional microwave oven (RCA Model, Curtis International Ltd. Etobicoke, Ontario, Canada) at 50% power for 2.5 min. The digestate was fully transferred into a 50 mL volumetric flask.

Plant Leaves

Leaf ashes were digested using an alternative acid digestion method (3). Both soil and plant digested samples were filtered through Whatman number two 70 mm filter circles and stored in centrifuge tubes in an acid storage cabinet until analysis.

Graphite Furnace Atomic Absorption Spectrophotometer (GFAAS) Analysis

The digested soil and leaf samples were analyzed for As, Pb, and Cd concentrations using the Graphite Furnace Atomic Absorption Spectrophotometer (GFAAS) (AAnalyst 600, Perkin Elmer, PA), in three technical triplicates. Winlab 32 software was used for atomization program for each metal analysis. Before analyzing the samples, the instrument was calibrated first using standards and matrix modifiers were used to reduce background noise. For example, palladium was used for As and ammonium phosphate for Cd and Pb. After analysis, a mean concentration from three technical triplicates was calculated for each sample.

Statistical Analysis

The data was analyzed using statistical software package, *PRIMER 6 (Primer-E Ltd, Plymouth, UK)*. Analysis of similarities

(ANOSIM) is an analog of univariate analysis of variance (ANOVA) and is used to analyze the differences in the heavy metal concentrations between the study sites (marsh soil and marsh grasses) and study months. Heavy metal (arsenic, cadmium and lead) data in 2014 for the *Phragmites* and *Spartina* soils and grasses was exported into the PRIMER-E program, these

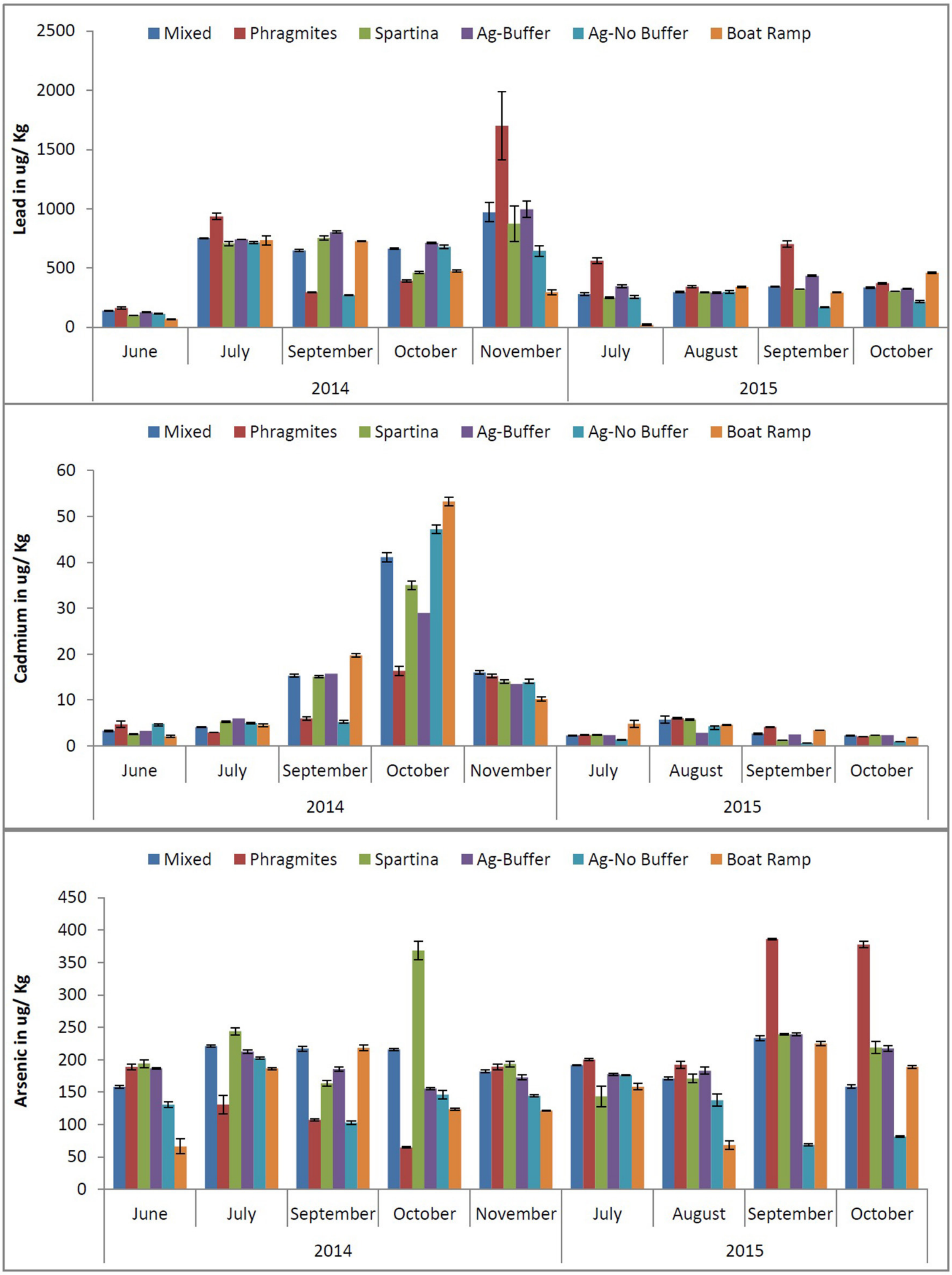

FIGURE 2 | The concentrations of heavy metals (Pb, Cd, and As) in the marsh soils for the six study sites observed during the years 2014 and 2015.

data were normalized, and a resemblance matrix was constructed between the samples using the Euclidean distances. ANOSIM was performed on the resemblance matrix, the factors considered in the analysis were the study sites (*Spartina* soil, *Phragmites* soil, *Spartina* grass and *Phragmites* grass). In this test "R" value varying from 0 to 1, indicates the strength of the factors on the samples. R values close to "0" indicate no separation between the factor groups while R values close to "1" indicate high levels of separation. Principal component analysis (PCA), a multivariate analysis was performed to determine the relationship patterns of heavy metal and ion concentrations during the study period.

RESULTS AND DISCUSSION

Heavy Metal Concentrations in the Soils

Arsenic concentrations in soils during the two-year study period ranged from 68 to 386 ug/ kg, while lead levels ranged from 67 to 1700 ug/ kg (**Figure 2**). Cadmium concentrations were comparatively low in the soils of BBC, ranging from 1 to 53 ug/ kg. As illustrated in **Figure 2**, temporal relationships between two sampling years showed a steady decrease in the concentrations of As, Cd, and Pb at all six study sites. An unusual spike in the Cd concentrations in October of 2014 may be associated with a storm event causing high levels of precipitation and flooding in and around the tidal marsh. There was a spike in Pb concentration in November for *Phragmites* site in 2014 followed by Mixed and Ag Buffer sites. The spike in Pb levels occurred 1 month after Cd spike for Boat Ramp followed by Mixed and Ag-No Buffer sites. This change could be expected as Cd might have been absorbed faster by the plants and the soil while Pb remained relatively intact the soil (28). Cadmium sorption to soil displayed greater pH dependence than Pb, it has been reported that Cd was absorbed via electrostatic surface reactions and/or possible inner-sphere complexation at pH 3.7 (29). In this study, pH at the boat ramp in October was 3.7 which might have resulted in higher and faster Cd absorption. It has been reported that Pb generally adsorbs more strongly than Cd in the soils (29) and poses less of a threat to underlying ground water systems due to its lower mobility and availability. However, the LEAD Group (30) reported that Cd is more readily taken up by plants than other metals such as Pb which can cause Cd concentrations in the soils to reduce.

The soils of monotypic stands of *Phragmites* (common reed) retain the highest levels of Pb than did *Spartina* (cord grass) soils whereas *Spartina* soils had higher levels of Cd than the *Phragmites* soils. Surprisingly, As levels were higher in *Spartina* soils in 2014 compared to *Phragmites*, while As levels of *Phragmites* soils were higher than *Spartina* in 2015. *Spartina* is known to excrete heavy metals through the salt glands present on the surface of its leaves (8). For majority of the study period, the Boat Ramp site had comparatively higher levels of heavy metals than the agricultural sites. More specifically Cd levels were higher in the Boat Ramp soil than all the other study sites. There were no significant trends observed in the levels of heavy metals between the other study sites.

Heavy Metals in Plant Leaves vs. Soils

Soil samples had much higher heavy metal concentrations than the leaves. **Figures 3**, **4** illustrate the relationships between As, Pb, and Cd concentrations in the 2014 soil and leaf samples at the *Phragmites* and *Spartina* study sites. At the *Phragmites* site (**Figure 3**), Pb concentrations in the soils and leaves were compared and there was a parallel increase of Pb in soils and leaves during June (the growing season), following the July samples, the relationship becomes inverse for Cd, As, and Pb. The concentration of Cd and Pb in both soils and leaves had an inverse relationship at the *Spartina* site (**Figure 4**) from the month of September, while As concentrations seem to have no trends. As shown in **Figures 3**, **4** during the month of November, the levels of As, Cd, and Pb were higher in soils than in the test plants. Marsh grasses in BBC started to senesce by the end of October or early November, reducing their potential to remove heavy metals from the soils as compared with the growing season. This may be one of the reasons why heavy metal concentrations are high in soils yet less in grasses during November.

ANOSIM results generated a R value equal to 0.389 for the study sites (*Phragmites* and *Spartina*), indicating that the study sites are not much different from each other in regard to the heavy metal concentrations. A P value of 0.001 was generated for this statistical test, suggesting that these results are statistically significant. ANOSIM results for the study months resulted in a R value of -0.073 (which is close to 0), implicating that there are no significant differences in the concentration of heavy metals between the study months, $P > 0.05$; therefore, the results are not statistically different.

Pairwise tests between the study groups (soil vs. grasses) were performed for the sampling time and the R and P values are given in **Table 1**. These results indicate that there are significant differences in the concentration of heavy metals present at *Spartina* and *Phragmites* grass sites ($R = 0.64$; $P < 0.05$) whereas, there is no significant difference in the heavy metal concentrations within their soils ($R = -0.02$ and $P > 0.05$). But significant differences were observed between *Phragmites* soil vs. *Phragmites* grasses ($R = 0.53$; $P < 0.05$) and *Spartina* soil vs. *Spartina* grasses (R=0.64; P<0.05). There were no significant differences between the study months ($R = -0.07$; $P = 0.84$) for the heavy metals analyzed in the marsh grasses and soils.

Heavy Metals vs. Co-existing Elements in Soils

Principle Component Analysis (PCA) of soil heavy metals and other co-existing important elements in 2014 displayed a 66% variation among the samples. According to the PCA plot (**Figure 5**), arsenic, cadmium, sulfur and sodium, in that order had greater effects on the study sites. This plot also showed that when arsenic levels increased, phosphorous levels decreased. Studies report that arsenic competes with phosphorous because both elements in anionic forms are taken by the plant through similar phosphate transporter system (31). The PCA plot also displays that there are no differences between the variables tested for the study months and the sites. But soil samples from the *Spartina* and mixed sites in October had higher levels of

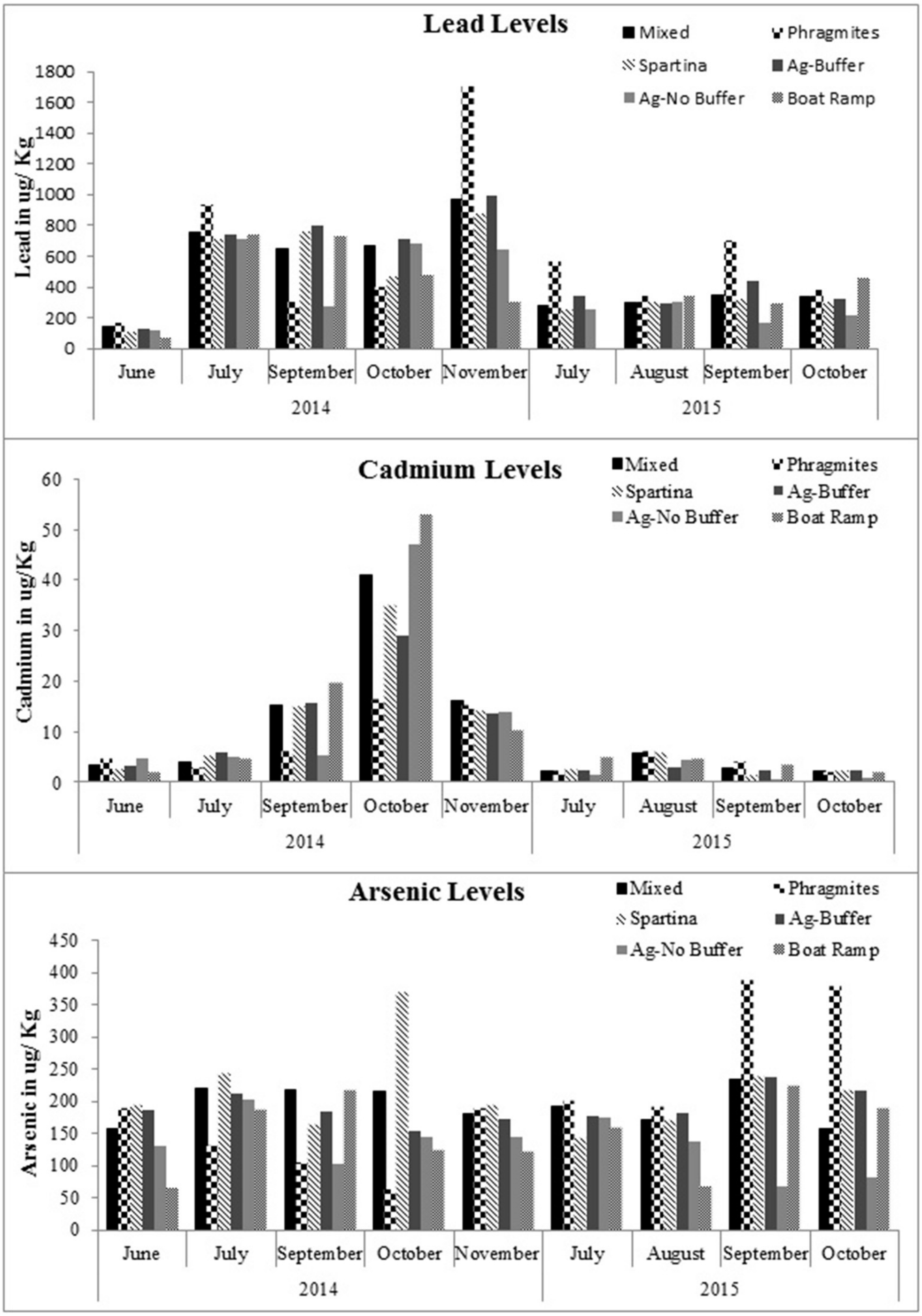

FIGURE 3 | Relationships for lead, cadmium and arsenic concentrations within the marsh soil and *Phragmites* leaves for the study year 2014.

arsenic while the mixed site also had higher levels of cadmium. In November, some soil samples from the *Phragmites* site had high levels of phosphorous, while all variables were high during June at all study sites. Generally, *Phragmites* and *Spartina* start dying in October, thus the plants do not use phosphorous for their growth which thereby increases phosphorous in the soils. Phosphorous levels were low in the *Spartina* site in comparison to the other sites (**Table 2**). Also, there was little difference in the soil phosphorous level between the agricultural sites with and without a buffer zone. June samples are clustered separately; this might be because this month is considered as early growth season where fertilizers might have been sprayed. In October 2014, sampling

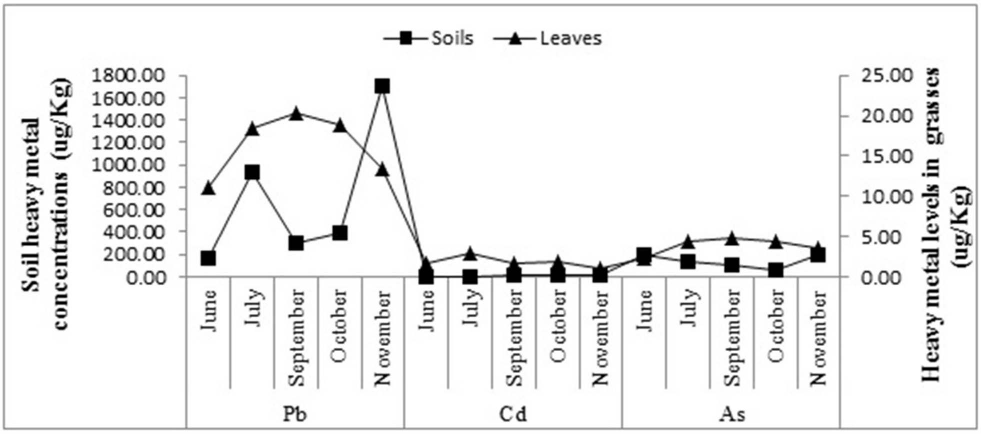

FIGURE 4 | Relationships for lead, cadmium and arsenic concentrations within the marsh soil and *Spartina* leaves for the study year 2014.

TABLE 1 | Pairwise comparisons for the heavy metal concentrations between the marsh grasses and marsh soils.

Groups	R value	P value
Spartina soil vs. *Phragmites* soil	−0.02	0.516
Spartina grass vs. *Phragmites* grass	0.64	0.008
Phragmites soil vs. *Phragmites* grass	0.53	0.008
Spartina soil *vs. Spartina* grass	0.64	0.008

for the soil samples was performed following a hurricane event and this might have impacted the levels of metals and the co-existing salt components at the study sites. This PCA plot also explains that as the iron and phosphorous levels decrease in the soils, the lead levels decrease accordingly.

The pore water pH, electrical conductivity (EC), salt components (sulfur, calcium, iron, sodium, phosphorous) and heavy metals are presented in **Table 2**. The pH values ranged from 3.1 to 7.3; the spatial variations observed among the study sites may be due to their pH and ion levels. The pH of samples decreased in September but increased in October at all study sites except for boat ramp and agriculture site without buffer. These sites contained less vegetation compared to the other study sites. These results are in consistence with previous studies (32) indicating that more oxidizing reactions occur in areas with vegetation thereby decreasing the pH. The protons generated by the oxidation reactions neutralize alkalinity of the water surrounding soil solid particles and consequently, lowered the pH (33, 34). Per our results, pH of soils might have been increased in October because the samples in this month were collected after the hurricane Gonzalo, which might have caused the soils to flood with storm water causing in pH changes. This pH increase can be observed more prominently in the sites with *Phragmites* (4.2–6.1) which is closer to the mouth of the bay.

PCA analysis shows that the variables such as sodium, EC, and pH are closely associated with arsenic and cadmium while lead and phosphorous were closely associated with each other (**Figure 6**). This indicates that when phosphorous levels increased in soils, lead levels increased and when sodium, EC levels increased in the soils then arsenic and cadmium levels increased. The pH values were comparatively lower in the *Spartina* sites than the other study sites. This might explain that the bioavailability of metals in soils to these marsh grasses is greatly altered because of pH, EC, and co-existing salt ions. It has been reported that acidity of soils has a greater impact on the bioavailability of heavy metals (35).

As shown in **Figure 6**, EC and salinity were directly proportional to the levels of arsenic and cadmium in soil samples. Our study results agree with previous studies by McLaughlin et al., Lin et al., Muhlingh et al. (36–38), in which cadmium levels were increased in potatoes, sunflower and wheat under increased saline conditions, even though soil cadmium levels were low. It has been mentioned that an elevated salinity enhances the solubility of heavy metals, as salt-derived anions react with heavy metals and thereby, increase the competition between the salt-derived cations and heavy metals for their adsorption to soil particles (39, 40). As shown in **Figure 6**, and the EC (salinity) of soils is high which means there are more soluble Na^{+} and Cl^{-} ions in the soil that can readily react with cadmium forming soluble complexes such as cadmium chloride (41).

Heavy metal concentrations were higher in year 2014 than 2015 (**Figure 7**). A resemblance matrix of the heavy metal data for 2014 and 2015 has been generated and MDS plots were created based on the Euclidean distances to study the relationships of the study sites in both study years. The MDS plot (**Figure 8**) shows that even though the data points from 2014 and 2015 are close, groupings were observed among the samples. This shows that the heavy metal concentrations in the samples from 2014 were different from those in 2015. The MDS plot with study site analysis shows that the data points from all the study sites are in close proximity in relation to the year (2014 and 2015). But the data points from the *Phragmites* site are more scattered than those of the *Spartina* site, which infers that a higher degree of dissimilarity exists between them. MDS plots in relation to months show that the samples from June 2014 have formed as a separate group and are distant from other 2014 samples. This

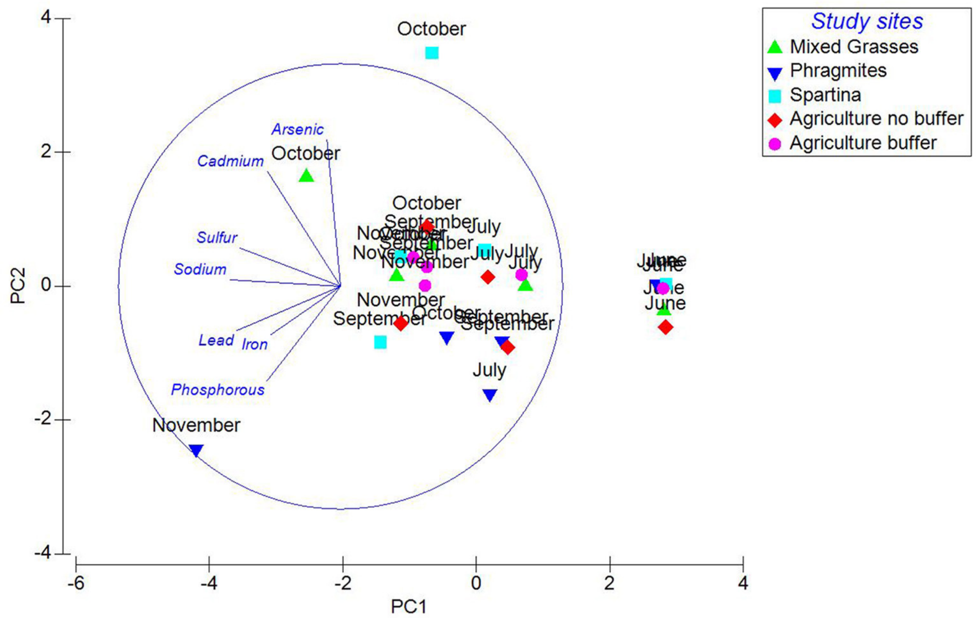

FIGURE 5 | Principal component analysis for heavy metals and ions at study sites with marsh grasses for the year 2014.

TABLE 2 | The concentrations of heavy metals and the ion compositions for the pore water samples in 2014.

Samples	Lead ug/kg	Cadmium ug/kg	Arsenic ug/kg	Sulfur (mg/l)	Calcium (mg/l)	Sodium (mg/l)	Phosphorous (mg/l)	Iron (mg/l)	pH	EC (mmhos/cm)
Mixed –J	752.5	4.08	220.83	166.99	84.4	1,170	0.04062	0.06296	6.4	7.75
Mixed –S	649.63	15.29	217	363	163.69	2,596	0.0634	0.07925	4	15.46
Mixed-O	664.4	41.08	215.67	742	263.36	2,066	0.06824	0.29897	4.1	14.05
Mixed-N	971.24	16	181.9	329.8	152.99	3,256	0.04514	0.05356	6.3	18.1
Phragmites-J	935.83	2.94	130.66	146.65	75.9	1,103	0.08	0.24	4.2	7.75
Phragmites-S	296.7	5.96	106.97	305.8	144.81	2,477	0.02	0.11	4.2	15.11
Phragmites-O	393.03	16.35	64.43	561.4	204.39	2,208	0.06	0.06	6.1	14.35
Phragmites-N	1,702.57	15.22	189.13	402.4	162.05	3,132	0.67	0.22	3.1	18.31
Spartina-J	708.6	5.31	243.83	366.7	152.5	1,335	0.01	0.12	5.1	8.93
Spartina-S	753.2	15.08	163.43	262.5	143.64	2,291	0.01	0.61	3.9	14.24
Spartina-O	460.97	35.01	368.33	316	143.05	2,408	0	0.04	5.2	14.9
Spartina-N	874.1	14.01	193.57	522.5	179.79	2,518	0.02	0.08	4	15.78
Ag No-Buffer-J	716.4	4.92	202.1	419.8	145.7	1,254	0.01554	0.07459	4.7	8.57
Ag No-Buffer-S	272.97	5.2	102.75	307.5	150.56	2,366	0.02934	0.10734	6.5	14.33
Ag No-Buffer-O	679.27	47.16	146.03	195.51	125.8	1,690	0.06122	0.11737	7.2	10.8
Ag No-Buffer-N	645.73	13.89	144.1	394.2	159.9	2,565	0.02195	0.35267	3.9	15.8
Ag Buffer-J	742.33	5.96	212.5	222.6	97.49	1,177	0.00402	0.05717	5.3	8.18
Ag Buffer-S	803.07	15.7	185.5	389.8	152.9	2,412	0.03898	0.07163	4	14.64
Ag Buffer-O	712.1	28.94	155.27	326.6	146.36	2,514	0.03629	0.11748	4.2	14.81
Ag Buffer-N	996.92	13.5	172.7	381.6	140.6	2,339	0.03268	0.03673	6.1	14.23
Boat Ramp-J	735.67	4.53	186.43	192.25	136.4	1,748	0.073	0.1	7.3	11.5
Boat Ramp-S	726.14	19.69	218.13	266.4	137.05	2,605	0.04	0.11	6.7	15.27
Boat Ramp-O	475.2	53.23	123.67	519.5	215.48	3,530	0.42	0.82	3.7	19.55
Boat Ramp-N	295.83	10.18	121.57	ISS	ISS	ISS	ISS	ISS	ISS	ISS

Results are provided for the months we sampled. J, July; S, September; O, October; N, November; Ag, Agriculture; ISS, Insufficient sample.

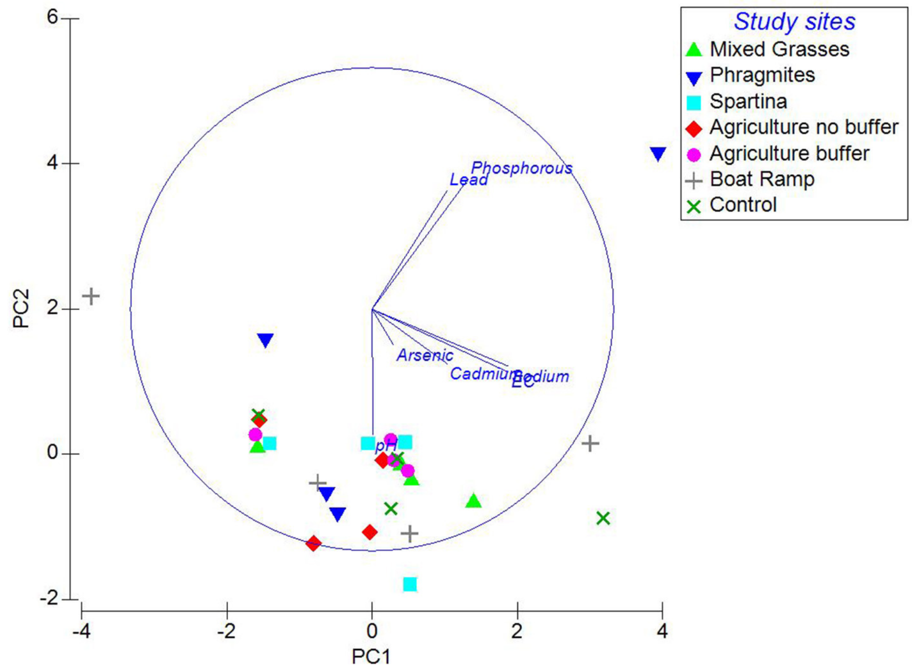

FIGURE 6 | Relationship between electrical conductivity, pH and phosphorous and the heavy metal concentrations of the soil samples.

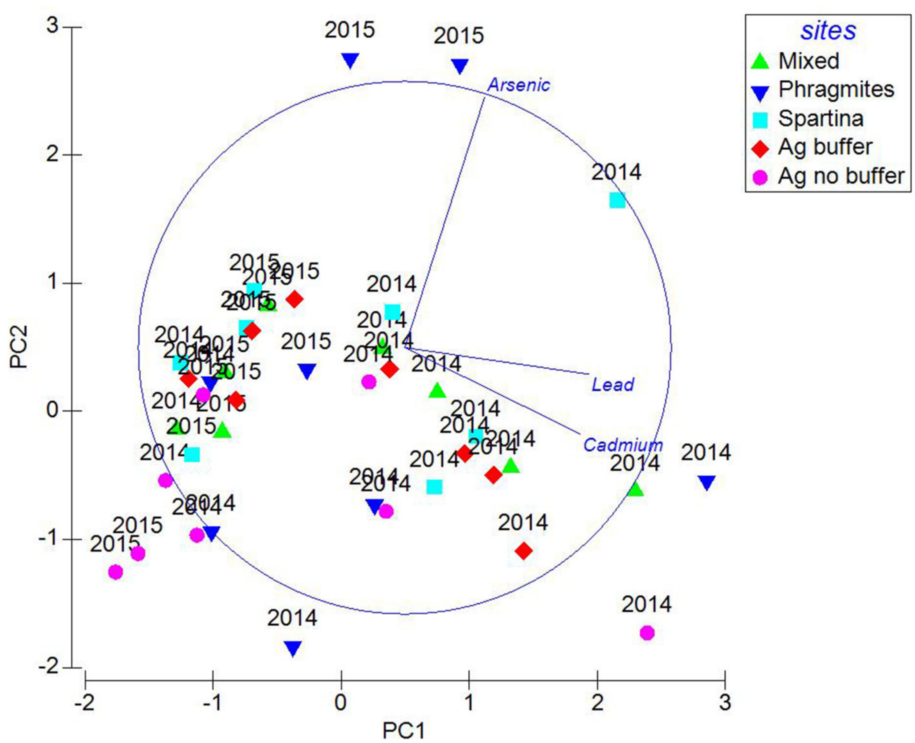

FIGURE 7 | Principal component analysis of heavy metals at the marsh grass sites for the years 2014 and 2015.

confirms that the heavy metal concentrations in June are different from those in the other months. The results from MDS analysis are in consistence with the PCA analysis.

The stress values generated for this plot is 0.03, indicating an excellent fit for the data points. The amount of stress generated from the MDS plot interprets the quality of analysis and whether

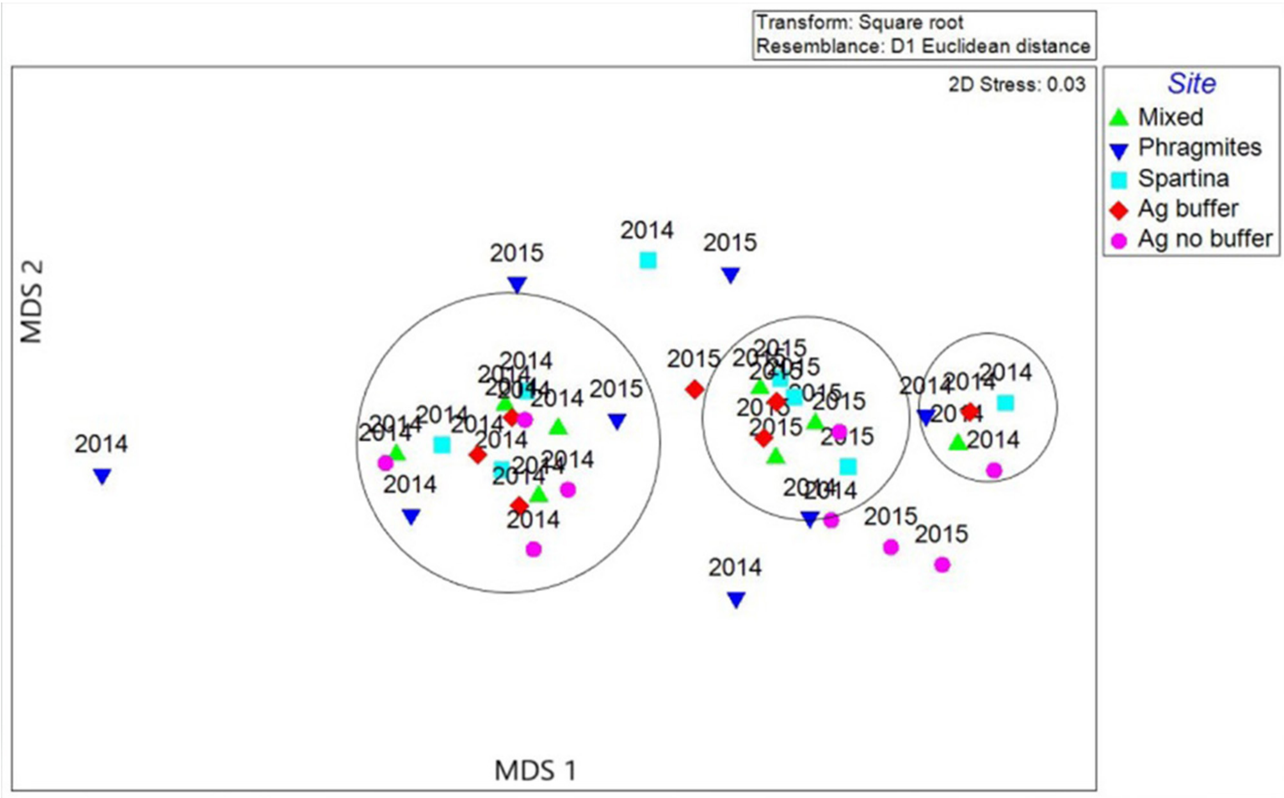

FIGURE 8 | Multidimensional analysis to study the similarities of the study sites for heavy metals during 2014 and 2015.

the analysis is suitable for the input data. Any stress values <0.025 is considered as an excellent fit (42, 43). Salt marsh estuaries are complex ecosystems. Studies show that the roots of marsh grasses carry diverse bacteria that can breakdown the humic acids and other compounds in the soil under changing pH and other characteristics, thereby altering the mobility and solubility of metal complexes (44, 45).

Our study results also show that the levels of sodium and sulfur were greater than iron and phosphorous at the study sites. It can be interpreted from the results that arsenic and phosphorous share inverse relationships. Studies suggest when arsenic uptake increases in plants, increased levels of phosphorous can be observed in the soil as both arsenic and phosphorous share similar phosphate transporter systems (46, 47). The solubility of most heavy metals is highly pH dependent (48). High alkaline pH and low electrical conductivity reduce the solubility of certain metals like zinc, cadmium, and copper because they may be precipitated as hydroxides or carbonates (49–52).

CONCLUSION

The present study results reveal both direct and inverse relationships between the heavy metal compositions in the soils and marsh plant leaves. The inverse relationships found at the *Phragmites* site seem to follow the growing seasonal patterns.

In conclusion, the type of metal up taken by the plants or insoluble metal complexes formed in the soil are all governed by the nature of the study site, soil characteristics, type of the vegetation at the site, weather conditions and human activities occurring within the ecosystem. Also, microorganisms that harbor in the roots of marsh grasses change depending on the type of plant species and this may impact the oxidation-reduction potential of soil nutrients. In addition, the season of the year can impact the availability of the heavy metals for the plants or their abundance in the soil because temperature, salinity and pH greatly shift their distribution and concentrations according to the season. Fertilizers used during the cropping season can alter the nutrient levels in the soil as they compete with heavy metal complexes making them unavailable to the plant such as relationship between phosphorus and arsenic. Thus, complex interactions occur in the soil specifically in tidal marshes where the environment continuously changes. In our study, relationships of ions to heavy metal concentrations explain complex relationships that are being supported by other researchers. Future studies will focus on the detailed analysis of pore water ions and heavy metals in relation to molecular assessment to understand the connection between the ion transport mechanisms to the levels of heavy metals in plants and soils.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/supplementary material.

AUTHOR CONTRIBUTIONS

LC planned this research, designed the experiment, trained the second author (undergraduate student), conducted the experiment, analyzed the results, and wrote the manuscript. KO collected the soil and plant samples, conducted the experiments, and was involved in writing the manuscript. GO was involved with initial field testing, planning, sample collection, student and staff training and supervision, laboratory logistics for analysis and obtaining resources for the project, and preparing the manuscript. All authors contributed to the article and approved the submitted version.

ACKNOWLEDGMENTS

We are grateful to NSF-EPSCoR (EPS-1301765) for funding this research and providing undergraduate student with financial support. We also would like to extend our gratitude to USDA-NIFA (Grant#2013-38821-21246) and USDA Evans-Allen (Grant# DELXDSUGO2015) for providing support for some supplies and instrument costs and providing undergraduate student with financial support. We would like specifically thank to Dr. Deb Jaisi (Associate Professor, University of Delaware) for his detailed review and valuable suggestions that helped improved this manuscript. We also thank Dr. Lauren Jescovitch, for her assistance in reviewing this article. Finally, we are grateful to Ms. Karen Gartley (Soil Testing Laboratory, University of Delaware) for her assistance with analysis of soil samples. We would also like to thank Matthew Stone for his assistance with the field sampling at the Blackbird Creek, Delaware.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Environmental Science

MINI REVIEW
published: 25 March 2022
doi: 10.3389/fenvs.2022.873499

Emerging Contaminants in Soil and Water

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The global population increase puts tremendous pressure on the already dwindling natural resources such as soil and freshwater. Healthy and productive soils as well as the availability of freshwater resources are critical for agricultural productivity. On the other hand, climate change and variability make the water scarcity problem even worse. Agriculture, being the biggest consumer of fresh water, is expected to be affected significantly. Yet, agriculture is expected to play a significant role in achieving greater food, and fiber needs to meet the growing global population. In addition, soil and water quality are also becoming a bigger threat to soil productivity and freshwater availability. Some portion of nutrients applied to agriculture and urban landscapes end up in runoff and leaching water that feeds streams, rivers, lakes, groundwater, etc. These excess nutrient loadings are causing soil and water quality deterioration, which could have severe impacts on human health, aquatic ecosystems, and environmental sustainability. In addition to nutrient and chemical pollutions, emerging contaminants such as heavy metals are showing an increasing trend in soil and freshwater bodies. These emerging contaminants not only impair soil quality and freshwater sources but could also get into the food chain and affect human and animal health. While growing evidence is becoming available on the increasing threats from emerging contaminants, research and understanding are still limited. This mini-review paper summarizes available research on types of emerging contaminants and their impacts on soil and water quality.

Keywords: water quailty, soil quality, emerging contaminants, agriculture, environment

OPEN ACCESS

Edited by:
Qibing Wang,
Institute of Botany (CAS), China

Reviewed by:
Tamer A. Elbana,
National Research Centre, Egypt

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Specialty section:
This article was submitted to Soil Processes, a section of the journal Frontiers in Environmental Science

Received: *10 February 2022*
Accepted: *01 March 2022*
Published: *25 March 2022*

Citation:
Bayabil HK, Teshome FT and Li YC (2022) Emerging Contaminants in Soil and Water. Front. Environ. Sci. 10:873499. doi: 10.3389/fenvs.2022.873499

INTRODUCTION

In 2050, demands for water and energy are projected to significantly increase (McDonald et al., 2011; Alexandratos, 2012; Ray et al., 2013; Ittersum et al., 2016; Boretti and Rosa, 2019). According to a report by FAO (FAO, 2009), 90% of the required global increase in crop production is expected to be achieved through greater yields and increased cropping intensity as an expansion of agricultural lands is impractical (Cassman, 1999; Guilpart et al., 2017; Wu et al., 2018). This is because land availability is limited, and agricultural land use is facing competition with urbanization and other land uses. Soil quality degradation is also putting lands out of production. In addition, the combined effects of more frequent droughts, climate change, variability, and competing needs from different sectors put greater pressure on natural resources (Elliott et al., 2014; Iizumi and Ramankutty, 2015). These would significantly impact agriculture since it relies on productive soils and the availability of water resources (McDonald et al., 2011; Yigzaw and Hossain, 2016; Kullberg et al., 2017).

With population growth and dwindling freshwater resources, the use of reclaimed water for irrigation has increased (Lavrnić et al., 2017). Despite the advantages of using reclaimed wastewater, safety concerns have been raised regarding the use of this supply for irrigation water (Sato et al., 2013; Paltiel et al., 2016). The main issue with reclaimed water is that it contains various organic contaminants that have been identified as emerging threats (Calderón-Preciado et al., 2011; Bueno et al., 2012). Effluent from these treatment facilities can contain various organic chemicals. Some of these could cause cancer and contaminate the surrounding soil and water sources (US EPA, 2014). Very little attention is paid to date on the status of these contaminants in treated wastewater at various levels of the treatment processes (Bolong et al., 2009). Lack of routine measurements of emerging contaminants in the influent water into the wastewater treatment plants or effluent water at various levels of wastewater treatments, i.e., secondary, or tertiary treatments, limits our understanding of removal of these contaminants, if any, at any level of the wastewater treatment process (von der Ohe et al., 2011). The effectiveness of water treatment steps in the removal of emerging contaminants is not conclusive. Bai et al. (2018) suggested that wastewater treatment plants were primary sources of emerging contaminants observed in surface water samples. Therefore, it is erroneous to assume that even tertiary treated wastewater is free of these emerging contaminants (Köck-Schulmeyer et al., 2011; Cabeza et al., 2012; López-Serna et al., 2012).

During recent years there has been an increased awareness and concern regarding the new group of contaminants in soil and water bodies (Bolong et al., 2009; Houtman, 2010; von der Ohe et al., 2011, US EPA., 2015; Bai et al., 2018, 201). These exist in trace concentrations but are highly toxic and often originate from the disposal of treated wastewater into the soil and surface and groundwater bodies (Bolong et al., 2009; Loos et al., 2013; Petrie et al., 2015). The most common contaminants are solids, dissolved or suspended particulates, nutrients, and heavy metals (Wuana and Okieimen, 2011; Gasser et al., 2014).

Soil is considered as one of the final destinations of chemical wastes (Sakshi et al., 2019). Prolonged soil pollution with chemical wastes can harm living organisms within the food chain (Jaishankar et al., 2014). The increasing levels of emerging contaminants in the soil and aquatic environments pose a threat to human health and ecosystems (Srikanth, 2019). Anthropogenic activities such as mining and industrial waste disposal, as well as the use of chemicals and chemical fertilizers such as arsenic (As)-based fertilizers have been identified as contributing to the increasing emerging contaminants in ecosystems (Bali et al., 2021). Wastewater is also reported as a source for emerging contaminants since traditional methods of treating wastewater are not efficient and costly to completely remove emerging contaminants (Divyapriya et al., 2021). Petrie et al. (2015) confirmed that wastewater treatment procedures used in the treatment plants were not effective in completely removing emerging contaminants.

Up until recently, very little attention was given to these new group of contaminants which could exist in very low concentrations but are quite harmful to marine life and humans if they enter the food chain (Houtman, 2010; von der Ohe et al., 2011; Petousi et al., 2019). Furthermore, there is no full understanding of how these emerging contaminants accumulate in the soil, especially after several years of use of treated wastewater for irrigation and uptake and bioaccumulation of these contaminants by the plants. This mini-review mainly focuses on the major types of emerging contaminants that are reported to impair soil and water quality.

POLYCYCLIC AROMATIC HYDROCARBONS

Polycyclic aromatic hydrocarbons (PAHs) are abundant chemicals found naturally in fossil fuels (Cao et al., 2017). Incomplete combustion of coal, gas, wood, and oil also produces PAHs (Hsu et al., 2016; Cao et al., 2017). Soil is one of the ultimate ecological destinations of PAHs (Agarwal et al., 2009). PAHs are known for their high rate of bioconcentration and quickly entering the food chain (Yang et al., 2022). The United States Environmental Protection Agency (US EPA) has identified 16 PAHs as top contaminants (Cao et al., 2017; Li et al., 2019). Due to their lipophilic and hydrophobic properties, PAHs are persistent; they can stay in the soil for long periods (Agarwal et al., 2009; Košnář et al., 2018; Li et al., 2019). They do not burn very easily or break down in the water (Li et al., 2019). The increasing molecular mass can logarithmically decrease the solubility PAHs in an aqueous solution (Johnsen et al., 2005). Due to less solubility and low volatility of PAHs with five or more rings, they are abundantly found in a granular type, attached to contaminated air, soil, or sediment particulates (Choi et al., 2010). In contrast, PAHs with low rings are readily available for biological uptake and degradation due to their easy solubility in water (Mackay and Callcott, 1998). In general, PAHs with higher rings are more persistent in the environment than the lower rings (Johnsen et al., 2005).

The International Agency for Research on Cancer (IARC) Monographs Programme studied carcinogenic properties of 60 PAHs (IARC, 2010). Among 60 PAHs examined, benzo [a] pyrene was categorized as carcinogenic to humans. Cyclopenta [cd]pyrene, dibenz [a,h] anthracene, and dibenzo [a,l] pyrene were categorized as probably carcinogenic to humans. A total of 11 other studied PAHs were categorized as possibly carcinogenic to humans (Poucke et al., 2012; Jameson, 2019).

Regarding the effects of PAHs on plants, however, there were mixed reports. Several studies have reported that PAHs had adverse effects on the development of plants (Alkio et al., 2005; Liu et al., 2009; An et al., 2018). Studies also reported that PAHs have either no effect or promoted plant growth (Maliszewska-Kordybach and Smreczak, 2000; Ling and Gao, 2004; Meng and Chi, 2015).

PHARMACEUTICAL AND PERSONAL CARE PRODUCTS

Pharmaceutical and personal care products (PPCPs) are products such as toothpaste, skincare products, fragrances, antibiotics, pharmaceutical medicines used by consumers for their health and cosmetic purposes, or veterinary drugs that are used by agroindustry to enhance the growth or health of livestock (Wang and Huang, 2019; Bishnoi et al., 2022). PPCPs are becoming very common in environments where the traditional wastewater treatment plants are not able to effectively remove them (Wang and Wang, 2016). Waste from animal farms and sewage treatment plants can also lead to the release of emerging contaminants into the aquatic and soil environments (Ebele et al., 2017). Sewage sludge from wastewater treatment plants is commonly used as a fertilizer for agriculture (Corradini, 2014). It contains various nutrients such as potassium, nitrogen, manganese, and iron (Mtshali et al., 2014). However, treated sewage sludge can also contain various emerging contaminants such as antibiotics, chemicals, and engineering nanomaterials (Koumaki et al., 2021). PPCPs are among the emerging contaminants found in sewage sludge that have potential adverse ecological impacts or human health risks if they are released into ecosystems (Van et al., 2021).

Due to little understanding of the possible environmental impacts of PPCPs, they are considered contaminants of emerging concern (CECs) (Vasilachi et al., 2021). The other source of PPCPs in the soil is treated wastewater or contaminated river water, which is used for irrigation (Gallego et al., 2021). Soils are often contaminated with CECs that have low hydrophobicity. These can then be accumulated in the soil through organic material interactions (Beltrán et al., 2020).

A study in Spain on 166 emerging contaminants and heavy metals (e.g., Cd, Ni, Pb, and Hg) found that 38 pharmaceuticals, albeit low concentrations, were detected in tertiary treated wastewater (Cabeza et al., 2012). This supports similar findings from other studies (Bolong et al., 2009; Ziylan and Ince, 2011; Cabeza et al., 2012) suggesting that wastewater treatment processes are not effective in removing some of the emerging contaminants. Incomplete removal of these contaminants, particularly pharmaceuticals, during the treatment process is the main reason for recent findings of these contaminants in the water bodies used for disposal of treated wastewater (Kasprzyk-Hordern et al., 2008a, 2008b; Cabeza et al., 2012). Bai et al. (2018) conducted a detailed study on the status of emerging contaminants in surface water sources in Denver, Colorado, where the surface water flow is influenced by snowmelt during spring and discharge from several wastewater treatment plants distributed across that region. Their findings showed that 76% (109 of 144) analyzed pharmaceutical compounds were found in water samples (Bai et al., 2018). Such high percent detection of emerging contaminants in water samples, despite the substantial dilution of treated wastewater by the natural water flow, suggests that discharge of treated wastewater from several wastewater treatment plants could be a major source of emerging contaminants (Bai et al., 2018). Similarly, Petrie et al. (2015) summarized the concentrations of several pharmaceuticals in influent and effluent water from the wastewater treatment plant as well as surface water samples in the United Kingdom. There was a clear trend of detection of emerging contaminants in the surface water samples that were exposed to treated wastewater with the effluent that has high concentrations.

PESTICIDES

A pesticide is a substance that works by killing pests or keeping them from damaging the environment (Aktar et al., 2009). Some examples of known pesticides are those used against insects, plant pathogens, and microorganisms. Although they are useful for keeping pests and diseases at bay, they can also cause toxicities to humans and other organisms (USGS, 2017). Over 95% of the chemicals used for pest control reach other places beyond their intended destinations such as air, water, and soils. A study conducted by the US Geological Survey (USGS) on the surface water of 38 streams in the US found top 10 most frequently detected anthropogenic contaminants were: eight pesticides (CIAT, chlorpyrifos, AMPA, metolachlor, dieldrin, atrazine, de-sulfinyl fipronil, and glyphosate) and two pharmaceutical drugs (caffeine, metformin) with 66–84% detection rates (Bradley et al., 2017). Pesticides are among the highly persistent chemicals in soil. The excessive use of these chemicals can lead to the formation of soil contaminants (Pullagurala et al., 2018). It has been revealed that the use of pesticides is increasing in some areas despite being banned (Pan et al., 2019). Organochlorine pesticides, also known as OCPs, are among the persistent organic pollutants. OCPs are known to have high toxicity, bioaccumulation, and biomagnification in the environment (Sparling, 2016). Bai et al. (2018) reported that surface water samples contained 39 of 72 (54%) of analyzed pesticides.

PHTHALATE ESTERS

Phthalate esters (PAEs) are often used as an additive to improve the flexibility of certain polyvinyl chloride (PVC) resins. They are also used in various other resins such as cellulose, vinyl acetate, and polyurethanes. The stability, fluidity, and low volatility of Phthalate esters make them ideal for plasticizers (Peijnenburg, 2008). These derivatives are produced by phthalic anhydride and are mixed with plastics to increase their properties, such as resilience, plasticity, and pellucidity (Thomas and Brogat, 2017). PAEs can also be used as enteric coating agents for various applications (Kapoor et al., 2020). End-user applications of these derivatives include resin houses, agricultural adjuvants, cosmetic products, soap and laundry detergents, toys, and various other applications. PAEs are poorly water-soluble chemicals. The water solubility of a chemical is also a vital factor that influences the biodegradability and aquatic toxicity of a chemical. It also affects the distribution of these chemicals. Although PAEs are known to have low aqueous solubility, they can be quickly absorbed by organic residue and solid surfaces in the environmental systems (John Autian, 1973). Slow and steady accumulation and release of these chemicals could affect the ecological conditions of water systems. Sludge-amended soils and wastewater treatment facilities are also affected by this condition (Staples et al., 1997). Due to the widespread use of PAEs, their ubiquity has led to the accumulation of these chemicals in several ecosystems' compartments. The accumulation of PAEs in agricultural soils could lead to the contamination of food chains and vegetables. It could also cause indirect or direct human exposure (Zeng et al., 2008).

HORMONES

Due to the industrial growth of the world, steroidal estrogen has been considered an emergent issue. It has been known to severely affect aquatic life and soil fertility (Singh et al., 2021). Steroidal hormones are either synthetic or naturally occurring forms of estrogen that are released from the adrenal cortex and other parts of the animal and human body (Biga et al., 2019). Many of these emerging contaminants, such as synthetic or natural hormones, are known as hormone disrupters (Preisendanz et al., 2021). The human population discharges about 30,000 kg of natural steroidal estrogens and 700 kg of synthetic estrogens solely from birth control pill practices each year. The release of estrogens from livestock can be quite high. In the US and European Union, for instance, it is estimated that about 83,000 kg of estrogens are released annually (Adeel et al., 2017). Natural estrogens discharged from animal and human waste have been considered a serious threat to the environment (Arnon et al., 2008). This environmental issue is especially alarming since the use of bio-solids such as animal manure for organic farming has been widely adopted in the field (Xuan et al., 2008). A study conducted by USGS and EPA in 1999 and 2000 revealed that out of the 139 streams analyzed, 82 chemicals were found in 80 percent of them. The most common types of chemicals were steroids hormones, antibiotics, and insect repellent (USGS, 2002).

PERFLUORINATED COMPOUNDS

Perfluorinated compounds (PFCs) are known to have various functional groups, such as perfluoroalkyl and perfluoro carboxylic acids (Corsini et al., 2014). Due to their high surface activities and chemical and thermal resistance, PFCs are commonly used as industrial chemicals in various industries such as textile, pesticides, and refrigeration (Prevedouros et al., 2006; US EPA, 2014; Liu et al., 2020). Perfluoroalkyl acids (PFAAs) are a type of perfluoroalkyl carboxylic acid. PFAAs are known to have widespread distribution and high abundance (Sha et al., 2022). Due to their persistence in the environment, PFAAs have been considered as an emerging contaminant of concern and a threat to human health and the environment (Kurtz et al., 2019). The PFAAs contaminate the soil in many ways, such as when the reclaimed wastewater is used for irrigation (Jürling, 2021)or biosolids are added as a fertilizer for crop production (Blaine et al., 2013). Biosolids are the organic materials produced by the treatment of sewage sludge. They are typically treated according to the regulations of their respective governments (Lu et al., 2012). In the US, around 60% of the land used for farming is devoted to the application of these materials (Blaine et al., 2013). Currently, the US Environmental Protection Agency enforces various regulations regarding the land use of biosolids (US EPA, 2013b). However, there is no regulation for PFAAs in biosolids. This means that repeated applications of biosolids could cause potential contamination of the environment including soil, surface, and groundwater (Müller et al., 2011).

ENGINEERED NANOMATERIALS

Engineered Nanomaterials (ENMs) are generally defined as particles with a dimension of less than 100 nm (US EPA, 2017). ENMs can be made through various chemical processes and physical steps, such as self-assembly or milling. ENMs exhibit special properties such as physicochemical, electrical conductivity, and mechanical strength (Luoma, 2008; US EPA, 2008). Due to their unique properties, nanomaterials are becoming more prevalent in various industries. However, their safety and environmental concerns are still unknown (US EPA, 2017). The release of ENMs into the soil during the field applications of biosolids and wastewater has been identified as a major source of pollution (Pan and Xing, 2012). They may also be released into the environment through manufacturing and ecological applications or inappropriate handling (US EPA, 2013a). The increasing number of ENM being deposited in terrestrial environments is expected to make these areas the largest repository for harmful materials.

The structure of nanomaterials can absorb toxic heavy metals such as copper, lead, mercury, and cadmium in the soil, air, and water. Due to their toxic properties, these metals can cause various disorders (Kamal et al., 2021). ENMs can also transform their properties depending on the environment's biological, chemical and physical processes (Nowack et al., 2012). Researchers have been trying to determine if models or experiments are needed to predict the distribution of ENM pollutants in different environmental compartments such as soil, water, and atmosphere (Wiesner et al., 2009; Westerhoff and Nowack, 2013).

The factors that determine the exposure risks of engineered nanomaterials will also be affected by the processes involved in their transformation. Not only does this process affect the release of ENM into the environment, but it also affects the products that contain it. Depending on the properties of the material and the transformation they undergo, released ENM may have a lesser or greater environmental impact than the materials that were initially produced. Although the released and transformed materials are the ones that are actually in the environment, the effects of these are still unknown (Nowack et al., 2012).

The effects ENMs on plants depends on several factors including soil properties and physicochemical characteristics of ENMs. Although the presence of other co-existing contaminants can affect the bioavailability of ENMs. Studies have shown that soil amendment with substances such as biochar can help minimize the uptake of certain ENMs by plants (Reddy et al., 2016; Deng et al., 2017; Servin et al., 2017; Pullagurala et al., 2018).

CONCLUSION

Increasing trends in emerging contaminants have been documented in several places throughout the world. Several studies have documented considerable evidence of widespread concern on the emerging contaminants contamination of soils and surface water linked to the discharge of treated wastewater. However, there is a lack of full understanding about the fate of these contaminants in treated wastewater when used for irrigation, in terms of crop uptake, bioaccumulation, getting into the food chain, and eventually health risks to humans and other living organisms. In addition, the effectiveness of different wastewater treatment procedures to remove emerging contaminants and/or their metabolites from the influent water is not clearly understood. As such, there is a critical need to develop standards and policy guidelines regarding limits of these emerging contaminant concentrations contaminant in soil and water. Therefore, this mini-review calls for the need for assessing the environmental and potential human exposure risks of emerging contaminants originating from the discharge of treated wastewater into natural water bodies. Specifically, there is a compelling need to investigate: 1) temporal variation in concentrations of various emerging contaminants in secondary and tertiary treated wastewater from wastewater treatment plants, depending on the level of wastewater treatment before it is disposed to surface or groundwater bodies or marine environment or used for irrigation of crops; 2) potential risks of these contaminants, if exist in treated wastewater in high concentrations, entry into the food chain by agricultural products which are irrigated by treated wastewater directly or surface water which receive treated wastewater discharge as disposal mechanism. The availability of such information will help to guide policy towards developing critically needed standards on threshold limits of such contaminants in discharge water from wastewater treatment plants and other point sources of pollution.

AUTHOR CONTRIBUTIONS

HB prepared the draft manuscript, FT conducted an additional literature review, HB, FT, and YL contributed to manuscript revision, proofreading. All authors have approved the submitted version of the manuscript.

FUNDING

This mini-review is based upon work that is supported by the National Institute of Food and Agriculture, US Department of Agriculture, under award number 2020-67019-31163. Any opinions, findings, conclusion, or recommendations expressed in this publication are those of the authors and do not necessarily reflect the view of the US Department of Agriculture.

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frontiers in Public Health

ORIGINAL RESEARCH
published: 29 March 2022
doi: 10.3389/fpubh.2022.858615

The "Regulator" Function of Viruses on Ecosystem Carbon Cycling in the Anthropocene

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OPEN ACCESS

Edited by:
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Reviewed by:
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Specialty section:
This article was submitted to Environmental health and Exposome, a section of the journal Frontiers in Public Health

Received: *20 January 2022*
Accepted: *07 March 2022*
Published: *29 March 2022*

Citation:
Gao Y, Lu Y, Dungait JAJ, Liu JB, Lin SH, Jia JJ and Yu GR (2022) The "Regulator" Function of Viruses on Ecosystem Carbon Cycling in the Anthropocene. Front. Public Health 10:858615. doi: 10.3389/fpubh.2022.858615

Viruses act as "regulators" of the global carbon cycle because they impact the material cycles and energy flows of food webs and the microbial loop. The average contribution of viruses to the Earth ecosystem carbon cycle is 8.6‰, of which its contribution to marine ecosystems (1.4‰) is less than its contribution to terrestrial (6.7‰) and freshwater (17.8‰) ecosystems. Over the past 2,000 years, anthropogenic activities and climate change have gradually altered the regulatory role of viruses in ecosystem carbon cycling processes. This has been particularly conspicuous over the past 200 years due to rapid industrialization and attendant population growth. The progressive acceleration of the spread and reproduction of viruses may subsequently accelerate the global C cycle.

Keywords: virus, carbon cycle, regulator, anthropogenic activity, climate change

INTRODUCTION

The scale of perturbation to Earth systems caused by human activity during the Holocene, and particularly over the last 2,000 years is now recognized as the Anthropocene epoch (1). Changes to Earth's ecosystems over millennia caused by human perturbation, including climate change, accelerating population growth and the globalization of trade and travel, have overridden biogeographic boundaries and allowed the rapid spread of viruses (2). This global phenomenon has drawn attention to the role of viruses in wider ecosystem functioning through their interactions with the global carbon cycle *via* the food web and the microbial loop in terrestrial and aquatic environments (3) that impose an indirect influence on climate change (4).

Disease-causing viruses diminish the fitness of their hosts, hinder development and reproduction, and may ultimately hasten their deaths (5, 6), driving the mineralization of organic carbon to inorganic carbon and its loss from food webs before it can flow to higher trophic levels (7). However, not all viruses are pathogens, and some are mutualistic, conferring benefits on hosts that include bacteria and fungi, plants, wasps and aphids, mice and humans (8).

Indeed, current innovation in the treatment of cancers are developing the use of viruses to kill cancer cells selectively (9). Thus, viruses change the function of entire ecosystems by altering the abundances and community structures of organisms in food webs at every trophic level, from simple microorganisms (10, 11) to complex plants and animals (12).

Natural fluctuations in climate have given way to human-induced global warming over the past 2,000 years, but most particularly since the beginning of the Chinese Common Era (CE) and European Industrial Revolution in the mid-18th century and latterly the "Great Acceleration" of the Anthropocene since the 1950's. Progressive increases in average global temperatures have driven changes in rainfall patterns and caused more frequent and intense extreme weather events that have direct and indirect effects on viral epidemiology. Climate change affects the frequencies and durations of viral epidemics by altering the distribution, abundance and activity of hosts, changing resistance to infection, the physiology of host-virus interactions, the rate of virus evolution and host adaptation (13–16). Evidence suggests that global warming is leading to increased epidemics and, in turn, species extinctions. But the relationship between climate and epidemics may be different for different regions and different species (17). For example, recent evidence from European ice cores showed a strong relationship between unusual weather (low temperatures and high rainfall) and the severity of the Spanish Flu epidemic during the First World War (18). As another example, significant negative correlations are observed between temperature and precipitation and China's epidemic Outbreak Index (i.e., caused by bacteria, viruses or parasites); epidemics have tended to be relatively more frequent in China during colder and drier periods and relatively rarer during warmer and humid periods (**Figure 1**, **Supplementary Table S1**). Thus, it appears that climate change and viral epidemics are closely intertwined and interdependent with profound consequences for human, animal and environmental health, calling for the development of cross-disciplinary "One Health" strategies (19).

The current "black swan event" of COVID-19 has created an opportunity to observe how rapidly viral disease outbreaks can fracture ecosystem carbon flows by changing human behavior. Vastly reduced fossil fuel use during national lockdowns swiftly moved the global carbon balance toward a new state *via* regulatory feedback mechanisms (20) which may cause long-term and far-reaching changes to earth system interactions (21, 22). Thus, evidence is emerging that viruses can act as "regulators" of ecosystem carbon cycling through their effect on host (human) fitness and behavior, and that anthropogenic activity and climate change can alter viral epidemiology. However, the strength of the contributing factors to this exchange need to be identified to develop "One Health" solutions. Therefore, the objectives of this study were to (i) systematically clarify how viruses regulate carbon cycling processes, and (ii) reveal how anthropogenic activity and climate change influence the way that viruses regulate carbon cycling processes using published relevant data and findings. This study also proposes adaptive countermeasures to help combat any future influences of viruses on global C cycling processes.

METHODS

In order to systematically elucidate how virus regulate carbon cycling processes, we adopted the most commonly used calculation formula of contribution rate of C (CRC) in the world and the results of two published models to decompose the mechanism of virus in C cycle. We scraped data on virus abundance, as well as soil, ocean, and atmospheric C pools from different literature, and combined them into a mechanism diagram (**Figure 4**) to illustrate the impact scale of virus. To reveal the modulation of this process by anthropogenic activity and climate change, we use a China-wide dataset containing precipitation, dust storm index (DSI), temperature, population, and epidemic outbreak index.

Modeling Viral Impacts on Ecosystem Carbon Cycles

This study applied the following formulae to estimate the CRC between viral lysing of bacteria and ecosystem DOC:

$$\mathrm{CRC} = \frac{\mathrm{VLBC}}{\mathrm{TCOE}} \tag{1}$$

$$\mathrm{VLBC} = \mathrm{FMVL} \times \mathrm{BCP} \tag{2}$$

$$\mathrm{MCP} = \mathrm{PP} \times 20 \times 10^{-9} \tag{3}$$

$$\mathrm{FMVL} = \frac{\mathrm{FVIC}}{[\gamma \ln 2 \times (1 - \varepsilon - \mathrm{FVIC})]} \tag{4}$$

where TCOE is the total ecosystem DOC concentration (soil: mg C·kg^{-1}/water: μg C·L^{-1}); VLBC is the carbon released by viral lysing of bacteria (soil: mg C·kg^{-1}/water: μg C·L^{-1}); BCP is bacterial carbon production (soil: mg C·kg^{-1}/water: μg C·L^{-1}); BP is bacterial production (cell·L^{-1}); FMVL is the fraction of mortality from viral lysis; FVIC is the frequency of visibly infected cells as seen under an electron microscope; γ is the ratio between the latent period and generation time; ε is the fraction of the latent period during which viral particles are not yet visible (23, 24). If $\gamma = 1$, $\varepsilon = 0.186$.

A steady-state model was used (shown in **Figure 4**) to determine the influence of virus under marine carbon cycling processes (25), which is a modification of the steady-state model developed by Jumars et al. (26) in that it allows for lysis of marine phytoplankton and marine bacterioplankton production. All values represent flux in photosynthetically fixed carbon (100%) and assume that all carbon in the pelagic zone eventually respires with negligible loss due to export. The data indicated that between 6 and 26% of the carbon fixed by primary producers enters the DOC pool *via* viral-induced lysis at different trophic levels (25).

This study applied the modified steady-state carbon flow model to determine a hypothetical aquatic microbial food web (27). The model showed that compared to a system devoid of virus, an otherwise identical food web with and without a viral component that is responsible for 50% of bacterial mortality and 7% of phytoplankton mortality underwent: (1) 33% more bacterial respiration and production; (2) 33% less bacterial grazing by protists; (3) 7% less microzooplankton production.

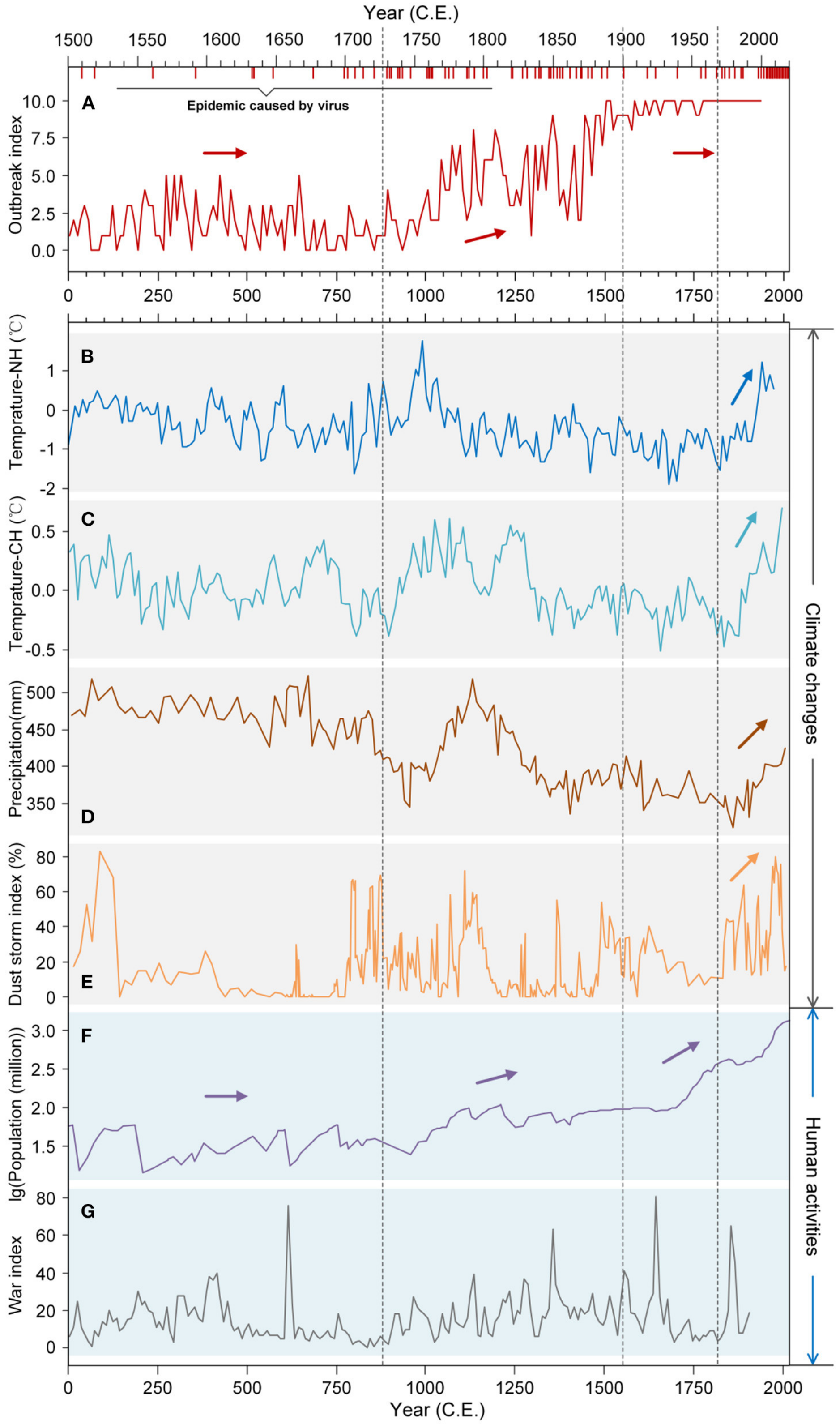

FIGURE 1 | Global trends in climate change and anthropogenic activity and relationships with Chinese epidemic status over the last 2000 years. **(A)** The epidemic Outbreak Index of China [the number of years epidemics (bacteria, viruses and parasites) were recorded in China], and incidence of major global viral epidemic events. Each red vertical bar represents a viral epidemic event. See **Supplementary Table S1** for detailed data information. **(B)** Temperature in the northern hemisphere

(Continued)

FIGURE 1 | (Temperature-NH); **(C)** temperature in China (Temperature-CH); **(D)** precipitation in the East Asian monsoon region; **(E)** dust storm index of North China; **(F)** population of China; **(G)** War Index, i.e., the total number of armed conflicts that occurred within China. Epidemic Outbreak Index values illustrating historical outbreak events can be roughly divided into three stages: the first stage (0 CE∼1,000 CE) where values were all below 5; the second stage (1,000 CE∼1,450 CE) of progressive increase in values from <5 toward 10; the third stage (1,450 CE∼1,949 CE) where values plateau close to 10 (wherein epidemics occurred almost every year). CE, Chinese Common Era.

The model confirmed the existence of a mechanism that showed that the viral lysis of phytoplankton would deprive the larger grazers and move material to smaller lifeforms.

Data Sources

In this study, the data sets for precipitation, dust storm index (DSI), temperature, population, epidemic index and epidemic outbreak index data over the past 2,000 years were summarized from published data as well as published research. The 20-yr resolution precipitation data set shown in **Figure 1** was based on pollen analysis from sediment cores in a reconstruction using the two-component weighted averaging partial least squares regression (WA-PLS) model (28). The dust storm index data set was reconstructed based on the coarse silt component (CSC) percentage in the sediment cores of Lake Gonghai (29). Northern Hemisphere temperature (Temperature-NH) data were reconstructed using the LOCal (LOC) method (30), and China temperature (Temperature-CH) data were reconstructed using principal component regression (PCR) and partial least squares (PLS) regression (31). Population, epidemic index and epidemic Outbreak Index data were extracted from regional publications and literature (32–34).

This study obtained total CO_2 emissions (TCOE), frequency of visible infected cells (FVIC), fraction of mortality from viral lysis (FMVL), bacterial carbon production (BCP) and bacterial production (BP) data through analysis of relevant literature (**Supplementary Table S2**). Since bacteria comprise most soil microorganisms and there exists an integral relationship between soil microorganisms and viruses (35), soil BCP was substituted for soil microbial carbon production in this study. Moreover, Equation (2) assumes that the carbon content in each bacterial cell is constant (20 fg C·cell^{-1}) (36). To date, no studies have been published on bacterial mortality caused by viral lysis in forest and desert soil. Therefore, we only estimated the CRC of wetland, cropland, pastureland and tundra ecosystem types. When the original data were presented in means or medians, the value was used directly; when the original data were a range, we used maximum and minimum values of the range for calculation.

Some data sets shown in **Figures 3**, **4** were extracted from published references (**Supplementary Tables S3, S4**). If the original data were a range, the median of the range was used. Floodplains and river reservoirs were regarded as lakes in this study. Data used in **Supplementary Table S5** were extracted from the most recent global, regional and country-level estimates on cause-specific disability-adjusted life year (DALYs), years of life lost (YLL) and years lost due to disability (YLD) metrics for the years 2000, 2010, 2015 and 2016 (37).

VIRAL REGULATION OF ECOSYSTEM CARBON CYCLING

Viruses regulate carbon cycling *via* their direct and indirect effects on the microbial loop and wider food web in terrestrial and aquatic ecosystems in three main ways.

(i) *Infection and cell lysis* Viruses (phages) accelerate the direct release of carbon from the microbial pool through microbial cell lysis (i.e., the "viral shunt"), especially bacteria in soils (35, 38–40) and plankton in aquatic systems (41–43) (**Figure 2A**).

(ii) *Gene transfer* Viruses indirectly regulate soil carbon cycling processes by affecting microbial host genes that encode for key biogeochemical functions, e.g., carbon metabolism and sporulation (44) through gene transfer (10, 11, 45), including the reprogramming of metabolic processes (becoming a "puppet master") of the host cell (46), thereby regulating carbon (and nutrient) cycling (47–49) (**Figure 2B**). These genes include auxiliary metabolic genes (AMGs) that can regulate host photosynthesis (46, 50), carbon metabolism (51) and other such processes, which can alter the number, community structure and function of microorganisms (52).

(iii) *Altered community structure* Viruses alter the abundance, diversity and structure of microorganisms, including changing the dominance of microbial species [e.g.; "Killing the Winner" mechanism (53)] by modifying the magnitude of organic inputs. Viral infections of plants and animals in the wider food web may initially increase organic inputs due to increased mortality, but may ultimately reduce inputs by decreasing their abundance, e.g., viral infections of green plants can reduce rates of photosynthesis by up to 50% (54). Gene transfer can alter the availability of different organic substrates by mediating carbon source diversification processes (53, 55) which play an important role in maintaining species richness and the amount of available genomic information (52) (**Figure 2C**).

VIRUS DISTRIBUTIONS IN ECOSYSTEMS

Viruses are extremely abundant infectious agents that are distributed throughout the biosphere (56), primarily in marine (55%) and freshwater (40%) ecosystems and to a much lesser extent in terrestrial ecosystems (<1%) (57).

In terrestrial systems, virions are easily adsorbed onto soil particles, and the degree of adsorption is commonly > 90% and reliant on soil properties including clay mineralogy, cation exchange capacity, soil organic matter and pH, as well as the type of virus (58). Thus, the migration rate of viruses in soil is very slow, which may explain why viruses have a weaker controlling effect on hosts in terrestrial ecosystems compared to freshwater and marine

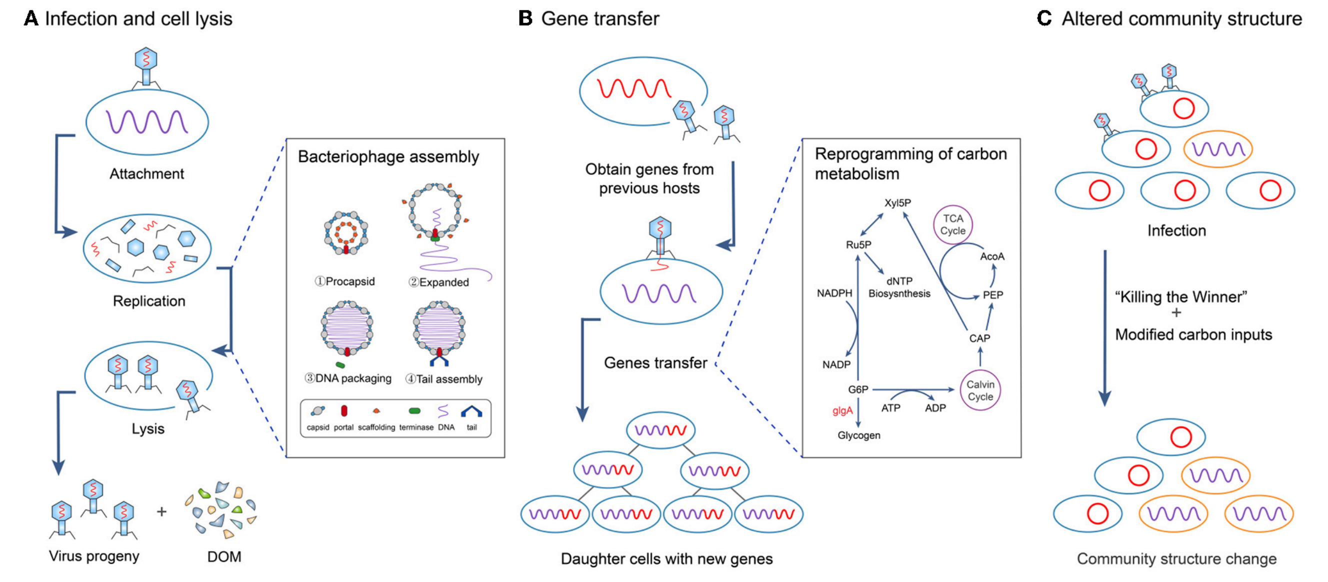

FIGURE 2 | Three major mechanisms by which viruses affect microbial community structures and regulate carbon cycling. **(A)** Viruses infect microbial hosts and invade and destroy microbial cells (lysis) leading to the direct release of carbon in dissolved organic matter (DOM). **(B)** After virus infection, gene transfer from the virus (and/or previous host) previous host reprograms carbon metabolism. **(C)** Virus infection changes the magnitude of carbon inputs and changes microbial community structure, e.g., "Killing the Winner" mechanism.

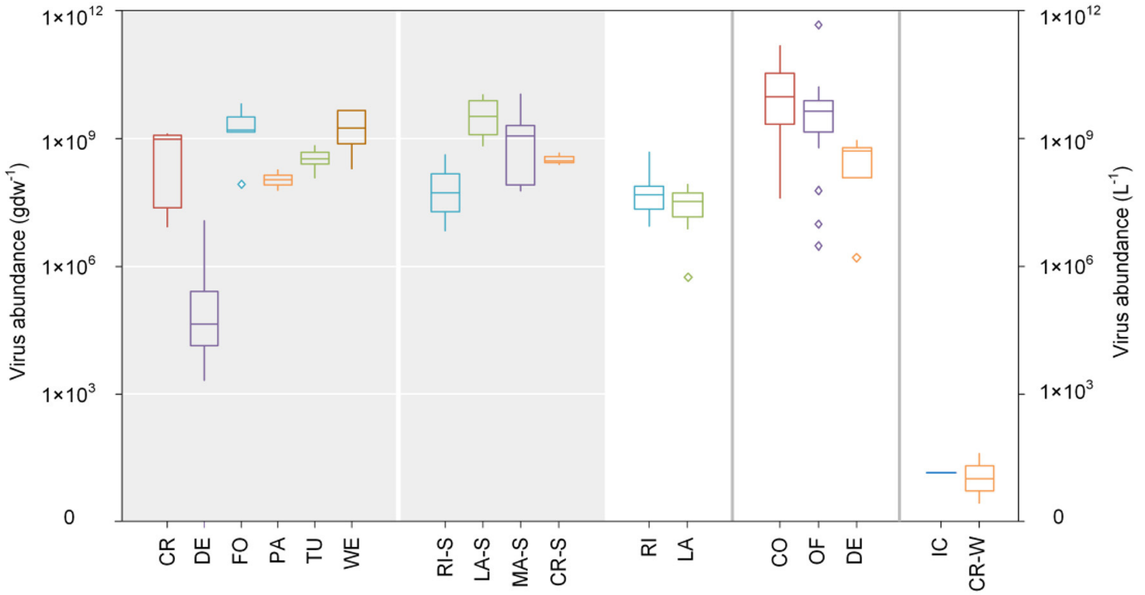

FIGURE 3 | Virus abundance within different ecosystems. Grayed and transparent areas represent virus abundance values in solid and liquid matrices, respectively. All data in this figure were obtained through logarithms. CR, cropland; DE, Desert; FO, Forest; PA, Pasture; TU, Tundra; WE, Wetland; RI-S, River-Sediment; LA-S, Lake-Sediment; MA-S, Marine-Sediment; CR-S, Cryoconite holes-Sediment; RI, River; LA, Lake; CO, Coastal; OF, Offshore; DE, Deep sea; IC, Ice; CR-W, Cryoconite holes-Water. See **Supplementary Table S3** for data sources.

ecosystems (59, 60). Water availability and temperature control virus abundance in soils (40); desert soils have the poorest virus abundance (4.7×10^4 gdw^{-1}), while forests and wetlands have the largest (4.9×10^8 gdw^{-1}) (**Figure 3**).

The abundance of phytoplankton hosts of viruses in rivers and lakes is $\sim 4.8 \times 10^7$ L^{-1} and 3.5×10^7 L^{-1} (**Figure 3**), respectively, which is frequently many times the magnitude of resident bacterial abundance (42). Virus abundance in river sediments is approximately 2.1×10^8 gdw^{-1}, which is less than

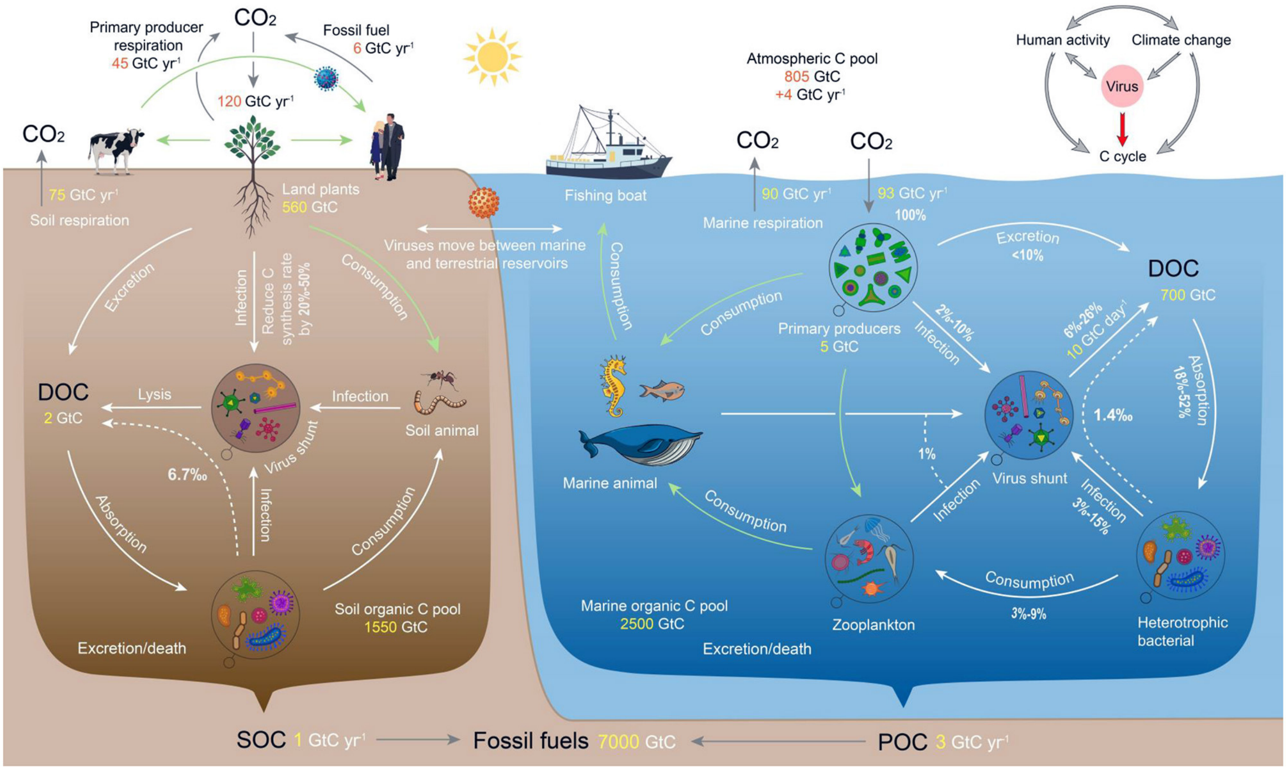

FIGURE 4 | Viruses are a "regulator" of the global ecosystem C cycle network. The gray arrows in the upper right corner of the diagram represent influence and the red arrow represents regulation. The arrows show the roles that viruses play in the traditional food web, the "microbial loop" and the C cycle network of ecosystems. Light green arrows represent the traditional food web, white arrows represent the microbial loop, white dotted arrows represent the contribution rate of C produced by viral lysing of bacteria to the ecosystem DOC pool, and gray arrows represent the intersystem migration C process. Additionally, C reserves and the C exchange volume are indicated in orange or yellow font. The schematic diagram of the freshwater ecosystem was similar to that of the marine ecosystem and is not shown separately. The "microbial loop" is an important supplement to the classic food chain, wherein dissolved organic matter (DOM) is ingested by heterotrophic "planktonic" bacteria during secondary production. These bacteria are then consumed by protozoa, copepods and other organisms, and eventually returned to the classical food chain. DOM includes three categories according to biological availability: labile DOM (LDOM; ~26 Gt C), semi-labile DOM (SLDOM; ~50 Gt C) and recalcitrant DOM (RDOM; ~624 Gt C). All percentage values represent the flux of C fixed by primary producers (100%). See the Methods Section and **Supplementary Table S4** for data sources.

in lake sediments (4.2×10^9 gdw^{-1}) (**Figure 3**). Virus abundance in rivers and lakes exhibit certain seasonal and spatial differences, wherein the peak of abundance generally occurs in summer and autumn (61). In wetland ecosystems, the average planktonic virus abundance is 2.7×10^{10} L^{-1}, wherein corresponding abundances during the rainy and dry seasons are 4.4×10^{10} L^{-1} and 9.7×10^9 L^{-1}, respectively (62).

Virus abundance in marine ecosystems is $> 10^{30}$ viruses, accounting for 89.7% of all viruses (63) and is $\sim 10^8 \sim 10^{11}$ L^{-1} in seawater. Compared to the seawater column, there are less viruses in marine sediments (1.1×10^9 gdw^{-1}) which is similar to the amount in lake sediments, and both hold more viruses than river sediments (**Figure 3**). There are more than 5,000 virus species in every 100 L of seawater and up to 1 million virus species per kilogram of marine sediment (45); consequently, viruses contribute ~94% of nucleic acid-containing particles in ocean water (10). Viruses exist in all marine environments, from shallow seas to deep oceans (64) and from low-latitudinal eutrophic regions to polar sea ice (48, 65) and their abundance is largest in the surface waters of tropical and subtropical oceans and smallest in polar regions. Virus abundance is least in the deep sea (5.2×10^8 L^{-1}) and mid-offshore surface waters (4.3×10^9 L^{-1}) and greatest in coastal waters (1.9×10^{10} L^{-1}) (**Figure 3**).

VIRAL IMPACTS ON ECOSYSTEM CARBON CYCLES

By infecting and lysing microorganisms, viruses remove biomass from the main food chain and convert particulate organic carbon (POC) to dissolved organic carbon (DOC), forming a "viral shunt" pathway (**Figure 4**) which accelerates the flow of energy and carbon in the microbial loops of ecosystems (66–68). Most DOC circulates several times within the bacteria-virus-DOC cycle before being mineralized by the bacterial community, reducing the potential for transfer to higher trophic levels (69).

On land, DOC produced by viral lysis of bacteria contributes ~2.6–12.6‰ to the soil DOC pool (excluding forest and desert; to date, no studies have been published on bacterial mortality caused by viral lysis in forest and desert soils) (**Figure 4**, **Supplementary Table S2**). The scale at which viruses contribute a regulatory carbon cycle function differs between terrestrial ecosystems but is always important. Even in glacial ecosystems where temperature maxima are $< 0.1^{\circ}C$, but that cover 15% of the landmass of the planet, viral activity persists and is relatively large in conditions that otherwise suppress most biological activity (70). In the four terrestrial ecosystems of Wetland, Cropland, Pasture and Tundra, viral lysis in tundra ecosystems contributed the most to soil DOC, producing carbon emissions of 927.1–4202.3 mg $C{\cdot}kg^{-1}$ and accounting for 2.9–22.2‰ of the total DOC pool, and least in wetland ecosystems, causing carbon emissions of 273.5–968.4 mg $C{\cdot}kg^{-1}$ and contributing 0.8–4.4‰ to the DOC pool (**Supplementary Table S2**). The reasons for the difference between terrestrial ecosystems are related to the potential for survival of viruses, and depends on the availability of appropriate hosts and, therefore, the factors controlling their community dynamics, e.g., water, temperature, carbon and nutrient availability (71), and management.

Viruses play an important role in the ecological regulation of lake carbon cycling processes, particularly in the flow and re-assimilation of organic carbon produced by bacterial lysis. In lake ecosystems, the mortality rate of bacteria caused by viral lysis ranges from 2.5 to 74.0%, which is larger than that caused by grazing by flagellates in certain lakes (72). The carbon emissions caused by this process range from 6.7 to 196.8 $\mu g\ C{\cdot}L^{-1}$, which account for 0.7–61.5‰ of the total DOC pool (**Supplementary Table S2**). In eutrophic lakes, ~29–79% of organic carbon may be reused and recycled within the bacterial-bacteriophage-DOC cycle (73). However, host mortality caused by viral lysis is larger in oligotrophic freshwater ecosystems and carbon release and recycling plays a critical role in microbial survival (74). Thus, in regions where the proportion of bacteria infected by virus is significantly larger, viruses may be the primary ecosystem regulators. In low-productivity freshwater ecosystems dominated by microorganisms (such as lakes in polar and high latitudinal regions), the microbial loop is the main flow pathway of energy and carbon (75, 76). For example, the carbon released by viral lysis is the main DOC source (60%) for lakes in Antarctica (77). Furthermore, the relative contribution of viral lysis to the DOC pool varies seasonally in polar and alpine regions where the rates in winter may be far greater (60%) compared to summer rates (<20%) (67). By comparison, in fluvial systems around one-third (33.6%, corresponding to 0.6 $Pg\ C\ yr^{-1}$) of globally-respired carbon may pass through a viral loop (78). The proportion of bacterial mortality caused by viral lysis in rivers is 0.8–17.9%, emitting 2.1–47.6 $\mu g\ C{\cdot}L^{-1}$ and accounting for 0.4–8.4‰ of the total DOC pool.

In marine ecosystems, ~25% of ocean surface primary productivity passes through the "viral shunt" pathway (**Figure 4**), which results in the rapid circulation of DOC *via* an increase in community respiration and a 33% decrease in carbon transfer into higher trophic levels (79, 80). This mechanism promotes carbon use efficiency and maintains sufficient carbon in surface seawater and thus allows for greater oxidation (**Figure 4**), thereby regulating marine carbon cycles (81) within the largest C pool (82, 83). Here, phytoplankton, bacteria and other ocean microorganisms are the main contributors to DOC (84, 85) and between 6 and 26% of primary production enters the DOC pool *via* viral-induced lysis (**Figure 4**).

Viral lysis of bacteria has obvious spatial characteristics within different ocean environments. In offshore waters, viral lysis causes the release of 0.2–3.2 $\mu g\ C{\cdot}L^{-1}$, which accounts for 0.3–4.0‰ of the total organic carbon pool, while the release of carbon in coastal waters is 0.5–3.4 $\mu g\ C{\cdot}L^{-1}$ (**Supplementary Table S2**). Most DOC produced by viral-induced marine lysis is reincorporated by heterotrophic bacteria as POC *via* the microbial loop, with the remainder as DOC (8–42% in coastal waters and 6.8–25.0% in offshore waters). In deep sea sediments, both viral infections and lysis can lead to the death of > 80% of prokaryotes (or even 100% when water depth exceeds 1,000 m) (84), releasing a large amount of DOC into the deep sea, which significantly narrows the food chain and hastens organic carbon recycling. Overall, viruses boost primary production and sequestration in the deep ocean by helping to maintain nutrients in surface waters that are accessible to sunlight.

INTERACTIONS BETWEEN VIRUSES, ANTHROPOGENIC ACTIVITY AND CLIMATE CHANGE

The changing relationships between humans and their environment due to population increase and consumption of natural resources tend to closer proximity between humans, between humans and other species, and between humans and environmental virus pools, intensifying the potential for the spread of viral infection (**Figure 5**). From 2000 to 2016, the average human death rate caused by viruses was $\sim 2.6 \times 10^8$ people per year, accounting for 12.9% of the total global annual death rate (**Supplementary Table S5**).

Human activity, including urban expansion, biological resource utilization and viral disease control measures, changes the distribution and activity of viruses (14). Fluctuations or changes in the regulatory state of viruses may subsequently impact human welfare. For example, human viral disease, including HIV/AIDS, measles, encephalitis, hepatitis and lower and upper respiratory infections (37), are more frequent during periods of social unrest and armed conflict (**Figure 1**). Indirect effects of human activity on viruses include environmental pollutants, such as chemical fertilizers (86), pesticides (87) and heavy metals (88), that have diverse effects on virus dynamics (89). The expansion of crop irrigation and the international trade in plant products promote favorable conditions for widespread outbreaks and destructive viral epidemics (6).

Shifting global weather patterns caused by climate change affect the spread of viruses among people and vary between ecosystems and geographical regions (6), altering the frequency of severe epidemics (90). Increasing temperature, extreme precipitation events and droughts caused by climate change may facilitate the spread of viruses (91–94), including the release

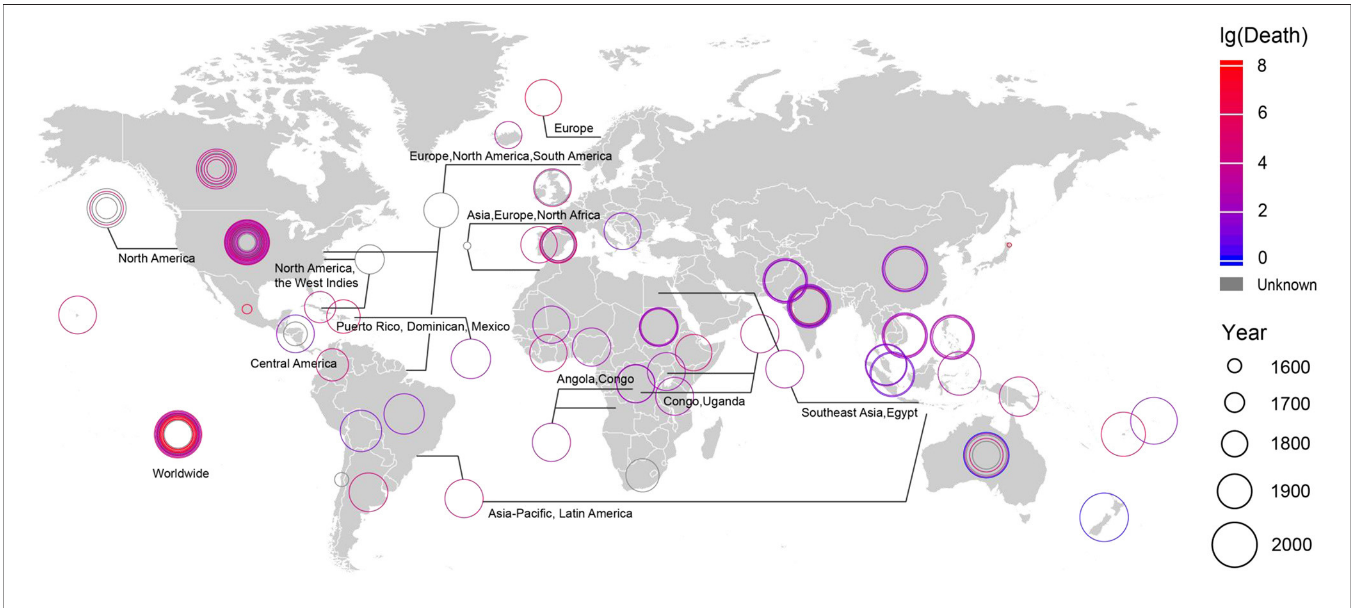

FIGURE 5 | The outbreak time, location and death toll of all viral epidemics on record. See **Supplementary Table S1** for detailed information.

of viruses that have been stored for many millennia into the meltwaters of retreating glaciers (95). However, climate change may also reduce the incidence of viral disease; for example, an increase in temperature can enhance enzyme activities, promoting the degradation of viral capsid proteins (96).

The direct effects of the increasing incidence of human viral disease on the carbon cycle is becoming clear through our collective experience during the current global COVID-19 pandemic. Alteration of human behavior enforced by policy to reduce the risk of viral infection, such as self-isolation, reduced travel and employment deferment, have caused decreased global C emissions by −17 (ranging from −11 to −25) Mt CO_2 d^{-1}, a reduction of 27 to 14% compared to the 2019 mean emission level (20, 97–99). This immediate pandemic-driven response has unintentionally proven the potential of national policy to make a significant impact on the global carbon cycle. A managed reduction of greenhouse gas emissions to avoid global warming of 0.3°C by reducing 30–40 Gt fossil fuel CO_2 emissions (22) appears to be achievable if long-term national socioeconomic polices are implemented.

Human well-being is threatened by insidious changes in viral epidemiology and climate change caused by anthropogenic activity. The global relationships between virus pandemics, global warming and human behavior is complex, but the overriding trend is toward the acceleration of the spread and reproduction of viruses, which may in turn accelerate the global carbon cycle. Overall, the prediction of virus regulation feedbacks in the Anthropocene must improve to provide theoretical and practical support that promotes the harmonious coexistence of humans and viruses as well as the stability and health of ecosystems globally.

UNSEEN IMPACTS OF COVID-19 ON GLOBAL CO_2 EMISSIONS

Historically, climate change and large-scale and sudden disasters have affected the survival and development of human societies, even triggering the rapid demise of great dynasties (100). Progressive growth of the global population enabled by technological progress has deepened the penetration of human activities into "ecosystem Earth" (101). Emerging interrelationships between climate change, anthropogenic activity and material cycles have been established. The intensification of globalization and global climate change since the beginning of the 20th century have co-occurred with the increased frequency of ecological catastrophes including human- and animal-borne diseases, biosecurity threats and super pests, and "natural disasters" such as extreme temperatures, large-scale forest fires, floods and droughts (**Figure 6**). Pressure on natural systems to meet increasing human demand for food and other animal products is driving increased emissions of CO_2 [currently 26% (102)]. Observed changes in the relationship between people and the wider food web during the COVID-19 pandemic presents opportunities to alter future trajectories of CO_2 emission from this source.

During 2020, restrictive policies on human activity imposed in response to the spread of COVID-19 in many countries and states across the world have seriously impacted the performance of global markets, leading to building pressure within national governments to release restrictions on human activity to support economic recovery. However, a beneficial by-product of the restrictive policies is a significant reduction in short-term carbon emissions caused by the change in human behavior (20, 22, 98), leading to calls for governments to use this opportunity to formulate and implement Green Economic Recovery policies

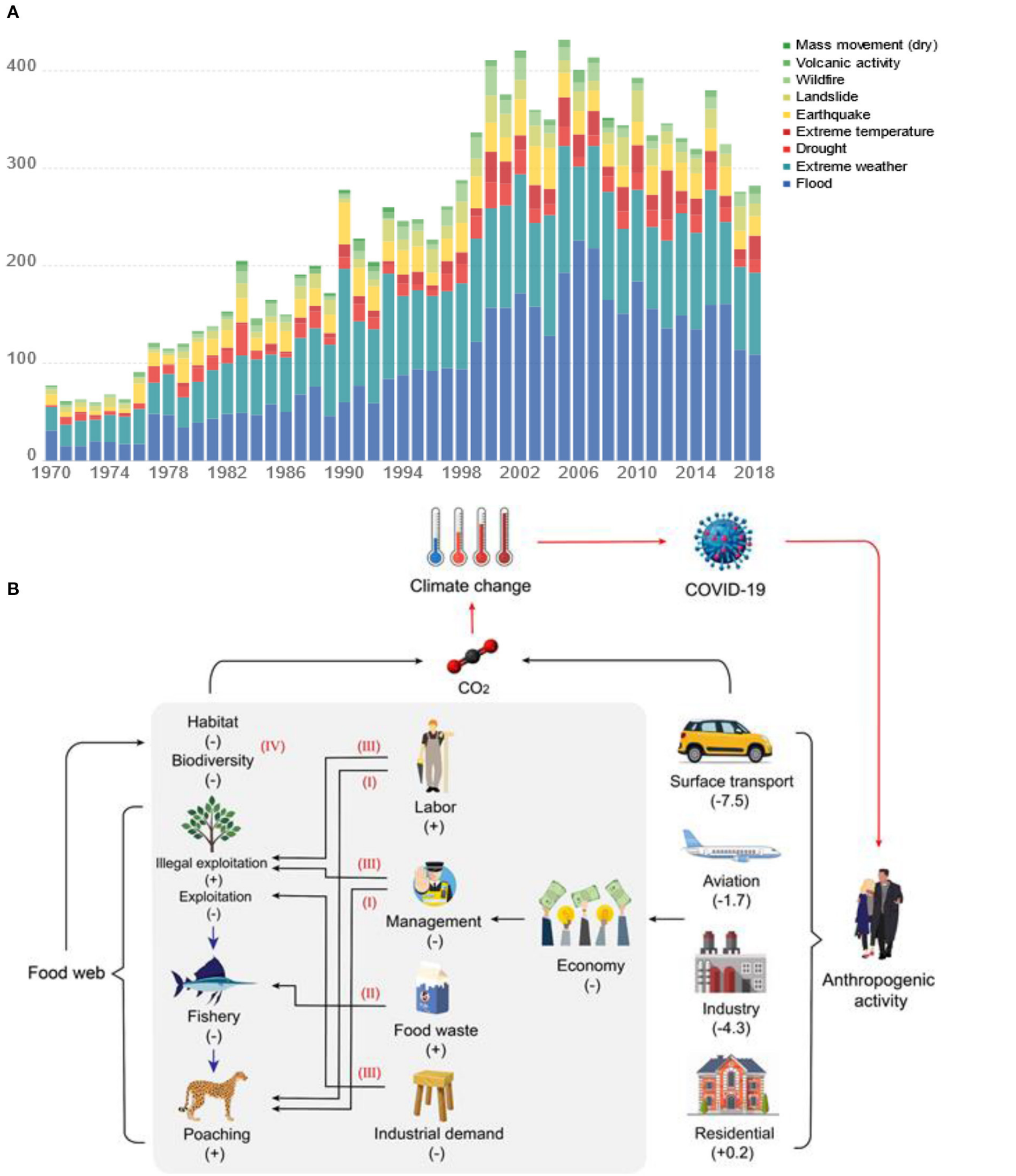

FIGURE 6 | Global reported natural disasters by type for 1970–2019 (https://ourworldindata.org/natural-disasters) **(A)** and the impact of the COVID-19 pandemic on carbon emissions **(B)**. Proposed omissions in carbon emissions related to the food web are described within the area of gray shading. The red roman numerals I-IV correspond to estimation omissions described in the text. The red arrows outside the gray shaded area represent feedbacks and interactions within the virus-climate change-anthropogenic activity-carbon cycle continuum. "+" indicates that the component is promoted and "-" indicates that the component is weakened. The values in brackets are range in daily fossil CO_2 emission on 7 April 2020 compared to mean daily 2019 levels [5], unit: $MtCO_2$ day^{-1}.

with the potential to reduce global warming to rates within planetary boundaries (22). Climate-related disasters this year (such as storms in Fiji, flooding in the middle and lower reaches of the Yangtze River in China, droughts in southern African, and bushfires in Australia and California in the United States) and the epidemic are intertwined (99). Poor human health, caused by exposure to the consequences of climate-driven disasters and other human-driven stressors of ecosystems, promotes susceptibility to COVID-19 infection; for example, lung disease due to increases in $PM_{2.5}$ caused by industrial air pollution (103) and wildfires. Balancing appropriate responses to these interdependent phenomena poses a tremendous policy challenge because of the growing recognition of feedbacks and interactions between the spread and severity of the virus, anthropogenic activity, the carbon cycle and climate change.

Global "black swan" events such as infectious disease outbreaks can alter carbon emissions over the short-term and may potentially affect the carbon balance of the Earth's ecosystems over the long-term. Viruses play key roles in regulating ecosystem carbon cycling processes by impacting material cycles and energy flows in the food web and the microbial loop that regulates CO_2 emissions from organic matter decomposition, under the influence of anthropogenic activity and climate change. Thus, sudden and large-scale viral outbreaks function as "regulators" of the global carbon cycle with the potential to rapidly sever the world's ecosystem carbon balance over a short timeframe (104). We are actively witnessing the importance of the COVID-19 pandemic as a factor in the reduction of anthropogenic-driven short-term carbon emissions, but are unable to yet comprehend the potentially far-reaching and longer-term impacts on carbon emissions from the entire food web, a factor which has not been taken into account in recent carbon emission estimation studies. Therefore, we propose that major estimation omissions have been made to actual carbon emission changes and the climate effects that these changes engender, that are created by human responses to the COVID-19 pandemic.

We propose that the reduction in emissions could be moderated *via* direct and indirect impacts on the economic activities of human society, particularly the consumption of animals as food or for leisure activity (**Figure 1B**). Potential unaccounted estimation omissions during the COVID-19 pandemic include:

(I) A halt in tourism and the withdrawal of labor from nature reserves have led to an increase in wildlife poaching [for example, recent rhino horn poaching incidents in India (105) and raptors and fish in Europe (106)] and financial crises in zoos and wildlife rehabilitation centers threaten the survival of species important for ecotourism, including orangutans in Borneo (107).

(II) Shrinking fresh food markets selling farmed and wild animal products in some regions including China and Africa (108), have led to a decrease in the legal capture of wild aquatic and terrestrial animals, with the fishing industry most affected (109); whilst direct sales of fresh produce from farms has increased as western consumers seek local and traceable food options (110). Globally, the pandemic has disrupted the food supply chain system. Disruptions in food markets and workforces are causing a doubling of people facing severe hunger and huge amounts of land, fertilizer, energy and water being wasted. Among them, food waste has increased from about 8% of global anthropogenic greenhouse gas emissions to a larger proportion. In India, migrant workers are confined to their home villages, leaving fresh fruit unpicked and rotting in the fields. In the United States, the embodied carbon footprint of livestock and dairy losses have reached at least 7.1 $MtCO_2e$. In the EU, the carbon footprint of potato waste (one of the lowest carbon footprint foods) comes to 0.5 $MtCO_2e$ (111).

(III) The global economic slowdown has decreased demand for industrially-produced commodities, thereby reducing direct environmental pressure (112); however, the decline in centralized management of protected areas may lead to higher rates of unlawful resource exploitation, such as illegal logging that causes the emission of previously sequestered carbon from standing biomass and degraded soils (113).

(IV) In economically deprived regions, spikes in unemployment and the loss of family income have increased the dependency on local natural resources for wild sources of food and fuel, and the increased exploitation of marginal lands for agriculture, increasing risks to ecosystem integrity associated with habitat and biodiversity loss (112, 114).

The prolonged economic downturn caused by the COVID-19 pandemic and resulting series of policy decisions during recovery may have a more profound and lasting impact on carbon emissions (21). We identified two dominant factors linked to changes in global carbon emissions caused by the COVID-19 pandemic, (1) the widely acknowledged reduction in carbon emissions through the sudden decline in fossil fuel use caused by a decrease in anthropogenic activity, and (2) the less well-documented change in carbon emission rates caused by the cumulative impact of altered human behavior propagating through the food web. We hypothesize that the net effect of these two factors on the environment is comparable to the effect of human population decrease because the degree of human intervention in the ecological environment during the viral outbreak is reduced, which is similar to the impact of population decline. In other words, a proportion of the reduction in overall carbon emissions is due to Earth ecosystem compensation and feedback mechanisms, resulting in a longer-term slowdown in carbon emissions than estimated through traditional methods. However, as we have described, the balance between promoting or reducing CO_2 emissions for the long term depends on the policy-driven encouragement of altered patterns of human consumption that reduce pressure on the natural environment *via* the food web.

CONCLUSION

Human well-being is threatened by insidious changes in viral epidemiology and climate change caused by anthropogenic activity. The global relationships between virus pandemics, global warming and human behavior is complex, but the overriding trend is toward the acceleration of the spread and reproduction of viruses, which may in turn accelerate the global carbon cycle. Overall, the prediction of virus regulation feedbacks in the Anthropocene must improve to provide theoretical and practical support that promotes the harmonious coexistence of humans and viruses as well as the stability and health of ecosystems globally.

The maintenance of Earth ecosystem integrity is crucial for the future sustainability of human society. COVID-19 has provided us with insight into the capability of people to effect change collaboratively in the face of a common threat. Post-pandemic, due to lags in feedback systems, the indirect effects of a short-term reduction in anthropogenic activities will gradually and distinctly manifest after lockdown restrictions are lifted, potentially altering the status of the carbon cycle balance of Earth's ecosystems for the long-term. Therefore, it is essential to secure a full comprehension of the role that virus plays in global carbon cycling to aid efforts to obtain more accurate measurements of actual carbon emissions.

During the formulation of COVID-19 economic recovery policies, policymakers must look beyond direct changes to carbon emissions to the role and contribution of indirect changes in carbon emissions. Critically, there is an urgent need for research to establish how changes in anthropogenic activities resonate through the food web and their consequent expression as indirect contributions to carbon emissions. This will allow for a more comprehensive and accurate platform from which to judge overall ecosystem carbon emissions. Globalization, urbanization and climate change are driving increases in human connectivity making future global viral epidemics inevitable. In response, we must attend to issues related to maintaining ecosystem integrity to inform appropriate policy responses through a detailed understanding of impacts and feedbacks within the climate change-anthropogenic activity-carbon cycle continuum.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding authors.

AUTHOR CONTRIBUTIONS

YG and GY: conceptualization. JJ, SL, and JL: resource and data curation. YL, JD, and YL: writing-original draft. YG and JD: writing-review and editing. All authors contributed to the article and approved the submitted version.

FUNDING

This study was financially supported by the National Nature Science Foundation of China (No. 31988102, 41922003, and 42141015).

ACKNOWLEDGMENTS

The authors of this study would like to thank all reviewers for their helpful remarks. We thank Brian Doonan (McGill University, Canada) for his help in writing this paper and provide useful suggestions.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.858615/full#supplementary-material

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frontiers | Frontiers in Microbiology

REVIEW
published: 26 April 2022
doi: 10.3389/fmicb.2022.869332

Pharmaceutical Pollution in Aquatic Environments: A Concise Review of Environmental Impacts and Bioremediation Systems

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OPEN ACCESS

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Specialty section:
This article was submitted to Microbiotechnology, a section of the journal Frontiers in Microbiology

Received: *04 February 2022*
Accepted: *30 March 2022*
Published: *26 April 2022*

Citation:
Ortúzar M, Esterhuizen M, Olicón-Hernández DR, González-López J and Aranda E (2022) Pharmaceutical Pollution in Aquatic Environments: A Concise Review of Environmental Impacts and Bioremediation Systems. Front. Microbiol. 13:869332. doi: 10.3389/fmicb.2022.869332

The presence of emerging contaminants in the environment, such as pharmaceuticals, is a growing global concern. The excessive use of medication globally, together with the recalcitrance of pharmaceuticals in traditional wastewater treatment systems, has caused these compounds to present a severe environmental problem. In recent years, the increase in their availability, access and use of drugs has caused concentrations in water bodies to rise substantially. Considered as emerging contaminants, pharmaceuticals represent a challenge in the field of environmental remediation; therefore, alternative add-on systems for traditional wastewater treatment plants are continuously being developed to mitigate their impact and reduce their effects on the environment and human health. In this review, we describe the current status and impact of pharmaceutical compounds as emerging contaminants, focusing on their presence in water bodies, and analyzing the development of bioremediation systems, especially mycoremediation, for the removal of these pharmaceutical compounds with a special focus on fungal technologies.

Keywords: pharmaceutical active compounds, bioremediation, wastewater, mycoremediation, emerging contaminants, pharmaceutical pollution

INTRODUCTION

In recent decades, the production and consumption of pharmaceutical products have rapidly increased with the development of medicine. Approximately 3,000 compounds are used as pharmaceuticals, and the annual production quantity exceeds hundreds of tons (Carvalho and Santos, 2016; Grenni et al., 2018). Anti-inflammatory drugs, antibiotics, and analgesics are the most common drugs used around the world. Consequently, the emergence of water-soluble and pharmacologically active organic micropollutants or pharmaceutical active compounds (PhACs) has gained much attention worldwide. Humans use a variety of these pharmaceuticals for their health in everyday life, but large quantities of these drugs are also used as veterinary medicine on farms around the world, to prevent and treat animal diseases and to increase economic benefits in intensive livestock (Blanco et al., 2017; Ekpeghere et al., 2017; Gros et al., 2019; Ramírez-Morales et al., 2021).

After ingestion, pharmaceuticals are excreted in urine and feces as active substances or metabolites (Sui et al., 2015; aus der Beek et al., 2016). These pharmaceuticals are present in both influent and effluent wastewater but can also be found in surface water bodies, including freshwater ecosystems and marine environments, as well as in groundwater due to effluent leachates generated under recharge conditions (Deo, 2014; Furlong et al., 2017; Ojemaye and Petrik, 2018; Reis-Santos et al., 2018; Fekadu et al., 2019; Letsinger et al., 2019; Zainab et al., 2020). The main concern is that conventional treatment plants are ineffective in removing some of these emerging contaminants (ECs), and new techniques are being sought and studied to achieve their total elimination, particularly advances in mycoremediation (Danner et al., 2019). The importance of the study of pharmaceuticals lies in the massive increase in their consumption worldwide, as well as in the environmental repercussions that this entails, including their recalcitrance in aquatic and terrestrial ecosystems. In the contexts of wastewater and bioremediation, pharmaceutical compounds are considered as ECs due to the lack of regulation for their environmental disposal, as well as the lack of information regarding their long-term effects on the environment (Dhangar and Kumar, 2020; Valdez-Carrillo et al., 2020; Chaturvedi et al., 2021b; Rathi et al., 2021), which remains unknown (Barber et al., 2015; Ahmed et al., 2017). The fact that some drugs are marketed without medical prescription or pre-registration and, therefore, are widely consumed worldwide, meaning that they are widely distributed in the environment (Gil et al., 2017), has contributed to this growing problem.

Considering pharmaceuticals as ECs and the continual production of new PhACs, this review aims to comprehensively present the pharmaceuticals commonly detected in water, surface and groundwater and their adverse environmental effects. Advances in bioremediation technologies, which can be used as add-on treatments in wastewater treatment plants (WWTPs) to reduce unprocessed pharmaceuticals released via effluent into the environment, are presented and critically discussed with an emphasis on mycoremediation.

COMMON PHARMACEUTICALS DETECTED IN WATER (SURFACE AND GROUNDWATER)

Pharmaceutical compounds that reach water bodies, both surface water and groundwater, came from a number of different sources (**Figure 1**). The first of these is urban wastewater, which contains a high load of pharmaceuticals from human excrement, and also the inadequate disposal of expired or unused drugs due to the scarce control in their management. Another major source of pharmaceuticals is agricultural and livestock waste, especially the latter, since in large farms for intensive livestock, animals are often fed with feed supplemented containing drugs and excreta are often used in agriculture as soil amendments, reaching groundwater by leaching (Kim et al., 2008; Barrios-Estrada et al., 2018). Effluents from the pharmaceutical industry are another important source, with high concentrations of pharmaceuticals being found due to discharges from factories in Asia, Europe and America, despite strict regulation of pharmaceutical production in Europe and the United States (Lin et al., 2008; Lin and Tsai, 2009; Phillips et al., 2010; Prasse et al., 2010; Sim et al., 2011; Cardoso et al., 2014). These industries are obliged to carry out treatment before discharge into the general urban sewer network (Lindberg et al., 2004; Brown et al., 2006).

Pharmaceuticals found in high concentrations in wastewater include non-steroidal anti-inflammatory drugs (NSAIDs), β-blockers ad psychoactive compounds, analgesics, antibiotics, endocrine disruptors, antiretroviral drugs, and drugs to treat cancer (Roberts and Thomas, 2006; Gros et al., 2010; Lian et al., 2017). These are the PhACs most commonly detected due to the analytical methods available and their resolution, although new methods for identifying these compounds are increasingly being developed (Pivetta et al., 2020; Zhang et al., 2020). **Table 1** shows the worldwide distribution of the drugs most commonly found in water (**Supplementary Figure 1**).

Non-steroidal anti-inflammatory drugs and analgesics are some of the most important groups of pharmaceutical products worldwide, with diverse chemical structures and similar therapeutic effects, having an estimated annual production of several hundred tons (Comber et al., 2018). Large amounts of anti-inflammatory drugs are prescribed in human care, but they are often sold in much higher amounts without a prescription (Ternes, 2001). NSAIDs and analgesics are often combined with antibiotics in veterinary medicine for problems such as pain, inflammation, fever, osteoarthritis and arthritis, and to reduce stress (Courtheyn et al., 2002; Bártíková et al., 2016). However, these two types of pharmaceuticals have numerous adverse effects in humans, including gastrointestinal disturbances, ulceration, renal failure with increased risk of post-operative bleeding, asthma, and rare allergic reactions (Ben Maamar et al., 2017; Morelli et al., 2017; Borgeat et al., 2018; Hurtado-Gonzalez et al., 2021). Approximately 35 million people use NSAIDs every day worldwide (Yu et al., 2013), and China increased its domestic production from 41,537 t in 2013 to 46,673 t in 2017 (Yan et al., 2021). They are currently monitored in effluents worldwide to check these drug concentrations and several studies show that both NSAIDs and analgesics are commonly detected in water bodies (Balakrishna et al., 2017; Świacka et al., 2021). In Cuernavaca (Mexico), high concentrations of naproxen (732–4,889 ng/L), acetaminophen (354–4,460 ng/L), and diclofenac (258–1,398 ng/L) have been detected in samples collected in different years, in the influent and effluent of a WWTP and in the surface waters of the Apatalco River (Rivera-Jaimes et al., 2018). Furthermore, the drugs diclofenac (10,221 ng/L highest concentration detected) and acetaminophen (1234-2346 ng/L), among others, have been detected in effluents from the Red Sea (Saudi Arabia) (Ali et al., 2017). On the other hand, in Brazil, acetaminophen (17.4–34.6 ng/L), diclofenac (19.4 ng/L), and ibuprofen (326.1–2,094.4 ng/L) have been detected in the surface and bottom water samples from Santos Bay (Pereira et al., 2016).

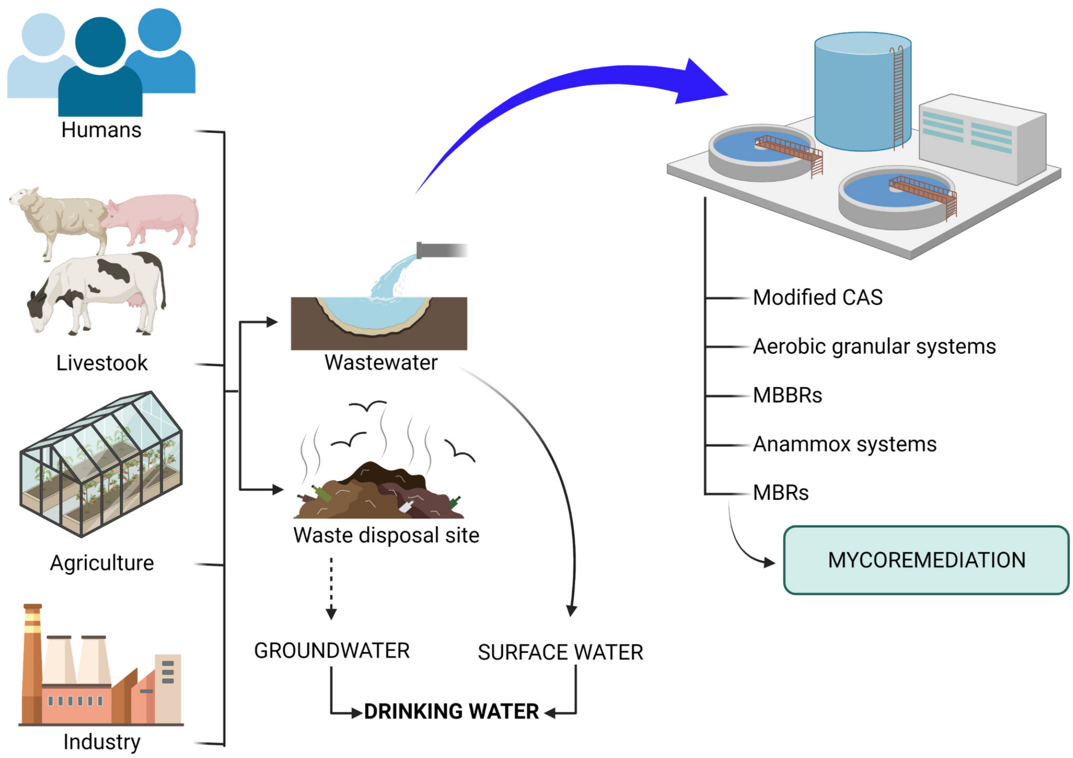

FIGURE 1 | Pharmaceuticals route to a body of water and bioremediation technologies. (→): Direct contamination. (- - →): Contamination through different steps. The monitoring suggests that contamination accumulates in surface water and groundwater.

These same drugs have also been detected in surface water on the northern Antarctic Peninsula region due to increased tourism in this area, with concentrations of 48.74, 15.09, and 10.05 ng/L of acetaminophen, diclofenac, and ibuprofen, reported respectively (González-Alonso et al., 2017).

Among the pharmaceutical compounds found in wastewater, antibiotics are of the greatest concern due to their persistent nature, partial metabolism, and easy movement through ecosystems (Mukhtar et al., 2020). Antibiotic production in China was approximately 92,700 tons, 48% destined for humans and the remaining for livestock; a total of 46% active metabolites were produced (Zafar et al., 2021). The antibiotics most commonly found in wastewater are sulfonamides, quinolones, tetracyclines, fluoroquinolones, and nitroimidazoles. The total concentrations of antibiotics vary depending on the body of water, in the case of wastewater, they can range between 0.0013 and 0.0125 μg/mL, in drinking water 0.0005 and 0.0214 μg/mL and river water 0.0003 and 0.0039 μg/mL (Zhang et al., 2015; Pan and Chu, 2017; Hanna et al., 2018). Antibiotic resistance of microorganisms to antimicrobials is becoming even stronger and more widespread over time and is expected to greatly increase human morbility and mortality in the near future (Bondarczuk and Piotrowska-Seget, 2019). Antibiotics have been found in rivers all over the world, including several in Spain (Ebro, Guadarrama and Manzanares Rivers), Italy (Arno River), South Korea (Han River), Taiwan (Xindian, Gaoping, Dahan and Po River), France (Seine River), United States (Ozark River), Sweden (Hoje River), and China (Pearl, Hai, Liao and Yellow Rivers) (Peng et al., 2008, 2011; Valcárcel et al., 2011; López-Serna et al., 2013; Bilal et al., 2020).

Endocrine disruptors were defined in 2002 by the International Programme on Chemical Safety (IPCS) of the United Nations Environment Programme (UNEP) and by the World Health Organization (WHO) as "an exogenous substance or mixture that alters the function(s) of the endocrine system and consequently causes adverse health effects in an intact organism or population". Among the most common endocrine disruptors are pesticides, bisphenols and natural hormones (Gore et al., 2014; Tijani et al., 2016). These substances are not removed from water by conventional treatment processes and are found in wastewater bodies in the order of nanograms to micrograms per liter (Andrade-Eiroa et al., 2016; Gröger et al., 2020; Li et al., 2020).

Antiretroviral drugs are frequently used to treat the human immunodeficiency virus (HIV), an epidemic that has developed worldwide and has its epicenter in South Africa (Tompsett, 2020). As a result, millions of people have access to these drugs on a daily basis, with more than 40 different antiretroviral drugs being used for the treatment of HIV. These include abacavir, efavirenz, lamivudine, nevirapine, tenofovir, and zidovudine; many of which are used in combination (Russo et al., 2018; Mlunguza et al., 2020). As a consequence of the increase in the rate of HIV infection over the years, there has been a significant increase in the production and consumption of

TABLE 1 | Types of pharmaceuticals and concentrations reported in countries worldwide.

Pharmaceutical type	Pharmaceutical	Max conc (ng/L)	Country	References
NSAIDs and analgesics	Naproxen	4,889	Mexico	Rivera-Jaimes et al., 2018
NSAIDs and analgesics	Acetaminophen	4,460	Mexico	Rivera-Jaimes et al., 2018
NSAIDs and analgesics	Diclofenac	1,398	Mexico	Rivera-Jaimes et al., 2018
NSAIDs and analgesics	Diclofenac	10,221	Saudi Arabia	Ali et al., 2017
NSAIDs and analgesics	Acetaminophen	2,346	Saudi Arabia	Ali et al., 2017
NSAIDs and analgesics	Ibuprofen	2,094.4	Brazil	Pereira et al., 2016
NSAIDs and analgesics	Acetaminophen	34.6	Brazil	Pereira et al., 2016
NSAIDs and analgesics	Diclofenac	19.4	Brazil	Pereira et al., 2016
NSAIDs and analgesics	Acetaminophen	48.74	Antartic Peninsula	González-Alonso et al., 2017
NSAIDs and analgesics	Diclofenac	15.09	Antartic Peninsula	González-Alonso et al., 2017
NSAIDs and analgesics	Ibuprofen	10.05	Antartic Peninsula	González-Alonso et al., 2017
NSAIDs and analgesics	Ibuprofen	414	South Korea	Kim et al., 2009
NSAIDs and analgesics	Ibuprofen	1,850	Vietnam	Tran et al., 2014
NSAIDs and analgesics	Diclofenac	1,630	Vietnam	Tran et al., 2014
NSAIDs and analgesics	Ketoprofen	1,620	Vietnam	Tran et al., 2014
NSAIDs and analgesics	Naproxen	1,110	Vietnam	Tran et al., 2014
NSAIDs and analgesics	Acetaminophen	12,430	Nigeria	Ebele et al., 2020
NSAIDs and analgesics	Ibuprofen	2,740	Nigeria	Ebele et al., 2020
NSAIDs and analgesics	Naproxen	2,120	Nigeria	Ebele et al., 2020
NSAIDs and analgesics	Diclofenac	200	Nigeria	Ebele et al., 2020
NSAIDs and analgesics	Ibuprofen	121	Singapore	Wu et al., 2010
NSAIDs and analgesics	Diclofenac	38	Singapore	Wu et al., 2010
NSAIDs and analgesics	Naproxen	30	Singapore	Wu et al., 2010
NSAIDs and analgesics	Ibuprofen	34.9	Baltic Sea/Polish	Borecka et al., 2015
NSAIDs and analgesics	Naproxen	13,100	United States/California	Vidal-Dorsch et al., 2012
NSAIDs and analgesics	Ibuprofen	12,000	United States/California	Vidal-Dorsch et al., 2012
NSAIDs and analgesics	Acetaminophen	11,000	United States/California	Vidal-Dorsch et al., 2012
NSAIDs and analgesics	Diclofenac	180	United States/California	Vidal-Dorsch et al., 2012
NSAIDs and analgesics	Diclofenac	843	China	Yang et al., 2011
NSAIDs and analgesics	Ibuprofen	2,200	Taiwan	Fang et al., 2012
NSAIDs and analgesics	Diclofenac	185	Taiwan	Fang et al., 2012
NSAIDs and analgesics	Ketoprofen	184	Taiwan	Fang et al., 2012
NSAIDs and analgesics	Ibuprofen	143,000	Spain	Santos et al., 2007
NSAIDs and analgesics	Ketoprofen	2,100	Spain	Santos et al., 2007
NSAIDs and analgesics	Diclofenac	280	Spain	Santos et al., 2007
NSAIDs and analgesics	Ibuprofen	1,130	Japan	Nakada et al., 2006
NSAIDs and analgesics	Ketoprofen	369	Japan	Nakada et al., 2006
NSAIDs and analgesics	Ibuprofen	16,500	Canada	Lishman et al., 2006
NSAIDs and analgesics	Diclofenac	1,010	Canada	Lishman et al., 2006
NSAIDs and analgesics	Ketoprofen	289	Canada	Lishman et al., 2006
NSAIDs and analgesics	Ibuprofen	1,900	United States/Maryland	Yu et al., 2006
NSAIDs and analgesics	Ketoprofen	1,200	United States/Maryland	Yu et al., 2006
NSAIDs and analgesics	Diclofenac	110	United States/Maryland	Yu et al., 2006
NSAIDs and analgesics	Diclofenac	4,114	Austria	Clara et al., 2005
NSAIDs and analgesics	Ibuprofen	2,679	Austria	Clara et al., 2005
NSAIDs and analgesics	Ibuprofen	1,400	Switzerland	Tixier et al., 2003
NSAIDs and analgesics	Diclofenac	990	Switzerland	Tixier et al., 2003
NSAIDs and analgesics	Ketoprofen	180	Switzerland	Tixier et al., 2003
NSAIDs and analgesics	Ibuprofen	3,400	Germany	Ternes, 1998
NSAIDs and analgesics	Diclofenac	2,100	Germany	Ternes, 1998
NSAIDs and analgesics	Ketoprofen	380	Germany	Ternes, 1998
NSAIDs and analgesics	Ibuprofen	4,201	United Kingdom	Ashton et al., 2004
NSAIDs and analgesics	Diclofenac	599	United Kingdom	Ashton et al., 2004

(Continued)

TABLE 1 | Continued

Pharmaceutical type	Pharmaceutical	Max conc (ng/L)	Country	References
Antibiotic	Azithromycin	597.5	Portugal	Rodriguez-Mozaz et al., 2020
Antibiotic	Ciprofloxacin	584.9	Portugal	Rodriguez-Mozaz et al., 2020
Antibiotic	Clarithromycin	313,2	Portugal	Rodriguez-Mozaz et al., 2020
Antibiotic	Tetracycline	231.2	Portugal	Rodriguez-Mozaz et al., 2020
Antibiotic	Trimethoprim	190.6	Portugal	Rodriguez-Mozaz et al., 2020
Antibiotic	Ofloxacin	184.9	Portugal	Rodriguez-Mozaz et al., 2020
Antibiotic	Clindamycin	86.6	Portugal	Rodriguez-Mozaz et al., 2020
Antibiotic	Sulfapyridine	48.8	Portugal	Rodriguez-Mozaz et al., 2020
Antibiotic	Cefalexin	38.4	Portugal	Rodriguez-Mozaz et al., 2020
Antibiotic	Sulfamethoxazole	30.2	Portugal	Rodriguez-Mozaz et al., 2020
Antibiotic	Pipemidic acid	20.1	Portugal	Rodriguez-Mozaz et al., 2020
Antibiotic	Azithromycin	299.5	Spain	Rodriguez-Mozaz et al., 2020
Antibiotic	Ciprofloxacin	200.3	Spain	Rodriguez-Mozaz et al., 2020
Antibiotic	Ofloxacin	142.3	Spain	Rodriguez-Mozaz et al., 2020
Antibiotic	Sulfamethoxazole	123.4	Spain	Rodriguez-Mozaz et al., 2020
Antibiotic	Clarithromycin	112	Spain	Rodriguez-Mozaz et al., 2020
Antibiotic	Trimethoprim	102.8	Spain	Rodriguez-Mozaz et al., 2020
Antibiotic	Clindamycin	101.4	Spain	Rodriguez-Mozaz et al., 2020
Antibiotic	Metronidazole	76.1	Spain	Rodriguez-Mozaz et al., 2020
Antibiotic	Enrofloxacin	69.4	Spain	Rodriguez-Mozaz et al., 2020
Antibiotic	Cefalexin	65.2	Spain	Rodriguez-Mozaz et al., 2020
Antibiotic	Sulfapyridine	63.9	Spain	Rodriguez-Mozaz et al., 2020
Antibiotic	Pipemidic acid	30.1	Spain	Rodriguez-Mozaz et al., 2020
Antibiotic	Ciprofloxacin	316.8	Cyprus	Rodriguez-Mozaz et al., 2020
Antibiotic	Ofloxacin	305.1	Cyprus	Rodriguez-Mozaz et al., 2020
Antibiotic	Trimethoprim	74.2	Cyprus	Rodriguez-Mozaz et al., 2020
Antibiotic	Sulfamethoxazole	68.5	Cyprus	Rodriguez-Mozaz et al., 2020
Antibiotic	Cefalexin	66.3	Cyprus	Rodriguez-Mozaz et al., 2020
Antibiotic	Sulfapyridine	48.7	Cyprus	Rodriguez-Mozaz et al., 2020
Antibiotic	Azithromycin	48	Cyprus	Rodriguez-Mozaz et al., 2020
Antibiotic	Tetracycline	36.9	Cyprus	Rodriguez-Mozaz et al., 2020
Antibiotic	Clindamycin	27.8	Cyprus	Rodriguez-Mozaz et al., 2020
Antibiotic	Metronidazole	19.6	Cyprus	Rodriguez-Mozaz et al., 2020
Antibiotic	Pipemidic acid	15.2	Cyprus	Rodriguez-Mozaz et al., 2020
Antibiotic	Clarithromycin	11.9	Cyprus	Rodriguez-Mozaz et al., 2020
Antibiotic	Orbifloxacin	6.7	Cyprus	Rodriguez-Mozaz et al., 2020
Antibiotic	Azithromycin	266.7	Ireland	Rodriguez-Mozaz et al., 2020
Antibiotic	Ciprofloxacin	259.8	Ireland	Rodriguez-Mozaz et al., 2020
Antibiotic	Clarithromycin	204.4	Ireland	Rodriguez-Mozaz et al., 2020
Antibiotic	Tetracycline	194.2	Ireland	Rodriguez-Mozaz et al., 2020
Antibiotic	Trimethoprim	141.3	Ireland	Rodriguez-Mozaz et al., 2020
Antibiotic	Ampicillin	99.4	Ireland	Rodriguez-Mozaz et al., 2020
Antibiotic	Sulfapyridine	95.5	Ireland	Rodriguez-Mozaz et al., 2020
Antibiotic	Metronidazole	88.6	Ireland	Rodriguez-Mozaz et al., 2020
Antibiotic	Cefalexin	87.6	Ireland	Rodriguez-Mozaz et al., 2020
Antibiotic	Ofloxacin	65.4	Ireland	Rodriguez-Mozaz et al., 2020
Antibiotic	Clindamycin	59.1	Ireland	Rodriguez-Mozaz et al., 2020
Antibiotic	Sulfamethoxazole	53	Ireland	Rodriguez-Mozaz et al., 2020
Antibiotic	Nalidixic acid	50.3	Ireland	Rodriguez-Mozaz et al., 2020
Antibiotic	Pipemidic acid	18.2	Ireland	Rodriguez-Mozaz et al., 2020
Antibiotic	Oxolinic Acid	5.3	Ireland	Rodriguez-Mozaz et al., 2020
Antibiotic	Azithromycin	290.4	Germany	Rodriguez-Mozaz et al., 2020
Antibiotic	Ciprofloxacin	230.6	Germany	Rodriguez-Mozaz et al., 2020
Antibiotic	Clarithromycin	123.4	Germany	Rodriguez-Mozaz et al., 2020
Antibiotic	Sulfapyridine	112	Germany	Rodriguez-Mozaz et al., 2020

(Continued)

TABLE 1 | Continued

Pharmaceutical type	Pharmaceutical	Max conc (ng/L)	Country	References
Antibiotic	Clindamycin	110.7	Germany	Rodriguez-Mozaz et al., 2020
Antibiotic	Trimethoprim	105	Germany	Rodriguez-Mozaz et al., 2020
Antibiotic	Ofloxacin	66.5	Germany	Rodriguez-Mozaz et al., 2020
Antibiotic	Sulfamethoxazole	34.9	Germany	Rodriguez-Mozaz et al., 2020
Antibiotic	Metronidazole	20.3	Germany	Rodriguez-Mozaz et al., 2020
Antibiotic	Tetracycline	15.4	Germany	Rodriguez-Mozaz et al., 2020
Antibiotic	Pipemidic acid	11.8	Germany	Rodriguez-Mozaz et al., 2020
Antibiotic	Cefalexin	308	Finland	Rodriguez-Mozaz et al., 2020
Antibiotic	Trimethoprim	186.7	Finland	Rodriguez-Mozaz et al., 2020
Antibiotic	Azithromycin	130.7	Finland	Rodriguez-Mozaz et al., 2020
Antibiotic	Sulfapyridine	98.8	Finland	Rodriguez-Mozaz et al., 2020
Antibiotic	Clindamycin	94.2	Finland	Rodriguez-Mozaz et al., 2020
Antibiotic	Tetracycline	70.6	Finland	Rodriguez-Mozaz et al., 2020
Antibiotic	Ciprofloxacin	43.2	Finland	Rodriguez-Mozaz et al., 2020
Antibiotic	Metronidazole	41.9	Finland	Rodriguez-Mozaz et al., 2020
Antibiotic	Ofloxacin	22.8	Finland	Rodriguez-Mozaz et al., 2020
Antibiotic	Clarithromycin	4.8	Finland	Rodriguez-Mozaz et al., 2020
Antibiotic	Pipemidic acid	4.8	Finland	Rodriguez-Mozaz et al., 2020
Antibiotic	Sulfapyridine	184	Norway	Rodriguez-Mozaz et al., 2020
Antibiotic	Tetracycline	179.2	Norway	Rodriguez-Mozaz et al., 2020
Antibiotic	Ciprofloxacin	159.2	Norway	Rodriguez-Mozaz et al., 2020
Antibiotic	Azithromycin	149.7	Norway	Rodriguez-Mozaz et al., 2020
Antibiotic	Trimethoprim	119.7	Norway	Rodriguez-Mozaz et al., 2020
Antibiotic	Clindamycin	97.1	Norway	Rodriguez-Mozaz et al., 2020
Antibiotic	Metronidazole	93.2	Norway	Rodriguez-Mozaz et al., 2020
Antibiotic	Cefalexin	60.7	Norway	Rodriguez-Mozaz et al., 2020
Antibiotic	Sulfamethoxazole	48.6	Norway	Rodriguez-Mozaz et al., 2020
Antibiotic	Ofloxacin	27.1	Norway	Rodriguez-Mozaz et al., 2020
Antibiotic	Clarithromycin	20.8	Norway	Rodriguez-Mozaz et al., 2020
Antibiotic	Pipemidic acid	7,5	Norway	Rodriguez-Mozaz et al., 2020
Antibiotic	Oxytetracycline	2,796.6	China	Wang et al., 2017
Antibiotic	Tetracycline	1,454.8	China	Wang et al., 2017
Antibiotic	Chlorotetracycline	876.2	China	Wang et al., 2017
Antibiotic	Sulfamethoxazole	715.3	China	Wang et al., 2017
Antibiotic	Sulfadiazine	499.5	China	Wang et al., 2017
Antibiotic	Sulfamerazine	329.1	China	Wang et al., 2017
Antibiotic	Fleroxacin	309.4	China	Wang et al., 2017
Antibiotic	Difloxacin	250.2	China	Wang et al., 2017
Antibiotic	Sulfanomethioxine	225.5	China	Wang et al., 2017
Antibiotic	Ofloxazin	203.7	China	Wang et al., 2017
Antibiotic	Sulfadiamidine	109.9	China	Wang et al., 2017
Antibiotic	Ciprofloxacin	106.2	China	Wang et al., 2017
Antibiotic	Sulfameter	6	China	Wang et al., 2017
Antibiotic	Sulfamethoxazole	2,010	Mexico	Rivera-Jaimes et al., 2018
Antibiotic	Trimethoprim	790	Mexico	Rivera-Jaimes et al., 2018
Antibiotic	Erythromycin	160	South Africa	Matongo et al., 2015
Antibiotic	Ciprofloxacin	14,300	South Africa	Agunbiade and Moodley, 2016
Antibiotic	Sulfaguanidine	46,000	South Africa	Madikizela et al., 2020
Antibiotic	Spiramycin	38,200	South Africa	Madikizela et al., 2020
Antibiotic	Fluoroquinolones	900	South Africa	Hendricks and Pool, 2012
Antibiotic	Ciprofloxacin	1,360	South Africa	Agunbiade and Moodley, 2016
Antibiotic	Erythromycin	10,600	Ghana	Azanu et al., 2018
Antibiotic	Sulfamethoxazole	3,600	Ghana	Azanu et al., 2018
Antibiotic	Metronidazole	363	Ghana	Azanu et al., 2018

(Continued)

TABLE 1 | Continued

Pharmaceutical type	Pharmaceutical	Max conc (ng/L)	Country	References
Antibiotic	Ciprofloxacin	15,730	Ghana	Azanu et al., 2018
Antibiotic	Erythromycin	16,400	Tunisia	Tahrani et al., 2017
Antibiotic	Ofloxacin	175	Tunisia	Harrabi et al., 2018
Antibiotic	Enrofloxacin	400	Tunisia	Harrabi et al., 2018
Antibiotic	Trimethoprim	7,800	Tunisia	Tahrani et al., 2017
Antibiotic	Sulfamethoxazole	53,800	Mozambique	Branchet et al., 2019
Antibiotic	Trimethoprim	11,400	Mozambique	Segura et al., 2015
Antibiotic	Sulfamethoxazole	23,300	Kenya	K'oreje et al., 2012
Antibiotic	Sulfadoxin	1,040	Kenya	K'oreje et al., 2018
Antibiotic	Doxycycline	32,200	Kenya	Kairigo et al., 2020
Antibiotic	Norfloxacin	26,600	Kenya	Kairigo et al., 2020
Antibiotic	Trimethoprim	94,800	Kenya	K'oreje et al., 2012
Antibiotic	Sulfamethoxazole	5,600	Uganda	Nantaba et al., 2020
Antibiotic	Trimethoprim	89	Uganda	Nantaba et al., 2020
Antibiotic	Enrofloxacin	440	Nigeria	Olaitan et al., 2017
Antibiotic	Oxytetracycline	26	Nigeria	Olaitan et al., 2017
Antibiotic	Cefuroxime	868	Nigeria	Olaitan et al., 2017
Antibiotic	Amoxicillin	272,200	Nigeria	Ebele et al., 2020
Endocrine disruptors	Di-(2-ethylhexyl) phthalate	589	Australia	Tan et al., 2007
Endocrine disruptors	nonylphenol	335	Australia	Tan et al., 2007
Endocrine disruptors	Dibutyl phthalate	101	Australia	Tan et al., 2007
Endocrine disruptors	Bisphenol A	86.7	Australia	Tan et al., 2007
Endocrine disruptors	Benzyl butyl phthalate	75.7	Australia	Tan et al., 2007
Endocrine disruptors	Diethyl phthalate	36.9	Australia	Tan et al., 2007
Endocrine disruptors	4-tert-octylphenol	23.5	Australia	Tan et al., 2007
Endocrine disruptors	4-cumylphenol	1.9	Australia	Tan et al., 2007
Antiretroviral	Efavirenz	37.3	South Africa	Mlunguza et al., 2020
Antiretroviral	Emtricitabine	1.47	South Africa	Mlunguza et al., 2020
Antiretroviral	Tenofovir disproxil	0.25	South Africa	Mlunguza et al., 2020
Antiretroviral	Lamvudine	118,970	Zambia	Ngumba et al., 2020
Antiretroviral	Zidovudine	66,590	Zambia	Ngumba et al., 2020
Antiretroviral	Nevirapine	1,720	Zambia	Ngumba et al., 2020
Antiretroviral	Nevirapine	33,440	Kenya	K'oreje et al., 2012
Antiretroviral	Zidovudine	18,300	Kenya	K'oreje et al., 2012
Antiretroviral	Lamvudine	3,150	Kenya	K'oreje et al., 2012
Antiretroviral	Valacyclovir	21	Japan	Azuma et al., 2019
Antiretroviral	Zidovudine	564	Germany	Prasse et al., 2010
Antiretroviral	Nevirapine	32.1	Germany	Boulard et al., 2018
Antiretroviral	Abacavir	10	Germany	Boulard et al., 2018
Antiretroviral	Darunavir	169	Poland	Giebułtowicz et al., 2018
Antiretroviral	Zidovudine	191	France	Aminot et al., 2015
Antiretroviral	Ritonavir	155	France	Aminot et al., 2015
Antiretroviral	Lamivudine	44	France	Aminot et al., 2015
Antiretroviral	Nevirapine	7.7	France	Aminot et al., 2015
Antiretroviral	Indinavir	1.5	France	Aminot et al., 2015
Antiretroviral	Saquinavir	0.2	France	Aminot et al., 2015
Antiretroviral	Lamivudine	507	Belgium	Vergeynst et al., 2015
Antiretroviral	Ritonavir	108	Switzerland	Kovalova et al., 2012
Antiretroviral	Lamivudine	355	United States	Masoner et al., 2014
Antiretroviral	Abacavir	185	United States	Masoner et al., 2014
Antiretroviral	Nevirapine	25.2	United States	Fisher et al., 2016
Anticancer	Capecitabine	46	Portugal	Cristóvão et al., 2021
Anticancer	Ifosamide	44	Portugal	Cristóvão et al., 2021
Anticancer	Cyclophosphamide	17	Portugal	Cristóvão et al., 2021
Anticancer	Tamoxifen	181	Spain	Negreira et al., 2014
Anticancer	Cytarabine	924	Canada	Vaudreuil et al., 2020
Anticancer	Difluorodeoxyuridine	300	Canada	Vaudreuil et al., 2020
Anticancer	Cyclophosphamide	118	Canada	Vaudreuil et al., 2020
Anticancer	Methotrexate	27.3	Canada	Vaudreuil et al., 2020

antiretroviral drugs worldwide (Nannou et al., 2020; Reddy et al., 2021). In addition, as consequence of the new pandemic coronavirus (COVID-19), antiretroviral drugs have also been used for the treatment of SARS-CoV-2. In some countries, such as China and Japan, clinical trials have been conducted to test the efficiency of using HIV drugs to treat COVID-19 (Reddy et al., 2021). At the moment, a scarcity of studies has dealt with this new issue. However, some studies have started to show a relevant problem that we will have in the very near future (Mupatsi, 2020).

In the coming decades, annual cancer cases are expected to increase to more than 20 million, which means an exponential increase in anticancer drugs and their subsequent release into wastewater (Ferlay et al., 2013). Most of these compounds are incompletely assimilated and metabolized by the human body, thus excreted in feces and urine. The most commonly administered anticancer drugs include cyclophosphamide, tamoxifen, ifosfamide and methotrexate, among others. These drugs have been detected in surface water, WWTP effluents and influents, and hospital effluents. Detected concentrations of cyclophosphamide range from 0.05 to 22,100 ng/L, ifosfamide 0.14–86,200 ng/L, methotrexate 1.6–4,756 ng/L, and tamoxifen 0.01–740 ng/L (Nassour et al., 2020). Several studies have detected these drugs in water masses, confirming that current water treatment systems fail to degrade them (Verlicchi et al., 2010; Cristóvão et al., 2019). Different international agencies have developed protocols for the handling and storing of pharmaceuticals to reduce their harmful effect on the environment (Bernabeu-Martínez et al., 2018). One of the main concerns is that these drugs may suffer biomagnification (Yadav et al., 2021).

IMPACT OF PHARMACEUTICALS ON THE ENVIRONMENT AND LIVING ORGANISMS

Since almost all drugs are not completely metabolized by organisms (usually a small fraction of the active site of drug metabolic enzymes are occupied, the half-life of drugs are limited, and drugs are administrated in higher amounts than necessary to increase efficiency) (Coleman, 2020), the compounds that can cause the most damage once they are excreted and reached wastewater are PhACs. They are also called active pharmaceutical ingredients or APIs and metabolites, referring to the molecules resulting from these original compounds due to structural changes that take place in organisms. In addition, the resulting molecules are also subject to changes in the environment (such as oxidation, photolysis, or biotransformation). These changes can occur through both biotic and abiotic processes. Thus, many pharmaceutical products are biotransformed by microorganisms (Kümmerer, 2009; Wu et al., 2012). Ecotoxicologists are increasingly concerned about the worldwide detection of pharmaceutical residues in aquatic environments since their long-term toxic effects are being increasingly studied. However, it is challenging to know these effects because of the short time period these substances have been present in the environment (Nantaba et al., 2020; Ramírez-Morales et al., 2020; Gani et al., 2021).

Different studies analyzed the microbiome of wastewater where, in the case of hospitals, an abundance of anaerobes related to pathogenic threats such as Bifidobacteriales, Bacteroidales, and Clostridiales was found (Buelow et al., 2018; Ogwugwa et al., 2021; Palanisamy et al., 2021). They also noted that compared to other locations, hospital wastewater contains microorganisms with higher relative levels of antimicrobial and antibiotic resistance genes (Buelow et al., 2018). The mycobiome of hospital wastewater has also been analyzed, indicating the presence of different opportunistic phyla such as *Mycosphaerella*, *Drechslera*, *Candida*, or *Cyphellophora* (Olicón-Hernández et al., 2021), whose risk that they may acquire resistance to antibiotics is of great concern and may have great repercussions for global health.

Beta-Blocker and Psychoactives

β-blockers are a group of pharmaceuticals that are commonly detected in the environment. This is because many wastewater plants are not adapted to remove these micropollutants. Detected concentrations vary from 3 to 6,167 ng/L, which are already sufficient to cause neurotoxic and reproductive disorders in living organisms (Godlewska et al., 2021). Bisoprolol causes immobilization in *Daphnia similis* (Godoy et al., 2019) and mortality in fish and green algae (Fonseca et al., 2021). Propranolol causes growth and development problems in algae such as *Synechococcus leopolensis* and *Cyclotella meneghiniana* (Ferrari et al., 2004), mortality in crustacea (*Ceriodaphnia dubia*) (Huggett et al., 2002), and embryonic development problems in *Danio rerio* (Bittner et al., 2018).

Psychoactive substances affect thought, emotion, will and behavior (Jin et al., 2022). According to their pharmacological properties, psychoactive substances (including legal and illegal drugs) are opioids, cannabis, central nervous system depressants, central nervous system stimulants, hallucinogens, and tobacco (Schlüsener et al., 2015; Tanoue et al., 2019). These substances have different effects on humans, such as analgesia, anesthesia, inability to concentrate, excitement, anxiety, and mania. Jin et al. (2022) indicated that ecological risk assessment is a crucial part of research on psychoactive substances, as the current relevant literature is scarce. Due to the biological activity of such substances, there is a need for rapid improvement of risk assessment, including acute, cone and developmental toxicity, neurotoxicity, and endocrine-disrupting effects, among others, as well as the development of remediation technologies.

Non-steroidal Anti-inflammatory Drugs and Analgesics

Pharmaceuticals are known to have biological effects on living organisms, but there is not enough information currently available to assess the possible ecotoxicological impacts. Below are some of the toxic and ecological risks of NSAIDs and analgesics, according to various studies and summarized in **Table 2**: (I) population declines of *Gyps* vultures in Asia due to high diclofenac concentration (Cuthbert et al., 2007); (II) diclofenac impairs prostate gland synthesis and damage to the gills, liver, and kidneys of *Salmo trutta f. fario* (Hoeger et al., 2005); (III) histological alterations of the kidneys and gills, cytological alterations of the liver, kidneys, and gills, and deterioration of ionic regulation in *Oncorhynchus mykiss* (Schwaiger et al., 2004; Triebskorn et al., 2004; Gravel et al., 2009); (IV) ibuprofen, diclofenac, naproxen and ketoprofen inhibits CYP2M in *Cyprinus carpio* (Thibaut et al., 2006); (V) ibuprofen change breeding pattern of *Oryzias latipes* (Flippin et al., 2007); (VI) ibuprofen, diclofenac, and acetaminophen cause cardiovascular abnormalities, hatch and motor behavior and interruption of oocyte maturation/ovulation in *D. rerio* (David and Pancharatna, 2009; Lister and Van Der Kraak, 2009; Xia et al., 2017); (VII) diclofenac alters estrogenic activity, response of specific tissue biomarkers, decreased superoxide dismutase, and glutathione reductase activities in gills, and high catalase activity and levels of lipid peroxidation in the digestive gland in *Mytilus galloprovincialis* (Gonzalez-Rey and Bebianno, 2014). As can be inferred, high concentrations of NSAIDs and analgesics in the environment, such as acetylsalicylic acid, acetaminophen, diclofenac, ibuprofen, and naproxen, cause serious environmental problems (Parolini, 2020). In addition to fish, the main organisms affected are invertebrates, including arthropods, mollusks, cnidarians and rotifers (Parolini, 2020). NSAIDs also affect the plant growth of species such as *Pisum sativum* and *Vigna unguiculata* (Svobodníková et al., 2020; Wijaya et al., 2020; **Table 2**).

Antibiotics

Due to the continuous introduction of antibiotics into the environment, aquatic and soil organisms are chronically exposed to these drugs (Gothwal and Shashidhar, 2015; Bengtsson-Palme and Larsson, 2016). Moreover, because they are active at very low concentrations, they have a toxic effect on organisms, and there is a synergistic effect when they are present together with other drugs and/or xenobiotic compounds (González-Pleiter et al., 2013). Algae and aquatic plants are severely affected by antibiotics (Brain et al., 2008; Brausch et al., 2012). Many of them have been found to be photosynthesis inhibitors, as they can block the electron chain of photosystems II and increase oxidative stress (Nie et al., 2013). However, microorganisms, including bacteria and fungi, are developing resistance to antibacterial substances due to exposure to low concentrations over several generations (Kollef et al., 2017; Willyard, 2017; García et al., 2020; Wang et al., 2020). Invertebrates such as *Hydra attenuata* and crustaceans such as *Artemia salina*, *Daphnia magna,* and *Ceriodaphnia dubia* show relatively low acute toxicity in the presence of antibiotics (Wollenberger et al., 2000; Kołodziejska et al., 2013; Minguez et al., 2016). On the other hand, in fish, acute toxicity was only found at high concentrations, but there were cases in which no toxicity was observed (Santos et al., 2010; Brausch et al., 2012; Minguez et al., 2016; **Table 2**). The other major problem is antibiotic resistance genes (ARGs), which are genes that confer antibiotic resistance to bacteria, and can proliferate through the reproduction of antibiotic-resistant bacteria from the host or through horizontal gene transfer, are present in the environment, and thus considered as emerging environmental contaminants (Nadimpalli et al., 2020; Hu et al., 2021). Although treated wastewater contains significantly lower amounts of ARGs than untreated wastewater, several studies show that aquatic environments downstream of treatment plants can increase the amounts of ARGs because they are carried by mobile genetic elements, such as conjugative plasmids, integrative and conjugative elements, and transposons and integrons (Amos et al., 2018; Freeman et al., 2018; Jäger et al., 2018; Karkman et al., 2018; Liu et al., 2018). These effective carriers of ARGs could confer multi-resistance. One of the most detected genetic components in both effluents and aquatic environments is Class 1 integron-integrase gene (*intI1*) associated more frequently with ARGs and involved in horizontal gene transfer (Gillings et al., 2015; Cacace et al., 2019).

Endocrine Disruptors

Endocrine disruptors seriously affect both human and animal health, as they act directly on the endocrine system and block or mimic the natural hormones responsible for the functioning of some organs (Vieira et al., 2020). These substances have been studied extensively in humans, nevertheless, much less in the environment. It is known that they can alter the reproductive system, cause Alzheimer's disease, thyroid problems, obesity and/or cancer (prostate, breast or endometrium cancer), among others (Heindel et al., 2015; Forte et al., 2016, 2019; Braun, 2017; Nadal et al., 2017; Marotta et al., 2019). In natural ecosystems, the reproductive system is also affected, as well as the levels of vitellogenin and hatchability and thus feminization with the consequent threat to the preservation of biodiversity (Vieira et al., 2020; Akhbarizadeh et al., 2021; **Table 2**).

Antiretrovirals

In contrast to other pharmaceuticals, antiretrovirals, despite being abundant in wastewater, are poorly monitored, although some studies report on them (Ngumba et al., 2016; Abafe et al., 2018; Rimayi et al., 2018; Mosekiemang et al., 2019; Mtolo et al., 2019). These drugs could pass through treated wastewater in WWTPs, reach drinking water sources, and cause serious ecotoxicological problems for human health (Hawkins, 2010; Ncube et al., 2018; Mlunguza et al., 2020). Currently, the greatest concern is that resistant strains of HIV can be created in the body through exposure to water contaminated with these drugs (Daouk et al., 2015; Ncube et al., 2018; **Table 2**).

Anticancer Drugs

Although anticancer drugs are designed to eliminate fast-growing cells, such as tumor cells, many of these drugs are not selective (Chari, 2008). This means that in addition to attacking healthy cells, they can cause cytotoxic, genotoxic, mutagenic, and teratogenic effects, i.e., cause adverse effects in any eukaryotic organism (Kümmerer et al., 2000; Johnson et al., 2008). For this reason, anticancer drugs are considered to be of great environmental concern, and especially the groups at greatest risk are children, pregnant women, and the elderly (Rowney et al., 2009). It has been shown that chronic exposure of two generations of *D. rerio* to anticancer drugs caused histopathological changes in the liver and kidney and impaired the integrity of their DNA, introducing massive changes in the

TABLE 2 | Impact of pharmaceuticals on the environment and humans.

Pharmaceutical type	Impact	References
β-blockers (bisoprolol)	Inmobilization in *Daphnia similis*	Godoy et al., 2019
β-blockers (bisoprolol)	Mortality in green algae	Fonseca et al., 2021
β-blockers (bisoprolol)	Mortality in fish	Fonseca et al., 2021
β-blockers (propanolol)	Growth and development problems in algae such as *Synechococcus leopolensis* and *Cyclotella meneghiniana*	Ferrari et al., 2004
β-blockers (propanolol)	Mortality in crustacea (*Ceriodaphnia dubia*)	Huggett et al., 2002
β-blockers (propanolol)	Embryonic development problems in *Danio rerio*	Bittner et al., 2018
NSAIDs and analgesics (Acetaminophen)	Cardiovascular abnormalities, hatch and motor behavior and interruption of oocyte maturation/ovulation in *Danio rerio*	David and Pancharatna, 2009; Lister and Van Der Kraak, 2009; Xia et al., 2017
NSAIDs and analgesics (Diclofenac)	Population declines of Gyps vultures	Cuthbert et al., 2007
NSAIDs and analgesics (Diclofenac)	Prostate gland synthesis and damage to the gills, liver, and kidneys of *Salmo trutta f. fario*	Hoeger et al., 2005
NSAIDs and analgesics (Diclofenac)	Histological alterations of the kidneys and gills, cytological alterations of the liver, kidneys, and gills, and deterioration of ionic regulation in *Oncorhynchus mykiss*	Schwaiger et al., 2004; Triebskorn et al., 2004; Gravel et al., 2009
NSAIDs and analgesics (Diclofenac)	Inhibits CYP2M in *Cyprinus carpio*	Thibaut et al., 2006
NSAIDs and analgesics (Diclofenac)	Cardiovascular abnormalities, hatch and motor behavior and interruption of oocyte maturation/ovulation in *Danio rerio*	David and Pancharatna, 2009; Lister and Van Der Kraak, 2009; Xia et al., 2017
NSAIDs and analgesics (Diclofenac)	Alteration of estrogenic activity, response of specific tissue biomarkers, decreased superoxide dismutase and glutathione reductase activities in gills, and high catalase activity and levels of lipid peroxidation in the digestive gland in *Mytilus galloprovincialis*	Gonzalez-Rey and Bebianno, 2014
NSAIDs and analgesics (Ibuprofen)	Inhibits CYP2M in *Cyprinus carpio*	Thibaut et al., 2006
NSAIDs and analgesics (Ibuprofen)	Change breeding pattern of *Oryzias latipes*	Flippin et al., 2007
NSAIDs and analgesics (Ibuprofen)	Cardiovascular abnormalities, hatch and motor behavior and interruption of oocyte maturation/ovulation in *Danio rerio*	David and Pancharatna, 2009; Lister and Van Der Kraak, 2009; Xia et al., 2017
NSAIDs and analgesics (Ibuprofen)	Reduce the shoot and root lengths, fresh and dry weights, leaf area, and chlorophyll a and b, carotenoid, total chlorophyll, mineral (K and Mg), glutathione reductase, and soluble protein contents of *Vigna unguiculata*	Wijaya et al., 2020
NSAIDs and analgesics (Ketoprofen)	Inhibits CYP2M in *Cyprinus carpio*	Thibaut et al., 2006
NSAIDs and analgesics (Naproxen)	Inhibits CYP2M in *Cyprinus carpio*	Thibaut et al., 2006
NSAIDs and analgesics (Naproxen)	*Pisum sativum*	Svobodníková et al., 2020
Antibiotics	Algae and aquatic plants are severely affected	Brain et al., 2008; Brausch et al., 2012
Antibiotics	Block the electron chain of photosystems II and increase oxidative stress (photosynthesis inhibitors)	Nie et al., 2013
Antibiotics	Bacteria seem to be developing resistance to antibacterial substances due to exposure to low concentrations over several generations	Kollef et al., 2017; Willyard, 2017; García et al., 2020; Wang et al., 2020;
Antibiotics	*Hydra attenuata* show relatively low toxicity	Wollenberger et al., 2000; Kołodziejska et al., 2013; Minguez et al., 2016
Antibiotics	Crustaceans such as *Artemia salina*, *Daphnia magna*, and *Ceriodaphnia dubia* show relatively low acute toxicity	Wollenberger et al., 2000; Kołodziejska et al., 2013; Minguez et al., 2016
Antibiotics	Invertebrates such as *Hydra attenuata* and crustaceans such as *Artemia salina*, *Daphnia magna*, and *Ceriodaphnia dubia* show relatively low acute toxicity in the presence of antibiotics	Wollenberger et al., 2000; Kołodziejska et al., 2013; Minguez et al., 2016
Endocrine disruptors	Block or imitate the natural hormones responsible for the functioning of some organs, in both humans and animals	Vieira et al., 2020
Endocrine disruptors	Alter the reproductive system	Heindel et al., 2015; Braun, 2017; Nadal et al., 2017
Endocrine disruptors	Cause Alzheimer's disease	Heindel et al., 2015; Braun, 2017; Nadal et al., 2017
Endocrine disruptors	Thyroid problems	Heindel et al., 2015; Braun, 2017; Nadal et al., 2017
Endocrine disruptors	Obesity and/or cancer	Heindel et al., 2015; Braun, 2017; Nadal et al., 2017
Endocrine disruptors	Affected the reproductive system	Vieira et al., 2020
Endocrine disruptors	Levels of vitellogenin and hatchability	Vieira et al., 2020
Anticancer drugs	Cytotoxic, genotoxic, mutagenic, and teratogenic effects in any eukaryotic organism	Kümmerer et al., 2000; Johnson et al., 2008

(Continued)

TABLE 2 | Continued

Pharmaceutical type	Impact	References
Anticancer drugs	Groups at greatest risk are children, pregnant women, and the elderly	Rowney et al., 2009
Anticancer drugs	Caused histopathological changes in the liver and kidney and impaired the integrity of their DNA, introducing massive changes in the entire transcriptome in *Danio rerio*	Kovács et al., 2015; Gajski et al., 2016
Antiretroviral drugs	Resistant strains of HIV can be created in the body through exposure to water contaminated with these drugs	Daouk et al., 2015; Ncube et al., 2018
Antiretroviral drugs	Anemia	Ncube et al., 2018
Antiretroviral drugs	Nausea	Ncube et al., 2018
Antiretroviral drugs	Hypersensitivity	Ncube et al., 2018
Antiretroviral drugs	Nephrotoxicity and renal failure	Ncube et al., 2018
Antiretroviral drugs	Rash	Ncube et al., 2018

entire transcriptome (Kovács et al., 2015; Gajski et al., 2016; **Table 2**).

Residues of pharmaceuticals in the environment typically occur as complex mixtures and even if the concentrations of an individual compound are low, the "cocktail effect" could be of significant ecotoxicological importance (Heath et al., 2016). To date, many works have focused on the study of individual organisms and analyzed a single drug or several drugs as a whole, but there are no works studying the impact of drugs on several populations simultaneously. This would provide essential information on ecotoxicity and the "domino effect" that affects individuals in a trophic chain since, in addition to bioaccumulation, the chain could be broken because a drug lethally affects a group of individuals.

DEVELOPMENT OF BIOREMEDIATION TECHNOLOGIES

Improving technologies for drug elimination from wastewater is an important task since pharmaceuticals have been detected in effluent from WWTPs and consequently surface water, groundwater, and drinking water globally (Bartolo et al., 2021). Although the pharmaceuticals are found in concentrations ranging from the nanogram to microgram per liter, which is too low to cause acute toxicity, they are biologically active compounds that have the potential for chronic toxicity, bioaccumulation, and biomagnification (Ruan et al., 2020). Additionally, microplastics have been shown to serve as vectors for pharmaceuticals (Santos et al., 2021), thus increasing the exposure potential. Because of incomplete elimination during conventional wastewater treatment (Reyes et al., 2021) and the potential risk posed to the environment, as discussed above, there has been pronounced interest in developing alternative treatments in recent years, specifically the biological transformation of these pollutants as a green technology (Domaradzka et al., 2015). The future inclusion of bioremediation technologies in traditional WWTP treatments is progressive as it will result in the detoxification of hazardous substances, it is less disruptive to the environment than harsh oxidative chemicals, and more cost-efficient. With perseverance, research into optimization could result in the complete eradication of target pollutants, rooting out release into the environment.

The wastewaters containing PhACs and their metabolites reaching WWTPs are commonly treated via purification systems. The potential of drug remediation via biological treatment utilizing microbes has been demonstrated (Kebede et al., 2018). Biological systems are often used in conjunction with advanced treatments and combined with conventional activated sludge (CAS) systems due to limitations associated with the process (Crini and Lichtfouse, 2019). Advanced biological treatments include modified CAS, aerobic granular systems, moving bed bioreactors (MBBRs), anammox systems, and membrane bioreactors (MBRs) (Grassi et al., 2012). However, some of these processes, such as MBRs, could result in the generation of biosolids or sewage sludge as byproducts of required maintenance. Sewage sludge, after different stabilization processes such as thermophilic anaerobic digestion, continues onto different processes, such as composting, which could facilitate the transfer of PhACs and their metabolites into various trophic levels of the food web when used as a soil amendment (Marcoux et al., 2013).

Bioremediation, utilizing native microbial monocultures or consortia or bioaugmentation, has been used for decades as a sustainable technology to manage anthropogenic pollution (Ahumada-Rudolph et al., 2021). The advantages of bioremediation include less input of hazardous chemicals, energy, and time, and it is cheap relative to other technologies (Azubuike et al., 2016). The major benefit of bioremediation is that the pollutant is chemically transformed and not only shifted from one environment to another (Mashi, 2013). However, a significant criticism of bioremediation has been that the remediation speed does not meet the requirements for the treatment capacity. Nonetheless, considering the benefits of the approach, attempts on optimizing the efficiency and decreasing retention times are being made and are reviewed below for mycoremediation. Developments in phyto- and phycoremediation of pharmaceuticals have been reported and recently reviewed (Vilvert et al., 2017; Rao et al., 2019; Kaloudas et al., 2021; Kurade et al., 2021) and thus, not included here.

Bacterial remediation has been reviewed to some extent (Shah and Shah, 2020), and, therefore, a brief overview of previously undiscussed advances are included here alongside mycoremediation. Bacterial communities have the ability to degrade and mineralize many xenobiotic compounds and have thus been used for centuries in wastewater-activated sludge (Xu et al., 2018). Bioremediation technologies have been advanced by studies elucidating the importance of facilitating biofilm growth in achieving maximum efficiency and community stability and survival (Edwards and Kjellerup, 2013). The majority of the available literature on bacterial remediation has focused on the aerobic degradation of pharmaceuticals by individual bacteria or consortia in which oxygenases are reported to be involved (Ferreira et al., 2018). Activated sludge, in which an uncharacterized bacterial consortium in suspension is responsible for the remediation, is one of the most widely used biological methods to treat pharmaceutical wastewater at a large scale (Bis et al., 2019). However, due to operational issues associated with the development of large amounts of sludge, research has been invested in developing bespoke bacterial consortia for remediation, including microalgae and bacterial-microalgae consortia (Mamta et al., 2020).

In the environment, fungi are excellent decomposers through the nonspecific nature of enzymes, both intracellular and extracellularly secreted, which exhibit significant capabilities to degrade organic material (Rouches et al., 2016). More specifically, the ligninolytic (including peroxidases and laccases) and cytochrome P450 systems have been proven to be involved in the exceptional capacity of white-rot fungi to degrade recalcitrant pollutants (Park and Choi, 2020). The nonspecific nature of these enzymes also makes them an ideal approach to deal with the diverse chemical structures of the many classes of pharmaceuticals. Many fungal species are also hyperaccumulators, capable of absorbing and bioaccumulating xenobiotics from their environment, as demonstrated by the ability of mushrooms (Braeuer et al., 2020). Furthermore, fungi are known for their capacities to adapt to severe environmental constraints (Jiao and Lu, 2020), making them more tolerant to environmental changes than other bioremediation organisms. Thus, mycoremediation, which results in the reduced toxicity of wastewater (Jelic et al., 2012; Akhtar and Mannan, 2020), offers a comparatively cost-effective, eco-friendly, and effective approach to pollution remediation.

Macromycetes, aka mushrooms or polypores, were previously proven efficient in remediating various pharmaceuticals (Migliore et al., 2012; Cruz-Morató et al., 2014), including β-blockers and psychoactive drugs, anti-inflammatory drugs, antibiotics and hormones (**Table 3**). Mostly, investigations into the efficiency of fungi to remediate pharmaceuticals have been performed in flask batch experiments with white-rot fungi, especially *Trametes versicolor,* which exhibited impressive capacities for eliminating a vast range of pharmaceuticals. In bioreactors-based studies, *T. versicolor* was equally efficient, able to degrade various pharmaceuticals, including codeine, diazepam, carbamazepine, and metoprolol (Asif et al., 2017). The role of redox-mediators has also been extensively studied in improving the performance of laccase-based treatments (Ashe et al., 2016; Shao et al., 2019), including the treatment of pharmaceuticals (Nguyen et al., 2013; Vasiliadou et al., 2019). Studies employing filamentous micromycetes have shown potential for pharmaceutical remediation from wastewaters as reviewed by Olicón-Hernández et al. (2017) but are limited compared to the literature on macromycetes (**Table 3**). The efficiency of bacteria and fungi to remediate different classes of pharmaceuticals is discussed in more detail below.

Beta-Blockers and Psychoactive Drugs

Carbamazepine, which is not adequately eliminated via standard wastewater treatments and is thus frequently detected in the environment (Ekpeghere et al., 2018), has been reported to be degraded by the macromycete *T. versicolor*. By employing *T. versicolor*, Jelic et al. (2012) achieved 94% degradation of carbamazepine (9 mg/L) after six days in flask experiments. With a reduced concentration (50 μg/L), Jelic et al. (2012) reported a lower remediation percentage of 61% achieved in seven days. The same group evaluated the fungus's remediation efficiency of carbamazepine in an air pulsed fluidized bed bioreactor operated in batch and continuous mode. In batch mode, 96% of the drug was eliminated after 2 days, with higher efficiency achieved in the bioreactor than in flasks explained by glucose addition, pH management and air supplementation. In continuous mode, carbamazepine was reduced by 54% in the outflow compared to the inflow concentration of 200 μg/L (Jelic et al., 2012). With *Pleurotus ostreatus*, another white-rot fungus, 68% carbamazepine was degraded in liquid culture after seven days with no further degradation after this time (Buchicchio et al., 2016).

The filamentous fungus *Trichoderma harzianum* was able to degrade 72% of environmentally detected concentrations of carbamazepine (4 μg/L) (Buchicchio et al., 2016), which was superior compared to the polypore *P. ostreatus*. In a non-sterile bioreactor, *Phanerochaete chrysosporium* was able to degrade up to 80% of 5 mg/L carbamazepine when supplied with a diluted synthetic feed (Zhang and Geißen, 2012). In a fed-batch stirred bioreactor, *P. chrysosporium* removed yo to 60% carbamazepine (0.5 mg/L); however, it was unable to degrade diazepam (0.25–0.5 mg/L) (Rodarte-Morales et al., 2012a). In a fixed bed reactor, where the pellets of *P. chrysoporium* were immobilized in polyurethane, the remediation efficiency of carbamazepine and diazepam was significantly improved (Rodarte-Morales et al., 2012b).

Even though nearly complete remediation of some beta-blockers and psychoactive drugs could be achieved in flask and lab bioreactor scale experiments, large or even pilot scale studies are needed to comprehensively evaluate the effect of upscaling on the remediation efficiency and the cost-effectiveness of using fungi for these drugs as an add-on treatment in WWTPs.

Non-steroidal Anti-inflammatory Drugs and Analgesics

Bioremediation using bacterial monocultures for the treatment of NSAIDs has not to date been successful (Wojcieszyńska et al., 2014). Some studies have shown the elimination of NSAIDs by bacterial consortia in WWTPs. One study showed that eliminating acetaminophen in an MBR was mainly associated with heterotrophic bacteria. They concluded that using a

TABLE 3 | Summary of fungal remediation studies on the removal efficiency of single PhAC.

Pharmaceutical	Species	Experimental type	Contact time (days)	Start conc (mg/L)	Efficiency (%)	References
Macromycetes						
Carbamazepine	*Trametes versicolor*	Lab, flask	6	9	94	Jelic et al., 2012
			7	0.05	61	
	T. versicolor	Air pulsed fluidized bed reactor-batch	2	0.2	96	Jelic et al., 2012
	T. versicolor	Air pulsed fluidized bed reactor–cont.	25	0.2	54	
	Pleurotus ostreatus	Lab, flask	7	0.04	68	Buchicchio et al., 2016
Diclofenac	*T. versicolor*	Cont. membrane reactor	1	0.3-1.5	55	Yang et al., 2013
Ofloxacin	*T. versicolor*	Lab, flask	7	10	80	Gros et al., 2014
		Fluidized air pulse bioreactor sterile	8	0.03	98.5	
		Fluidized air pulse bioreactor nonsterile	5	0.003	99	
	Irpex lacteus	Lab, flask	10	10	100	Čvanžarová et al., 2015
Cefuroxime axetil	*Imleria badia*	Lab, flask	7	400, 1000, 1600	100	Dąbrowska et al., 2018
	Lentinula edodes	Lab, flask	7	400, 1000, 1600	100	
Oxacillin	*Leptosphaerulina* sp.	Lab, flask	6	16	100	Copete-Pertuz et al., 2018
Cloxacillin	*Leptosphaerulina* sp.	Lab, flask	7	17.5	100	
Dicloxacillin	*Leptosphaerulina* sp.	Lab, flask	8	19	100	
Clarithromycin	*P. ostreatus*	Lab, flask	7	0.00003	55	Buchicchio et al., 2016
Oxytetracycline	*P. ostreatus*	Lab, flask	14	50, 100	100	Migliore et al., 2012
Flumequine	*I. lacteus*	Lab, flask	10	10	100	Čvanžarová et al., 2015
Ciprofloxacin	*I. lacteus*	Lab, flask	10	10	100	
Testosterone	*L. edodes*	Lab, flask	21	100000, 200000	100	Muszyńska et al., 2018
17α-Ethinylestradiol	*L. edodes*	Lab, flask	21	400, 800	100	
	L edodes (stalk)	Bioabsorption	0.02	2	100	de Jesus Menk et al., 2019
	L. edodes (substrate)	Bioabsorption	0.02	2	80	
	Agaricus bisporus (stalk)	Bioabsorption	0.02	2	100	
Micromycetes						
Carbamazepine	*Trichoderma harzianum*	Lab, flask	7	0.004	72	Buchicchio et al., 2016
	Phanerochaete chrysosporium	Bioreactor, nonsterile	100	5	80	Zhang and Geißen, 2012
		Continuously stirred bioreactor	50	0.5	63	Rodarte-Morales et al., 2012b
Diclofenac	*Penicillium oxalicum*	Lab, flask	1	29	100	Olicón-Hernández et al., 2019
	Mucor hiemalis	Lab, flask	6	0.05	97	Esterhuizen-Londt et al., 2017
	P. chrysosporium	Fed-batch stirred bioreactor	1	0.8	99	Rodarte-Morales et al., 2012a
		Continuously stirred bioractor	1	1	93	Rodarte-Morales et al., 2012b
Acetaminophen	*M. hiemalis*	Lab, flask	1	0.02	< 50	Esterhuizen-Londt et al., 2016b,a
	P. chrysosporium	Lab, flask	7	0.25	99	Esterhuizen et al., 2021
Ibuprofen	*P. chrysosporium*	Fed-batch stirred bioreactor	0.63	0.8	99	Rodarte-Morales et al., 2012a
		Continuously stirred bioractor	1	1	93	Rodarte-Morales et al., 2012b
Naproxen	*P. chrysosporium*	Fed-batch stirred bioreactor	1	0.8	99	Rodarte-Morales et al., 2012a
		Continuously stirred bioractor	3	1	90	Rodarte-Morales et al., 2012b
Clarithromycin	*T. harzianum*	Lab, flask	7	0.00003	57	Buchicchio et al., 2016
Oxytetracycline	*Penicillium commune*	Lab, flask	15	250	68	Ahumada-Rudolph et al., 2021
	Epicoccum nigrum,	Lab, flask	15	250	76	
	Trichoderma harzianum	Lab, flask	15	250	77	
	Aspergillus terreus	Lab, flask	15	250	74	
	Beauveria bassiana	Lab, flask	15	250	78	
Erythromycin	*Penicillium oxalicum* RJJ-2	Lab, flask	4	100	84	Ren et al., 2021
17 β-estradiol (E2)	*Trichoderma citrinoviride AJAC3*	Lab, flask	4	200	100	Chatterjee and Abraham, 2019

microbial consortium in an MBR could be complimentary for post-treating effluents from treatment plants containing pharmaceutical products (De Gusseme et al., 2011). However, as seen with the consortia in CAS treatments, which are unidentified and often change in conjunction with the wastewater being treated, consortia in bioreactors may also change, resulting in decreased efficiency. To further explore the use of bacterial consortia in bioreactors, long-term studies need to be conducted on-site in WWTPs to evaluate the composition and stability of the bacterial assemblage, and it should be modeled how shifts could influence remediation.

In terms of mycoremediation, *T. versicolor* has shown very promising results in the remediation of NSAIDs (Asif et al., 2017; Tińma et al., 2021). In a continuous MBR (with a hydraulic retention time of one day), *T. versicolor* eliminated 55% of diclofenac added at concentrations ranging from 0.3 to 1.5 mg/L (Yang et al., 2013). Another fungus that demonstrated the potential to degrade anti-inflammatory drugs is the edible fungus *Lentinula edodes* (shiitake mushroom). The degradation products of piroxicam produced by *L. edodes* degradation has already been described (Muszyńska et al., 2019); however, the remediation percentage was not reported.

Penicillium oxalicum was capable of totally degrading diclofenac in 24 h, starting from an initial concentration of 29.6 mg/L (100 μM) (Olicón-Hernández et al., 2019). For *Mucor hiemalis* f. *irnsingii* (DSM 14200; Zygomycota), a strain isolated from a groundwater source in Germany, the diclofenac (10–50 μg/L) removal percentages ranged between 90 and 97% after 6 days (Esterhuizen-Londt et al., 2017). The same micromycete was also employed for the remediation of acetaminophen. After 24 h of exposure to environmentally relevant concentrations of acetaminophen (up to 20 μg/L), *M. hiemalis* was able to degrade up to 50% (Esterhuizen-Londt et al., 2016b,a). However, after 24 h, diclofenac remediation halted; nevertheless, pH maintenance could overcome this (Esterhuizen et al., 2021). The acetaminophen remediation efficiency of *Phanerochaete chrysosporium* (97 and 99% of 250 μg/L APAP after 3 and 7 days, respectively) was far superior to that of *M. hiemalis,* and co-cultivation of the two species resulted in a decreased remediation efficiency compared to *P. chrysosporium* in single (Esterhuizen et al., 2021).

Furthermore, Olicón-Hernández et al. (2020) studied the degradation of a mixture of acetaminophen, diclofenac, ibuprofen, ketoprofen and naproxen with *P. oxalicum*, starting from an initial concentration of 50 μM of each compound in both flasks and bench fluidized bioreactors. *P. oxalicum* showed higher degradation percentages in the bioreactor than at the flask scale. The authors reported that with glucose addition in the fluidized bed bioreactor, degradation of all drugs was complete after eight days (Olicón-Hernández et al., 2020).

In a fed-batch stirred bioreactor, *P. chrysosporium* oxidatively degraded up to 99% of diclofenac, ibuprofen, and naproxen each at a concentration of 0.8 mg/L (Rodarte-Morales et al., 2012a). However, in continuously stirred bioreactors, *P. chrysosporium* degraded diclofenac, ibuprofen, and naproxen (1 mg/L each) up to 95%.

With these preliminary flask and laboratory-scale reactor experiments, the potential of using mycoremediation to treat NSAIDs is highlighted. However, data on the performance of the fungi in WWTPs is lacking, making a consequential evaluation impossible. A potential issue that may arise in practice is the need for maintenance and controlled conditions, as highlighted by the study conducted by Esterhuizen et al. (2021), which showed the need for maintaining pH conditions.

To overcome the limitations of monocultures for the remediation of these pollutants, the use of microorganism-consortia has been explored. Consortia of microorganisms that complement each other could improve biological wastewater treatment technologies significantly. For example, Nguyen et al. (2013) found that a mixed bacterial culture in conjunction with *T. versicolor* in an augmented MBR better degraded PhACs than a system containing the fungus or bacteria alone (Nguyen et al., 2013). In addition, bioaugmentation technologies using adapted fungi, such as *P. oxalicum,* have proven an interesting technology to overcome the problem of competition with autochthonous microbiota, as demonstrated by Olicón-Hernández et al. (2021). However, more data are needed to define complementary species since the study by Esterhuizen et al. (2021) revealed that co-culture of certain species could reduce the remediation efficiency.

Antibiotics

In general, low remediation efficiencies for most antibiotics from wastewaters have been reported using CAS treatment (Chaturvedi et al., 2021a; Zou et al., 2022). Thus, CAS could be applied to treat some antibiotics; however, not all. More recently, increased antibiotic removal percentages have been reported with anoxic/anaerobic/oxic granular and suspended activated sludge processes, specifically with sulfamethoxazole (Kang et al., 2018). The shortcoming could be improved by supplementing the sludge with bacteria capable of better remediation or even mixing treatments and complementing CAS with mycoremediation with macromycetes has been proven to be very effective for antibiotics.

T. versicolor, in flask experiments, degraded the antibiotic ofloxacin (10 mg/L) with 80% efficiency. When upscaled to 10 L fluidized air-pulse bioreactors, ofloxacin spiked into hospital waste was removed by 98.5% under sterile conditions and 99% under nonsterile conditions (Gros et al., 2014).

Buchicchio et al. (2016) reported the elimination of 55% clarithromycin (0.03 μg/L) by edible mushroom *P. ostreatus* and 57% by the micromycete *T. harzianum*. In flask experiments, *P. ostreatus* could also eliminate oxytetracycline (50 and 100 mg/L) after 14 days (Migliore et al., 2012). The antifungal drugs bifonazole and clotrimazole were also bioaccumulated and eliminated by the mycelia of the edible fungus *Lentinus edodes* (Kryczyk-Poprawa et al., 2019). In flask experiments, the cephalosporin antibiotic cefuroxime axetil was entirely eradicated by both the edible mushrooms *Imleria badia* and *L. edodes* within seven days at all concentrations tested (400, 1,000, 1,600 mg/L) (Dąbrowska et al., 2018).

Leptosphaerulina sp. removed oxacillin (16 mg/L, in 6 days), cloxacillin (17.5 mg/L, in 7 days) and dicloxacillin (19 mg/L, in 8 days) from water in flask experiments by the action of laccase and peroxidase. With synthetic hospital waste, oxacillin was reduced by 60% within two days and wholly eradicated after six days by the *Leptosphaerulina* sp. (Copete-Pertuz et al., 2018).

In a comparative study investigating the degradation efficiencies of five ligninolytic fungi, the polypore *Irpex lacteus* degraded the fluoroquinolone antibiotic flumequine, ciprofloxacin and ofloxacin effectively within six days (Èvanèarová et al., 2013; Čvanǎrová et al., 2015). *I. lacteus* also removed the residual antibacterial activity of norfloxacin and ofloxacin via the action of manganese peroxidase (Čvanǎrová et al., 2015).

Ahumada-Rudolph et al. (2021) evaluated fifty fungal isolates from sediments of salmon hatcheries for their oxytetracycline remediation abilities. The filamentous fungi *Penicillium commune*, *Epicoccum nigrum*, *T. harzianum*, *Aspergillus terreus*, and *Beauveria bassiana* were identified as having the best remediation rates amounting to a maximum of 78% removal of a 250 mg/L oxytetracycline concentration in flask experiments (Ahumada-Rudolph et al., 2021). *P. oxalicum* RJJ-2 has also been studied in the degradation of erythromycin and degraded 84.88% erythromycin after 96-h incubation used as the sole carbon source producing different metabolites (Ren et al., 2021).

The studies on the efficiency to remove antibiotics reported to date have focused on the efficiency under set conditions. However, in a WWTP, environmental conditions and even the water's parameter would fluctuate from time to time. How this could affect the remediation efficiency and fungal longevity over time is unknown. Nevertheless, this information could be essential in evaluating this technique's applicability in the field. It is importante to note the relevance of the use of fungi in removing antibiotics since bacteria can adquire rapidly antibiotic resistance genes during bioremediation and contribute to the widespread of ARGs.

Endocrine Disruptors

The fate of estrogenic hormones treated via activated sludge systems in full-scale WWTPs was reviewed by Hamid and Eskicioglu (2012). Activated sludge systems with nutrient removal achieved more than 90% degradation in most studies (Hamid and Eskicioglu, 2012).

Degradation of testosterone and 17α-ethinylestradiol (EE2) by the fungus *L. edodes* was reported by Muszyńska et al. (2018), with no testosterone or 17α-ethynylestradiol detected after 21 days (Muszyńska et al., 2018). Interestingly, the white-rot fungus *P. ostreatus* HK 35, in the presence of the natural water microbiota of a WWTP, degraded up to 90% of 17β-estradiol (E2) within 12 days in various bioreactor sizes and under different regimes (Křesinová et al., 2018). The micromycete *Trichoderma citrinoviride* AJAC3 degraded 99.6% 17 β-estradiol (E2) (at a starting concentration of 200 mg/L) after four days attributed to the secretion of ligninolytic enzymes (Chatterjee and Abraham, 2019). A study investigating the efficiency of mycoremediation to remove 17 β-estradiol (E2) from poultry litter found that the polypore *Pycnoporus* sp. SYBC-L3 could remove up to 78.4% via solid-state cultivation supplemented with citric acid and lignocellulosic biomasses to boost laccase activity (Liu et al., 2016), an approach that could be tested for increasing remediation from wastewaters.

Even though the hormone remediation percentage reported with mycoremediation is, in some cases, higher than the CAS studies reviewed by Hamid and Eskicioglu (2012), a comparison is not possible since the studies on the fungal efficiency were performed in the laboratory in comparison to the CAS studies completed on-site at WWTPs. In addition to excluding several variables that could impact the remediation efficiency, these studies have established the remediation efficiencies for individual compounds. In wastewater effluent, a mixture of not only PhACs are present, and the synergistic effect of all these compounds could affect the efficiencies reported (Chatterjee and Abraham, 2019).

Bioabsorption is another approach to PhAC remediation with fungi. *L. edodes* and *Agaricus bisporus* (champignon) stalks removal 100% of 17α-ethinylestradiol (EE2) in 20 and 30 min, respectively via absorption, whereas Shiitake substrate absorbed 80% (de Jesus Menk et al., 2019).

Despite the high hormone remediation percentages achieved with fungi described above, few studies have been published on this topic in the last decade, and renewed investigations would greatly benefit the development of this technique to elevate the environmental impacts of hormones released untreated from WWTPs.

Mixed Effluents

Cruz-Morató et al. (2013) studied the degradation of pharmaceuticals in hospital effluent by *T. versicolor*. By employing fluidized bed bioreactor in fed-batch mode, *T. versicolor* could eliminate ibuprofen (2.34 mg/L), acetaminophen (1.56 mg/L), ketoprofen (0.08 mg/L), propranolol (0.06 mg/L), and azithromycin (4.31 mg/L). By running the fluidized bed reactor in continuous mode, the efficiency was increased, and the fungus was able to completely remove acetaminophen (109 mg/L), naproxen (1.62 mg/L), ibuprofen (35.5 mg/L), diclofenac (0.477 mg/L), codeine (0.606 mg/L), trimethoprim (0.853 mg/L), and sulfamethoxazole 1.41 mg/L 100%, and partially remove several other drugs. However, salicylic acid, tetracycline, and carbamazepine were not degraded (Cruz-Morató et al., 2013, 2014). *T. versicolor* was also investigated for its performance to remediate PhACs from veterinary hospital wastewater; however, only 66% removal efficiency was achieved in a non-sterile batch bioreactor (Badia-Fabregat et al., 2016).

P. oxalicum XD.3.1 has also been used in batch bench-scale bioreactors to test the remediation efficiency with real hospital effluents. Within 24 h, *P. oxalicum* was able to reduce the majority of the PhAC present in the effluent, including ketoprofen, naproxen and paracetamol. Interestingly, *P. oxalicum* also affected the native microbiota, including opportunistic pathogens (Olicón-Hernández et al., 2021). In fluidized bed bioreactor studies, including hospital wastewater spiked with 10 mg/L each diclofenac, ketoprofen, and atenolol, *P. ostreatus* completely remediated diclofenac in 24 h and 50% of the ketoprofen in 5 days. However, atenolol was not removed (Palli et al., 2017). These studies demonstrated the complexity of degrading PhAC in mixed matrix effluents, which could drastically reduce the remediation efficiency. Therefore, more studies should be conducted at a larger scale employing real effluents to develop mycoremediation using fungi.

Currently, mycoremediation studies on other emerging PhACs, such as anticancer and antiretrovirals, are lacking. Testing fungal species capable of degrading pharmaceuticals at a laboratory scale is ongoing; however, it is difficult to predict how biological organisms would cope in a treatment facility exposed to chemical mixtures over long periods. Thus, recognizing the potential of mycoremediation for the treatment of pharmaceuticals demonstrated to date, studies regarding functioning and long-term applicability in practical terms to evaluate the feasibility of mycoremediation fully are still lacking. However, limitations such as partial degradation of pharmaceuticals and reduced efficiency at lower PhAC concentrations have been identified but could be overcome by using consortia or optimizing enzyme extraction and isolation to reduce costs.

The exact mechanism of degradation for each fungal type and PhACs is still vague due to its complexity and all the counterparts involved (Dąbrowska et al., 2018). However, the degradation seems to include activities of the intracellular enzymatic system such as the cytochrome P450 system, mainly in fungi lacking ligninolityc enzymes, and the extracellular enzymatic system, including lignin peroxidase, manganese peroxidase, laccase, versatile peroxidase as well as hydroxyl and free radical, in the case of lignin degrading enzymes producers (Dąbrowska et al., 2018; Barh et al., 2019). Nevertheless, elimination is reported to produce no toxic byproducts (Copete-Pertuz et al., 2018), therefore necessitating further studies into mycoremediation optimization for an add-on in WWTPs and elucidating the mechanism of action.

ISOLATED FUNGAL ENZYMES

The use of isolated fungal enzymes could also overcome some limitations associated with mycoremediation. Fungal enzymes, specifically the ligninolytic enzymes, have been recognized for their abilities to transform a broad range of recalcitrant PhACs. However, difficulties in growing fungi on a large scale, together with the long incubation processes, extensive growth phase, and spore formation, have prompted the exploration of extracted crude and isolated enzymes (Stadlmair et al., 2018). Though, to date, the main limiting factor has been the high cost of the enzyme purification procedure.

Commercially available laccases from *T. versicolor* efficiently degraded diclofenac, trimethoprim, carbamazepine and sulfamethoxazole as individual drugs, but the remediation efficiency decreased when applied to mixtures of the drugs (Alharbi et al., 2019). Kang et al. (2021) isolated laccases from *Bjerkandera* spp., which could efficiently remediate acetaminophen under a range of pH conditions (Kang et al., 2021). In a study employing immobilized laccases from *Trametes hirsuta*, Hachi et al. (2017) reported better remediation efficiencies for carbamazepine and acetaminophen (40 and 70%) in single compared to in mixtures (5 and 25%) (Hachi et al., 2017).

Using laccases (2,000 U/L) isolated from *Myceliophthora thermophile,* 94.1 and 95.5% of estrone E1 and 17β-estradiol E2 could be degraded within 8 h in the presence of a natural mediator in a fed-batch bioreactor. In an enzymatic membrane reactor (EMR) with a stir-tank configuration, this percentage was increased to 95% for E1 and near total E2 degradation (Lloret et al., 2010). This indicates that the bioreactor type significantly impacts the remediation efficiency regarding isolated enzymes. In a study by Becker et al. (2017), immobilized laccase from *T. versicolor* and *M. thermophila* could degrade 83 and 87%, respectively, of estrogenic compounds (E1 estrone; E2 17β-estradiol; EE2 17α-ethinylestradiol) in mixtures with other endocrine-disrupting compounds within 6h (Becker et al., 2017). Golveia et al. (2018) reported 96.5% remediation of 10 mg/L 17-α-ethinylestradiol by *Pycnoporus sanguineus* laccase (1,642 U/mL) after 8 h (Golveia et al., 2018). It would be noted that 1% (v/w) was added to the fungal culture to promote optimal laccase production concentration before extraction.

Utilizing isolated enzymes has the advantages of reducing the remediation time by avoiding the lag phase of fungal growth, reducing sludge production, and facilitating process control (Jebapriya and Gnanadoss, 2013). Apart from the high cost as a disadvantage, a study by Nguyen et al. (2014) demonstrated another drawback of using isolated enzymes (Nguyen et al., 2014). In a direct comparison, whole-cell culture degraded trace organic compounds with higher efficiency, which is said to be facilitated by biosorption and the activity of both intracellular and mycelium associated enzymes.

CONCLUSION

The environmental impact of pharmaceuticals and their proper elimination from wastewaters have gained interest in recent years, mostly due to the intrinsic characteristics of these compounds, their massive use, and the negative effects on the environment and humans. Although they are medicinal substances developed to aid in the well-being of organisms, their indiscriminate use can lead to irreversible environmental problems. Therefore, it is important to create legislation according to the current standards of using substances and eco-friendly trends. More versatile and efficient systems for eliminating PhACs such as mycoremediation are being developed to lessen or avoid the problems associated with pharmaceutical pollution in the environment. However, these promising techniques are still at a laboratory scale and data regarding the application in WWTPs are still lacking. Even though new techniques for the remediation of PhAC are being developed and optimized, relative to the development of new drugs, implementing these techniques into practice is slow. New promising approaches for this purpose, such as genetic engineering, are still in their infancy. Thus, the new editing tool, such as CRISPR-Cas9, could help to introduce metabolic genes focused on target recalcitrant compounds. Much more studies are still necessary to deal with the problem of PhACs.

AUTHOR CONTRIBUTIONS

ME, EA, DRO-H: conceptualization. MO and ME: literature search and data analysis and original draft preparation. MO, ME, DRO-H, JG-L, and EA: critical revision of the work. All authors contributed to the article and approved the submitted version.

FUNDING

MO received a Ph.D. grant from the Junta de Castilla y León (Spain). Open Access Funding was provided by the University of Helsinki.

ACKNOWLEDGMENTS

DRO-H thanks National Council of Science and Technology (CONACyT) and Secretariat of Research and Postgraduate Studies of the IPN project 20220492. We gratefully acknowledge the Spanish Ministry for Economy and Competitiveness within the context of the research projects CTM2017-84332-R (MINECO/AEI/FEDER/UE).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmicb.2022.869332/full#supplementary-material

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frontiers | Frontiers in Public Health

ORIGINAL RESEARCH
published: 26 May 2022
doi: 10.3389/fpubh.2022.880399

Contaminant Discharge From Outfalls and Subsequent Aquatic Ecological Risks in the River Systems in Dhaka City: Extent of Waste Load Contribution in Pollution

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OPEN ACCESS

Edited by:
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Specialty section:
This article was submitted to Environmental health and Exposome, a section of the journal Frontiers in Public Health

Received: *21 February 2022*
Accepted: *04 April 2022*
Published: *26 May 2022*

Citation:
Majed N and Islam MAS (2022) Contaminant Discharge From Outfalls and Subsequent Aquatic Ecological Risks in the River Systems in Dhaka City: Extent of Waste Load Contribution in Pollution. Front. Public Health 10:880399. doi: 10.3389/fpubh.2022.880399

Dhaka, the capital city, which is the nerve center of Bangladesh, is crisscrossed by six different rivers. A network of peripheral rivers connects the city and functions as a natural drainage system for a massive amount of wastewater and sewage by the increased number of inhabitants impacting the overall environmental soundness and human health. This study intended to identify and characterize the outfalls along the peripheral rivers of Dhaka city with the assessment of different pollution indices such as comprehensive pollution index (CPI), organic pollution index (OPI), and ecological risk indices (E_{RI}). The study evaluated the status of the pollution in the aquatic system in terms of ambient water quality parameters along the peripheral rivers due to discharge from outfalls with a particular focus on waste load contribution. Among the identified outfalls, the majority are industrial discharge (60%), and some are originated from municipal (30%), or domestic sewers (10%). Water quality parameters such as suspended solids (SS), 5-day biochemical oxygen demand (BOD_5), and Ammoniacal Nitrogen (NH_3-N) for most of the peripheral rivers deviated by as much as 40–50% from industrial discharge standards by the environment conservation rules, Bangladesh, 1997. Based on the CPI, the rivers Buriganga, Dhaleshwari, and Turag could be termed as severely polluted (CPI $>$ 2.0), while the OPI indicated heavy organic pollutant (OPI $>$ 4) contamination in the Dhaleshwari and Buriganga rivers. The associated pollution indices demonstrate a trend for each subsequent peripheral river with significant pollution toward the downstream areas. The demonstrated waste loading map from the outfalls identified sources of significant environmental contaminants in different rivers leading to subsequent ecological risks. The study outcomes emphasize the necessity of systematic investigation and monitoring while controlling the point and non-point urban pollution sources discharging into the peripheral rivers of Dhaka city.

Keywords: environmental and human health, aquatic system pollution, ecological risk, environmental contaminants, waste load, outfalls

INTRODUCTION

Water has been established as a significant source of myriads of services since it is required for the survival of all living species (1). The majority of the world's civilizations are inextricably linked to river water, where all civilizations began and flourished. The rivers and tributaries typically support a diverse range of biodiversity and create a diverse ecosystem comprised of ecologically sensitive and interconnected chemical, physical, and biological elements (2). For the manufacturing industries (like Dying, Garments, etc.), agricultural sectors, households, transport and communication, moreover for many living species, the river is a vital resource of water. On the other hand, Humans and other living creatures abound along the river's course. However, anthropogenic activities have been deteriorating river water in Bangladesh, making it unfit for human consumption or other uses (3). Some other causes of concern are water quality, particularly surface water, which is essential for drinking, fishing, agricultural, and industrial uses (4). Anthropogenic activities such as excessive urban development, uncontrolled industrialization, inadequate effluent treatment, and population growth have all caused significant concerns to the aquatic environment. As a consequence of the degradation of water quality, the aquatic environment is harmed, and the water becomes unsuitable for human consumption (5, 6).

With more than 230 primary. and minor rivers running throughout the country, Bangladesh is a low-lying riverine nation (3, 7), and Dhaka, which is the capital of Bangladesh, is shaded and connected through six different rivers. Being one of the fastest-growing capital cities, Dhaka is experiencing industrialization along the banks of the rivers. Because of the easy access to dumping facilities, and consequently, most water-contaminated regions are located in these industrialized districts (8). Because of the propensity for significant ecological and human health problems, such contaminated river water is unsuitable for human consumption, fishing, and agriculture (9). As per the findings, the physicochemical characteristics of water and relative environmental damage level in Dhaka's surrounding rivers have significantly deteriorated in terms of water quality indicators (10). Multiple industrial facilities, particularly Garment industries, have been developed in the current decades in Dhaka district's Savar Upazila, primarily along the Dhaleshwari river's bank. Garment industries are perhaps the most significant contributors among all of them together, accounting for 82% of total export income (28 billion USD/year) (11). Numerous industrial operations developed in the Hazaribagh region along the Buriganga river, including dyeing, textiles, batteries, and glass businesses. As a result of industrial activities, industrial pollution and effluents, including diverse environmental pollutants, significant waste loads are being contributed into the neighboring water bodies of Dhaka City. Furthermore, agricultural wash and urban municipal wastewater aggravate the potential risk associated with river water contamination. Heavy metals including Cadmium, Mercury, Lead, Copper, and Zinc are recognized important marine pollutants because of their toxicity, presence in food chains, and propensity to survive in the environment for an extended period of time (12, 13). Leather manufacturing involves many chemical products such as chromium sulfate, tannins, bactericides, and ammonia salt (14). The heavy metals may find their way into ecosystems and contribute contaminants of non-degradable nature. As a result, these heavy metals like Cadmium (Cd), Lead (Pd), and Zinc (Zn) continue to exist in the ecological system and pose a risk to humans and other animals (15). The heavy metals incorporate into the water body from anthropogenic sources though the protracted discharge of untreated or partially-treated waste, whereas metals are also introduced into agricultural land through the use of fertilizers and pesticides (16). Accumulation of metals in sediments and water at a significant quantity allows these metals to eventually enter the food chain *via* water and vegetation (17). In aquatic systems, heavy metals limit the generation of reactive oxygen species (ROS), affecting fish and the other aquatic creatures (18). These heavy metals are problematic because of their non-degradability; upon entering the ecosystem, they persist for a long time (19). Moreover, their distribution and accumulation in the aquatic ecosystem is a significant factor of concern due to the poisonous and pervasive nature of the metals. Which may create severe difficulties due to their ability to accumulate in live creatures and be bioaccumulated at relatively high trophic concentrations (20, 21). As a result, there is a high risk of river water contamination in Bangladesh's capital, which might have severe consequences for the riverine ecology and nearby residents by producing health problems from immediate consumption, ingestion and dermal exposure (22).

In response to such a demanding situation, supervision and assessment of surface water quality have become an international obligation (23). In emerging nations, maintaining sanitary systems is falling behind the speed of development and urbanization. Therefore, the current study aimed to analyze subsequent aquatic ecological threats in river systems of Dhaka City. This analysis also depicts the contribution of waste load to pollution in terms of discharge from outfalls. However, no comprehensive scientific investigation of waste load contribution toward pollution in the surface water of Dhaka's river systems as a whole has been published. A particular focus of this study consists of evaluating different pollution indices such as comprehensive pollution index (CPI), organic pollution index (OPI), and ecological risk index (E_{RI}). To assess the state of contamination in the aquatic system in terms of ambient water quality indicators along peripheral rivers caused by outfall discharge. This would pave the way for and compel strategies to reduce the intensity and contribution of toxicity from outfalls into the rivers.

ARTICLE TYPES

Original Research—Special Topic.

Study Area

The river system of Dhaka city is primarily composed of three distinct systems: the Balu-Lakhya River System, the Bangsi-Turag-Buriganga-Dhaleshwari River System, and the Dhaleswari-Kaliganga River System (24) (**Figure 1**). To the

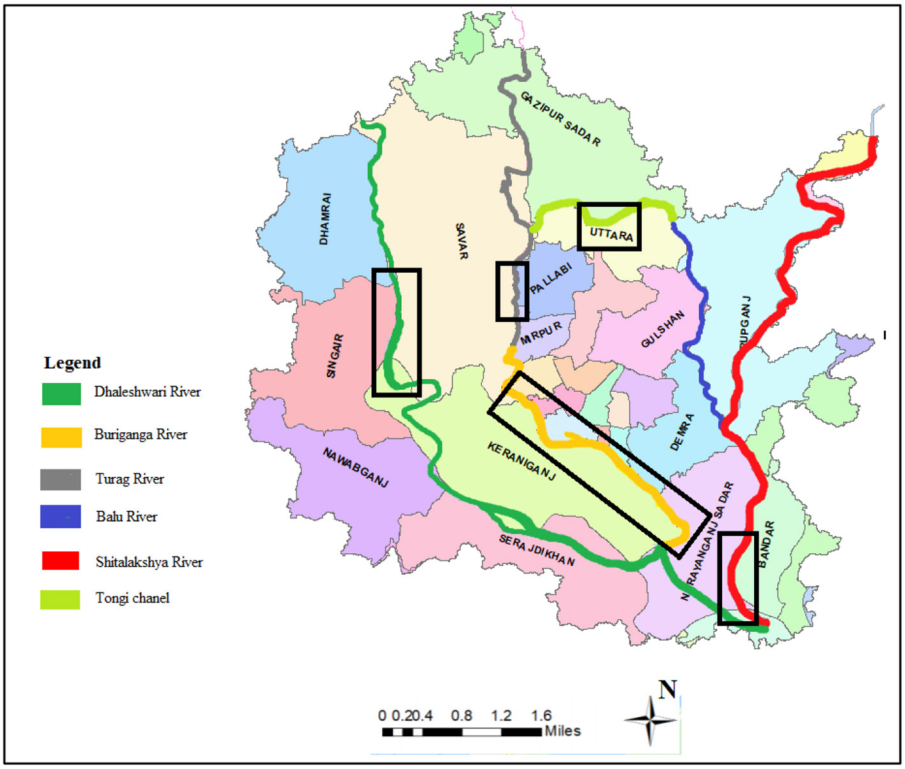

FIGURE 1 | GIS map showing peripheral rivers around Dhaka watershed (boxes representing the sampling stretches along the rivers).

west of Dhaka, the Dhaleswari-Kaliganga River and Bangsi-Shitalakshya-Turag-Buriganga River systems are located, while the Balu-Lakhya River system is located to the east. The Dhaleshwari River begins in the Jamuna River at the Tangail district's northwestern border and finally flows into the Shitalakshya River around the Narayanganj district (10). The Dhaleshwari River is one of the main tributaries of the Jamuna River in Dhaka, central Bangladesh, which is 160 km long and has an overall depth of 37 m (10). The Buriganga River system is situated in Bangladesh's North Central Zone's southeastern region, near the Padma (Ganges) and Upper Meghna rivers. The Buriganga River is a branch of the Dhaleswari River, the second largest river in the North Central Region, just after the Old Brahmaputra River. In fact, the Buriganga River is not inaccessible from a hydrological perspective, as previously stated. Around Dhaka, the Buriganga River has an average width of over 500 m and a length of almost 27 km (25). The majority of the Buriganga's water flow comes from the Turag River, which collects runoff from nearby rains and spillover from the Jamuna's left bank. The Turag River, which originates in the neighboring district of Gazipur, is about 63 km long (26). Between the middle forest and the Old Brahmaputra, the Lakhya River drains a substantial catchment area. A distributive tributary of the Brahmaputra, the Shitalakshya River travels in a northwesterly direction. Later, it makes a diversion to the east of Narayanganj and ends up at Kalagachhiya, where it joins the Dhaleshwari river. Near Narayanganj, this river has an average width of 300 m and a length of 110 km (27). A smaller catchment to the west of the Lakhya River feeds the Balu River; the Ichamati and Karnatali Rivers, which transport mostly overflows from the Padma and Jamuna Rivers, respectively, also contribute to the system's intakes (24). Tongi canal connects the Turag and Balu rivers on the western side, and the length of the canal is ∼15 km (28). Buriganga, Shitalakshya, Turag, Tongi Canal, and Dhaleshwari rivers were chosen for the study to explore the aquatic ecological threats in Dhaka City's River systems. **Figure 1** depicts the peripheral waterways system surrounding Dhaka Watershed, with the black boxes indicating the sampling sites from the rivers that are shown. Comprehensive identification of outfalls along each of the mentioned rivers was accomplished in terms of location and type which were then plotted on digitized map of the Dhaka Whatershed. For pollution study, outfalls on each of the rivers were selected according to the density of industrialized areas and the availability of garbage dumping stations along the banks of the rivers. Detailed figures for sampling locations and identified outfalls along each of the rivers are provided separately in the **Supplementary Material**.

Identification of Outfalls and Collection of Sample

Outfalls from five distinct rivers were chosen for the current study, with 41 selected outfalls in total. The exact location of each sample site was determined using Global positioning system

(GPS) data. The types of the outfalls and the locations are provided in **Supplementary Material**.

In total, 41 samples were collected from selected outfalls to analyse water quality parameters. From 27 km of primary tributaries of the Buriganga River, 24 outfalls were selected for present study from Aminbazar to Fatullah (Narayanganj), which covered 24 km of the river. Such comprehensive sampling was done for Buriganga river due to the densely located industries along the bank of the river. While six outfalls were assessed for Shitalakshya River from Kadamrasul to Mukterpur, the selected stretches encircled about 10 km of the river. For Turag River and Tongi Canal, three outfalls were chosen for each of the rivers, and each river covered 5 and 4 km, respectively. Furthermore, five outfalls were selected from about 8 km stretch for the Dhaleshwari River. Starting from the Savar Tannery area, the selected stretch of the Dhaleshwari River ended at Nama Bazar. Five additional samples were obtained from the Dhaleshwari River for heavy metals analysis. From the middle of the river's course, unfiltered samples of water were gathered. Following that, the samples were put in 100 mL polypropylene bottles and sealed. Before sending the samples to the University of Dhaka's Department of Soil, Water, and Environment Laboratory for heavy metals analysis, 1 mL of ultrapure nitric acid was added to each polypropylene bottle to produce a pH $\sim$ 1 (29). The standard sampling protocol was performed for all the samples at each sampling site (30).

Analysis of Water Quality Parameters

Water samples collected from all the rivers were analyzed in the Environmental Engineering Laboratory, Department of Civil Engineering, University of Asia Pacific for water quality characteristics. Total dissolved solids (TDS) concentrations were determined using DO700 EXTECH (Łódz, Poland) standard equipment (10). Electrical conductivity (EC), and total suspended solids (TSS) were measured with an EZDO (Taipei City, Taiwan) model "CTS-406" meter. A Twin (Santee, USA) model "B-221 pH" pH meter and a model "YK-22DO" dissolved oxygen meter were used to measure pH and dissolved oxygen (DO) (EZDO, Taipei City, Taiwan) (10) respectively. The 5-day biochemical oxygen demand (BOD_5) was measured using the BODTRAK technique with a BOD Trak II (Model: Hach) and a BOD incubator (Model: Hach FOC120E) with potassium hydroxide and BOD nutrient buffer pillow reagents (31). The chemical oxygen demand (COD) was determined using a COD reactor (Model: Hach DRB200) and a spectrophotometer (Model: Hach DR 6000) through the reactor digestion technique (32). Colorimetric vanadomolybdophosphoric acid was used to detect phosphate (10). The colorimetric approach was used to assess nitrite by forming a reddish-purple azo dye at pH 2.0–2.5 by combining diazotized sulfanilamide with N-(1-naphthyl)-ethylenediamine dihydrochloride. A Shimadzu (Model: 1800 UV-Vis) spectrophotometer was used in colorimetric procedures (10).

Analysis of Heavy Metals

Heavy metals, including cadmium (Cd), lead (Pb), and zinc (Zn) were analyzed in the Department of Soil, Water, and Environment, University of Dhaka. Shimadzu's (Model: AA-7000, South San Francisco, USA) atomic absorption spectrometer was used to determine the dangerous metal concentrations. All measurements were carried out using a precise (Model: ABS 220-4, Ziegelei, Balingen, Germany) precision electrical balance produced by KERN. A nylon membrane filter (47 mm diameter, Whatman, Washington, USA) was used (33). Each sample was obtained into a Pyrex volumetric flask containing 100 mL for heavy metal analysis. Following that, 9 mL of 1 M HCl and 3 mL of 1 M HNO_3 were added. To lower the moisture content of the volumetric flask, it was gently heated in a sand bath under a fume hood. After the flask had been brought to room temperature, deionized water was poured. The filtrate was collected in a 250 mL HDPE screw-cap plastic container tube with a polypropylene/low-density polyethylene (LDPE) coated lid; Thermo Scientific, Washington, USA (10). Last but not least, a small number of samples were saved for use in calculating metal concentration. Different reference concentrations were used to calibrate the Atomic Absorption Spectrometer (AAS) for all metals. The average of three separate measurements was calculated for each data point. The detection limit was set at 0.001 mg/L in this study. In order to determine the level of metals in the sample, an oven was employed (Model: GAF-7000, ESCO, Changi South Street, Singapore).

Comprehensive Pollution Index (CPI) and Organic Pollution Index (OPI)

Using monitoring data, the Comprehensive Pollution Index (CPI) determines the pollution level of a water body (34). Previously, Zaghden et al. (35) have also evaluated CPI to assess the ecological threats and status of discharge. The formula to calculate CPI is presented as follows:

$$\mathrm{CPI} = \frac{1}{n}\sum_{i=1}^{n} \mathrm{PL_i}$$

Where CPI is the Comprehensive Pollution Index; n is the number of variables under observation; PI_i is the pollution index number of ith observation. PI_i is calculated according to the following formula:

$$\mathrm{PI_i} = \frac{\mathrm{Ci}}{\mathrm{Si}}$$

where C_i is the measurement of parameter's concentration in water and S_i is the allowable number of parameters in accordance with environmental standards. Mishra et al. (36) classified CPI into five categories (provided in the **Supplementary Material**) which was utilized to evaluate the pollution categories relevant for the rivers based on the estimated values of CPI for the outfalls discharging into the rivers.

OPI is a tool for assessing a watershed's pollution intensity depending on four distinct characteristics such as dissolved inorganic phosphate, COD, and dissolved inorganic nitrogen (2), as well as the concentration of dissolved organic carbon (DIP). Dou et al. (37) analyzed OPI to evaluate environmental risks from sewage discharge in urban area. The following equation represents the organic pollution index (OPI):

$$OPI = \frac{COD}{CODs} + \frac{DIN}{DINs} + \frac{DIP}{DIPs} + \frac{DO}{DOs}$$

According to the environmental standard, CODs, DOs, are the standard concentrations of COD, and DO; DINs are the total restricted concentration of Nitrate, Nitrite, and Ammoniacal Nitrogen; and DIPs are the limited concentration of Phosphate.

According to the OPI value, water quality could well be categorized into six different levels according to (38) which are provided in **Supplementary Material**. OPI values were evaluated for OPI based categorization of risk from all the outfalls discharging into the respective rivers.

Assessment of Ecological Risk Index

A sedimentological technique proposed by Hakanson (39) might be used to first identify how heavy metal contaminants behave naturally and environmentally. Toxic response indicators, a precise pollution measurement, and a probable ecological risk index are all incorporated in the process of determining pollution coefficients. The following equations yielded the ecological risk index (E_{RI}) for the study area (39):

$$E_r^i = T_r^i \left(C^i / C_o^i\right)$$
$$E_{RI} = \sum E_r^i$$

Where C^i and C_o^i denotes the amounts of specific heavy metals and their allowable reference value, respectively, and E_r^i denotes an ecological risk factor. Each metal has a different toxicity factor (Cd = 30, Pb = 5, and Zn = 1) which is referred as T_r^i (40). The ecological risk index (E_{RI}) quantifies the sensitivity of biological populations to certain metals in the region under consideration. **Table 4** shows the ranges of the indices of T_r^i and E_{RI} based on which the categorization of risk was evaluated for the outfalls discharging into the rivers. Li et al. (41) also analyzed Ecological Risk Index to evaluate subsequent ecological threats from industrial wastewater discharge. Accordingly, the present study accomplished the categorization of ecological danger associated with hazardous metals in the selected outfalls following the Classification of Ecological risk index. Furthermore, E_{RI} of heavy metal pollution (42) which is provided in the **Supplementary Material**.

Waste Loading Estimation

The authors estimated the flow rates of the rivers Buriganga, Shitalakshya, Turag, Tongi Canal, and Dhaleshwari according to the procedure described in Alam et al. (43) which determined the waste loading rate using a distance technique rather than particular flow measurement equipment. The first step was to determine the cross-sectional area of the outfall. Then, using a specific distance, the velocity of outfalls was determined. The cross-sectional flowing area was multiplied by the measured discharge speed to get the flow rate. Direct measurements of the flow rates at all sample outfalls were made during the field visit. Following the flow measurement, the waste loading rate of the particular pollutant was determined by following equations which yielded the waste load for the study area (44):

$$\text{Wasteload} = \text{Flowrate} * \text{Concentration}$$

Where, Flow rate represents the flow rate of particular outfall and Concentration denotes level of concentration of a specific pollutant. Waste loads were estimated for the parameters including 5-day biochemical oxygen demand (BOD_5), chemical oxygen demand (COD), ammoniacal nitrogen (NH_3-N), total suspended solids (TSS), total dissolved solids (TDS), and electrical conductivity (EC). Digitized waste load maps were prepared to demonstrate the waste load contribution of the outfalls in the selected rivers.

RESULTS

Identification of Outfalls Along Dhaka Watershed

Several industrial outfalls (tanneries, dyeing, textiles, power plants, etc.), storm sewer outfalls, and domestic outfalls have been identified in the Dhaka Watershed for the present study. Runoff from streets, wastewater from marketplaces, vehicle workshops, clinics, hospitals, and other outfalls bring in contaminants from several sources. Aside from that, the Buriganga River has four known illegal storm sewage outfalls (box culverts). Field surveys, analysis of available maps (on the drainage of Dhaka City and storm sewer network), and discussions with officials of the Dhaka Water Supply and Sewerage Authority (DWASA), which is responsible for managing both domestic sewage and stormwater drainage, were used to identify outfalls along the Dhaka Watershed. **Table 1** depicts the identified outfalls along with significant parts of the river stretches of Dhaka Watershed. A thorough inventory of outfalls was compiled (including information on outfall location, type of discharge, and the number of outfalls) and is reported in the current study. This observation of outfalls showed that nearby industrial sources heavily influenced surface water quality indicators. Comprehensive identification of outfalls revealed that the majority of the outfalls (around 60%) are industrial discharge, and some are originated from municipal (just below 30%) or municipal sewers (near about 10%).

The majority of the outfalls were located in areas with high industrial disposals, agricultural activity intensities and numerous sources of pollution, both point and non-point. Additionally, several of the discharge points serve as municipal supplies of water. Point sources include a variety of Industrial fields, including leather, Dying, Textiles, and Metals manufacturing. Industrial processes such as the production of textiles, inks, batteries, and metal melting furnaces are also considered point sources of pollution. Point sources such as garbage disposal sites, toxic sewage, ports, and landing stations are all contributing factors to pollution. The figure demonstrating the identified outfalls in Dhaka Watershed as digitized have been provided in the **Supplementary Material**.

TABLE 1 | Identified outfalls along the river stretches of Dhaka Watershed.

Rivers	Type of discharge	Number	Outfall location
Dhaleshwari River	Tannery	8	Kolatoli and Hemayetppur
	Dyeing	6	Savar
	Garments	15	Savar
	Power plant	3	Narayanganj
	Jute mill	4	Narayanganj
	Cement factories	2	Narayanganj
	Municipal sewer	8	Savar and Sudkhira
Buriganga River	Power plants	2	Fatullah
	Garments	5	Fatullah
	Tannery	10	Hazaribagh Area
	Dyeing	3	Shyampur and Postogola
	Storm sewage	4	Hazaribagh Area and Shyampur
	Municipal sewer	10	Shyampur and Postogola
Shitalakshya River	Cement	8	Narayanganj and Fatullah
	Garment	14	Narayanganj and Fatullah
	Jute mills	7	Narayanganj and Fatullah
	Power plants	5	Narayanganj and Fatullah
	Dyeing	2	Narayanganj and Fatullah
	Municipal sewer	10	Narayanganj and Fatullah
Turag River	Garments	5	Kaundiya
	Dyeing	2	Diabari Ghat
	Municipal sewer	4	Miepur Bridge Road
Tongi Canal	Garments	15	Bismillah Market
	Dyeing	3	West Abdullapur
	Municipal sewer	3	Tongi Bridge

Assessment of Water Quality Parameters of Outfalls

Water samples from the outfalls of the rivers of Dhaka city were examined for several water quality parameters. Using the Environmental Conservation Rule, Bangladesh (ECR'97), assessment of outfall discharge quality was made and averaged for the respective rivers which are summarized in **Table 2**.

It is shown in **Tables 1**, **2** that how the combined discharge from several point sources are contributing together from outfalls at many locations. With ECR'97 standards in red dotted lines, **Figures 2A,B** show the maximum and minimum levels of pH and BOD_5 respectively for the selected outfalls along each of the rivers in Dhaka City.

Dhaleshwari, Buriganga, Shitalakshya, and Balu rivers, in particular, were discovered to be black in color visually and were experienced with unpleasant smells during the visual investigation. With pH levels ranging from 7.38 to 11.6 for the Dhaleshwari River outfalls. The maximum pH value was observed at outfall D-1 (Savar Tannery), and the minimum pH value was recorded at outfall D-4 (AKS dying). Except for Dhaleshwari for maximum level (pH = 11.6) and Shitalakshya for minimum level (pH = 5), all of the other outfalls on the rivers in Dhaka Watershed were found to have pH values within the acceptable range for this study (**Figure 2A**). The most acidic outfall of all the Peripheral Rivers in the Dhaka region was observed in the Shitalakshya River.

Organic contamination may best be assessed using BOD_5 analysis, the standard for this kind of analysis (45). The BOD_5 concentration of the outfalls of Buriganga River varied between 18.4 and 284.2 mg/L from 24 outfalls. Indicating that there is significant variation of the organic content among the outfalls while the maximum value indicates the highest discharge level among all the rivers making it the most polluted of all the rivers under study (**Figure 2B**). Similarly, the observed average BOD_5 values of the outfalls in Dhaleshwari river (86.72 mg/L), Turag River (128.4 mg/L), Tongi Canal (88.4 mg/L), and Shitalakshya River (126.2 mg/L), respectively, exceeded the BECR guidelines (50 mg/L) for the permissible limit of BOD_5 (**Figure 2B**). The BOD_5 standard for discharge from public sewerage system connected to treatment at the second stage is 250 mg/L, and that for irrigated land is 100 mg/L (46). Since the outfalls pass through a densely inhabited and industrialized sector along the riverbanks, the BOD_5 concentration was more significant around the particular periphery of the waterways segment of Dhaka city. A variety of organic and chemical pollutants can build up in the waterways because of the discharge of organic materials due to the inefficiency of sewage treatment plants, stormwater runoff, agricultural slurries, domestic waste (food and human waste), industrial waste (waste from food processing, tanning, and dying), and silage liquor. There is a consistent, similar rate of discharge of organic compounds and resulting contamination in all of the surrounding rivers, as shown by this observation.

With ECR'97 standards in red dotted lines, **Figures 3A,B** shows the maximum and minimum levels of COD and TDS, respectively, for the outfalls along the rivers in Dhaka City. The capability of industrial waste and sewage to resist pollutants and the amount of oxygen needed to oxidize organic and inorganic components in a sample may both be determined using the COD method (chemical oxygen demand) (47). COD values ranged from 305–1,353.6 mg/L for the outfalls in Turag River, 305–753.6 mg/L for those in Tongi Canal, 89–949 mg/L for those in Buriganga River, 311–609 mg/L for the ones in Dhaleshwari River, and 122–552 mg/L for the ones in Shitalakshya River. The results are suggesting a high level of contamination in these rivers based on the ECR'97 guideline (200 mg/L) (**Figure 3A**). Turag River has the highest level of organic forms of discharge, as observed among all the rivers in Dhaka City. Outfalls with greater COD levels are more likely to include industrial pollutants comprising inorganic and organic chemicals, which indicates a higher toxicity level than samples with lower COD levels (48).

TABLE 2 | Results of water quality parameters of the selected outfalls from peripheral rivers of Dhaka City.

Parameter	Unit	Standard*	Average ± standard error of mean				
			Dhaleshwari River ($n = 5$)	Turag River ($n = 3$)	Tongi Canal ($n = 3$)	Buriganga River ($n = 24$)	Shitalakshya River ($n = 6$)
pH		6–9	9.1± 1.8	8.28 ± 0.48	7.28 ± 0.93	7.12 ± 0.35	6.52 ± 0.71
TSS		150	424.8 ± 165.8	131 ± 1.41	131 ± 1.41	242 ± 93.11	298.33 ± 153.88
TDS	mg/L	2,100	2,325.8 ± 368.2	606 ± 72.12	606 ± 69.29	561.08 ± 94.57	661.17 ± 157.7
BOD_5	mg/L	50	86.72 ± 30.8	128.4 ± 7.07	88.4 ± 7.07	181.9 ± 31.86	126.2 ± 32.63
COD	mg/L	200	486.6 ± 114.5	1,222.8 ± 184.9	722.8 ± 43.55	549.41 ± 157.32	306.17 ± 142.28
DO	mg/L	4.5–8	0.52 ± 0.6	1.14 ± 0.83	1.49 ± 0.08	1.43 ± 1.51	0.85 ± 0.52
NH_3-N	mg/L	50	71.96 ± 19.8	50.3 ± 4.52	35.3 ± 2.54	44.88 ± 33.53	25.15 ± 17.9
EC	μS/cm	1,200	2,277.8 ± 191.3	1,512 ± 438.40	1,412 ± 155.56	1,271.17 ± 176.48	1,386.5 ± 262.86

**Standards for waste from industrial units or projects waste: the environment conservation rules, Bangladesh, 1997 (ECR'97), n = number of outfalls.*

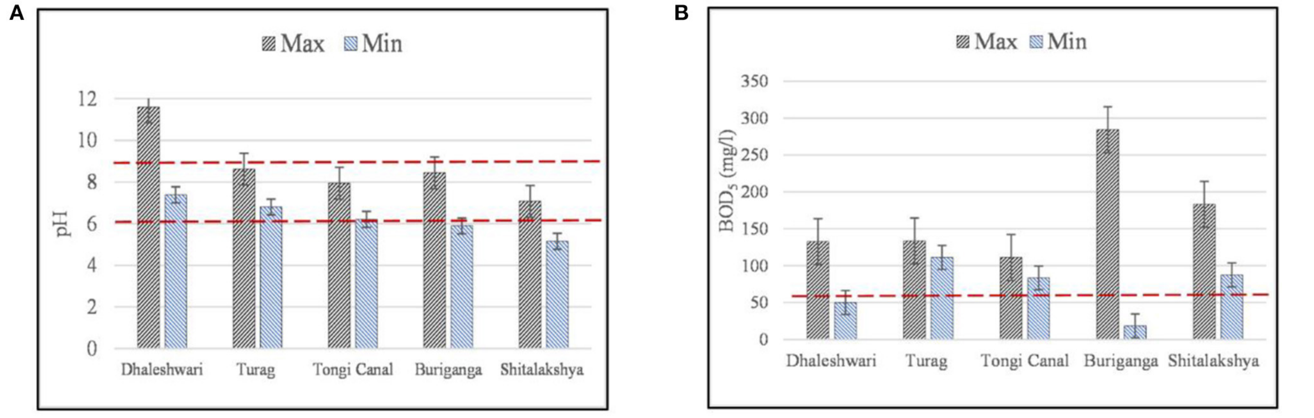

FIGURE 2 | (A,B) Maximum and minimum concentrations of pH and BOD_5 for the selected outfalls along the peripheral rivers of Dhaka (error bars indicate standard error of mean and red dotted lines indicate the Bangladesh standards of water quality according to ECR'97).

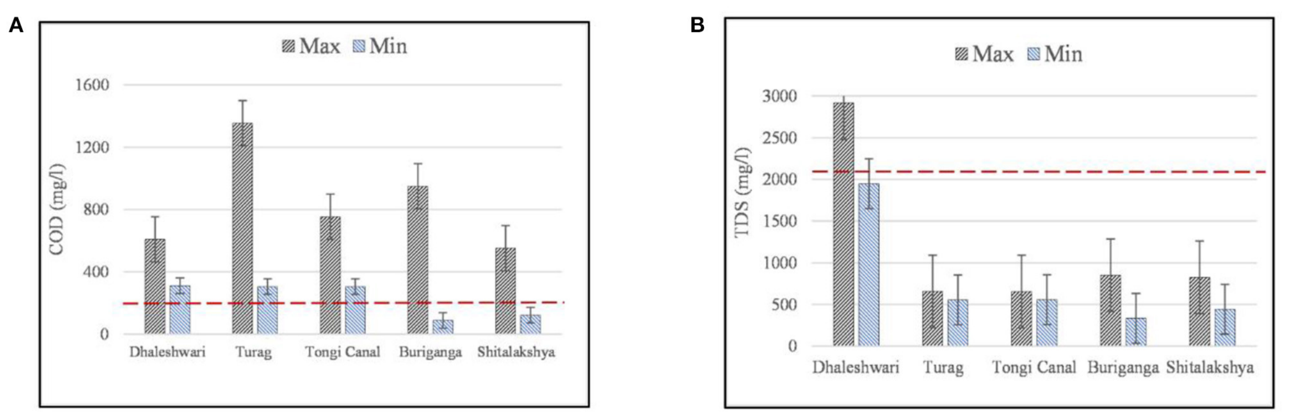

FIGURE 3 | (A,B) Maximum and minimum concentrations of COD and TDS for the selected outfalls along the peripheral rivers of Dhaka (error bars indicate standard error of mean and red dotted lines indicate the Bangladesh standards of water quality according to ECR'97).

Minerals, alkalis, certain colloidal and dissolved solids in water, some acids, sulfates, metallic ions, etc., are all included in the total dissolved solids (TDS) category (49). TDS levels in the Dhaleshwari River water varied from 1,948 to 2,914 mg/L, with the highest level found at outfall D-1 (Savar Tannery) and the lowest level recorded at outfall D-2 (Sudkhira) (**Figure 3B**). Savar

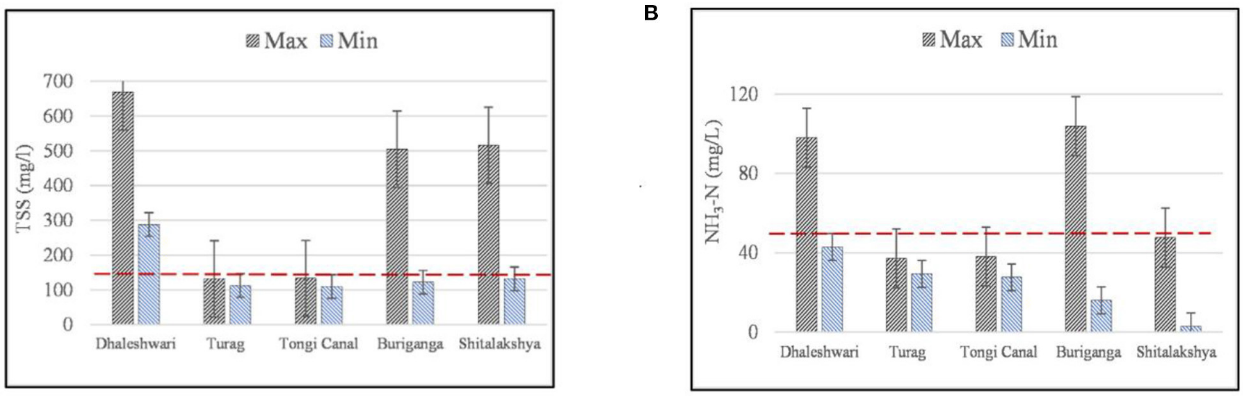

FIGURE 4 | (A,B) Maximum and minimum concentrations of TSS and NH_3 for the selected outfalls along the peripheral rivers of Dhaka (error bars indicate standard error of mean and red dotted lines indicate the Bangladesh standards of water quality according to ECR'97).

Tannery (D-1) is the only designated outfall in Dhaka City that exceeds the allowable level of ECR'97 standards for the discharge standard (2,100 mg/L), which discharges into the Dhaleshwari River system. When the TDS level reaches 1,000 mg/L, the water becomes murkier and saltier, which severely influences aquatic life (50, 51). As a result, humans, agriculture, and animals all are affected. However, during the monsoon season, runoff water flow may fluctuate while influencing the irrigation system. An increase in TDS levels has been linked to dyeing unit discharge in other dyeing-heavy locations (52).

With ECR'97 standards in red dotted lines, **Figures 4A,B** shows the maximum and minimum levels of TSS and NH_3-N, respectively, for the outfalls along the rivers in Dhaka City. Total suspended solids (TSS) levels in the outfall discharge along Dhaleshwari River varied from 288 to 669 mg/L, varied from 122 to 505 mg/L for Buriganga River and varied from 132 to 516 mg/L for Shitalakshya River (**Figure 4A**). The results descrived above are exceeding ECR'97 guidelines (150 mg/L) for the permissible limit of TSS discharge standard. As important as the analysis of BOD_5 is the assessment of suspended particles in sewage and other wastewater investigations (53). To avoid putrefaction, it is best if there are no suspended solids in the canal. However, various organic compounds may also be present in the suspended particles.

The Ammoniacal Nitrogen (NH_3-N) values in the outfalls along the Dhaleshwari River varied from 42.9 to 98 mg/L and varied from 16 to 103.8 mg/L for Buriganga River, exceeding ECR'97 guidelines (50 mg/L) for the permissible limit of NH_3-N as shown in **Figure 4B**. Both maximum and minimum levels of NH_3-N discharge levels were below the standard limits along Turag, Tongi Canal and Shitalakshya rivers. Industries along Buriganga and Dhaleshwari seem to be contributing toward elevated ammonia levels along the rivers in relevance to the inadequacy in their treatment of effluents.

With ECR'97 standards in red dotted lines, **Figures 5A,B** show the maximum and minimum levels of DO and EC for the outfalls along the rivers in Dhaka City. It is essential for aquatic species in surface waters to have a high quantity of dissolved oxygen (DO) (54, 55). Oxygen-depleting pollutants may be detected by decreasing dissolved oxygen (DO) concentration in the water body. Many water quality elements and processes, such as bacterial metabolism, algal photosynthesis etc., are influenced by the amount of dissolved oxygen available in the medium (56). DO levels varied within 0.07–1.45 mg/L for the outfalls in Dhaleshwari River, 0.04–5.4 mg/L for those in Buriganga River, 0.35–1.73 mg/L for those in Shitalakshya River, 0.55–5.12 mg/L for the ones in Turag River, and 1.43–2.12 mg/L for the ones in Tongi Canal (**Figure 5A**). For the waste discharged from industrial units into inland surface water, these levels should be within 4.5–8 mg/L, according to the ECR'97 recommendations adding enough DO in the river water. The lowest level of DO was obtained next to the Savar tannery area. The following DO criteria are permissible following the Environmental Quality Standard (EQS): Fish and domesticated animals need 4–6 mg/L; 6 mg/L for drinking, 4–5 mg/L for industrial purposes, and up to 5 mg/L for industrial applications (57). Organic chemicals released from sources such as wastewater treatment facilities, storm floods, slurry agriculture, and alcohol silage are possible explanations for the depleted dissolved oxygen levels in the water. Biodegradable waste from industrial and household sources has a rapid decrease in DO level by supporting microbes in the water body. Oxygen is essential for all aquatic organisms with aerobic respiration biochemistry to operate appropriately (58). The quantity of dissolved oxygen (DO) decreases when BOD_5 levels are high since microorganisms consume the oxygen they acquire from the water (59). As a result, fish and other aquatic animals cannot thrive in oxygen-depleted environments.

EC varied from 554 to 1,822 µS/cm for the outfalls along the Turag River, 1,302 to 1,554 µS/cm for those in the Tongi Canal, 775 to 1,835 µS/cm for those in the Buriganga River, 1,102 to 1,722 µS/cm for the ones in the Shitalakshya River, and 1,950 to 2,428 µS/cm for those in the Dhaleshwari River (**Figure 5B**). According to WHO standards, rivers in these areas contain high amounts of ionic pollution. According to WHO guidelines, a body of water with an EC of more than 1,200 µS/cm

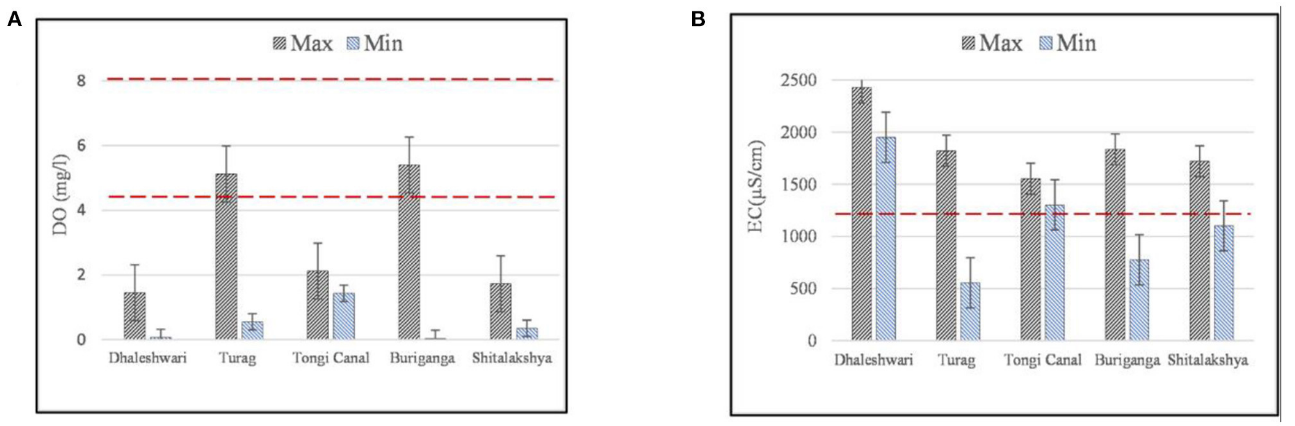

FIGURE 5 | (A,B) Maximum and minimum concentrations of DO and EC for the selected outfalls along the peripheral rivers of Dhaka (error bars indicate standard error of mean and red dotted lines indicate the Bangladesh standards of water quality according to ECR'97).

is not acceptable for agriculture, home use, swimming, industrial use, or drinking. Electrical conductivity may have increased due to tannery and metal plating industry emissions. Heavy metals are also produced in the textile and dyeing industries. Plants and other organisms in the environment may be affected by high levels of EC, which may have a physiological impact (10). Water from industrial and municipal sources and effluent from sewage treatment plants have been shown to contain significant quantities of ionic pollutants, which may harm aquatic species.

Comparative Assessment of Heavy Metal Contamination

The heavy metals concentrations in the outfalls along the Dhaleshwari River investigated are shown in **Table 3**. Additionally, this table includes the concentrations of heavy metals in theother outlying rivers of Dhaka, as reported in prior research. Furthermore, **Table 3** also comprises ECR'97 discharge standard guidelines. However, when it came to heavy metal concentrations, Zn was at the highest level, followed by Pb and Cd.

Savar tannery industrial zone had the most significant concentrations of Cd pollution at outfall D-1 (0.42 mg/L), whereas outfall D-3 (Sudkhira) (0.015 mg/L) in the Dhaleshwari River (0.015 mg/L) had the lowest concentration (**Table 3**). However, permissible levels of Environmental Conservation Rules (0.005 mg/L), World Health Organization (0.003 mg/L), and Food and Agriculture Organization (0.01 mg/L) were all surpassed in these experiments (64, 65). In the high Cd-containing region of the Savar District, one of the oldest and most popular wholesale fish markets is located. Higher levels of Cd might fluctuate with the capacity of river water, with the decreased flow of water promoting metals to precipitate in sediment, raising Cd concentrations (66). Tongi Canal and Shitalakshya river both demonstrated Cd concentrations of 0.02 and 0.025 mg/L, according to Sunjida et al. (63) and Haque (61). Cd levels in the Buriganga River were found to be as high as 1.34 mg/L in a previous study (60). Chromium-based chemicals might have contaminated the Buriganga River from cooling towers. Industrial activities, leachates from defused batteries, and Cd-plated materials might contribute to the high amount of Cd in the Buriganga River and Dhaleshwari River (67, 68). Although near the Savar tannery effluent zone along the selected stretches of the Dhaleswari River, the concentration of Cd seems higher than that in Buriganga, which is also above the acceptable limit. Because water cotyledons (*E. crassipes*) grew around the sample location during the investigation, these water cotyledons accumulated Cd and were dubbed as chrome-sorbent plants (69, 70).

TABLE 3 | Heavy metals concentration (mg/L) levels in the outfalls of the Dhaleshwari River and the other selected peripheral rivers in Dhaka city.

	Cd	Pb	Zn	References
D-1	0.42	3.9	5.49	Present Study
D-2	0.25	0.63	1.6	Present Study
D-3	0.13	1.53	2.21	Present Study
D-4	0.21	0.49	2.33	Present Study
D-5	0.38	1.97	4.29	Present Study
Buriganga River	0.34	3.42	3.15	(60)
Shitalakshya River	0.025	1.112	3.12	(61)
Turag River	0.005	0.084	3.1	(62)
Tongi Canal	0.08	1.34	4.65	(63)
ECR'97[a]	0.05	1	5	(53)

[a]ECR'97 = The Environment Conservation Rules, Bangladesh

[a]*Standards for waste from industrial units or projects waste: the environment conservation rules, Bangladesh, 1997 (ECR'97).*

Lead (Pb) is a significant contributor of pollution from sources connected to battery recycling plants, and it is also thought to be a good indicator of contamination from urban runoff water (71). Outfalls along the Dhaleshwari River showed varying levels of Pb ranging from 0.49 to 3.9 mg/L. According to the Environmental Conservation Rules, Bangladesh, the permissible level of Pb in drinking water is 1 milligram per liter [**Table 3**; (53)]. The primary sources of Pb in the urban area include municipal runoffs, untreated or poorly treated industrial effluents, atmospheric deposition (72) and similar activities observed along the Buriganga and Dhaleshwari river bank. Batteries, pigments, and plating enterprises are among the possible sources of Lead in the outfalls discharging into the Dhaleshwari River (73). The highest level of Pb was obtained at outfall D-1 (3.9 mg/L), which is greater than the ECR'97 permitted limit (1 mg/L), and quite possibly could be attributed to Savar tannery effluents. Except for D-2 and D-4, every outfall in the vicinity of Savar City's industrial district has a Pb concentration that exceeds the allowable limit. A long-term lead consumption exceeding the permissible level might induce allergic skin reactions (74). In Alexandria, Egypt, El-Ebiary et al. (69) observed that red tilapia mortality was induced by exposure to high levels of cadmium and Lead. Zn concentration levels in the selected rivers of Dhaka City are shown in **Table 3**. Zinc (Zn) concentrations in the outfalls along the Dhaleshwari River ranged from 1.6 to 5.49 mg/L (**Table 3**). Except for D-1, all of the outfalls in the Dhaleshwari River contained the maximum Zn concentration below the levels permitted by the ECR'97 (5 mg/L). Despite this, the present investigation found that the content of Zn in selected peripheral rivers in Dhaka city exceeded the water quality standard limit for Zn (5 mg/L) (23). In the Shitalakshya River, Haque (61) had reported an average (the arithmetic mean) concentration of Zn of 3.12 mg/L, while Jahan (60) found it to be 3.15 mg/L for the Buriganga River. The levels of discharge provide an indication of the heavy metal concentrations that can be potentially contributed from industries. Chronic exposure to zinc, a carcinogenic metal that damages the liver and heart and lowers metabolism and skin sensitivity, may even cause cancer (75).

Characterization Based on Pollution Indices (CPI)

Using a simple numerical measurement, the comprehensive pollution index (CPI) can express the overall quality of the discharge and categorize it into numerous subcategories (76). This study uses the holistic and detailed pollution analysis technique to characterize the discharge quality of outfalls along the selected rivers of Dhaka Watershed to depict the river's quality based on single-factor analysis in a comprehensive manner. Using the ECR'97 standard limit as a guide, this research performed the Characterization based on Pollution Indices (CPI). **Figures 6A–E** illustrates the CPI ranges for water quality of identified outfalls in the respective rivers. According to CPI, scores vary from 4.73 to 16.29 for selected outfalls from the Dhaka Watershed, indicating that the Dhaleshwari, Buriganga, Shitalakshya, Turag, and Tongi Canal rivers are seriously contaminated (CPI $\geq$ 2) (**Figure 6**) and should not be used for irrigation. Due to substantial and direct inputs of industrial wastes from a Box culvert in the Hazaribagh region in the Buriganga River, the outfalls B-8 to B-10 (more than 2) have earned the highest score.

The present study discovered that the water of the selected river is inappropriate owing to its high COD and deficient DO levels as contributed by the outfalls. Consequently, it might show that the river's assimilation or resistance ability has been aggravated. Due to pollution caused by frequent human interventions, including cremation, sewage discharge, agricultural runoff, as well as detergents from textile washing and bathing (77). According to CPI: 11.2–15.84, the Dhaleshwari River has been highly contaminated. The CPI calculated for each sampling outfalls of Shitalakshya, Turag and Tongi Canal are also observed to be severely polluted (CPI $\geq$ 2.0). Compared to the other rivers under evaluation, the Buriganga River's water quality is shown to be typically poorer, whereas Tongi Canal was found to be less contaminated in terms of CPI. In general, the water quality of each river in the Dhaka Watershed has deteriorated over time due to increased anthropogenic pressure that exceeds the river's capacity for assimilation or tolerance (36).

Organic Pollution Index (OPI)

The Organic Pollution Index (OPI) is a commonly used metric for determining the degree of organic pollution (78). **Figures 7A–E** illustrate the assessment of OPI from different identified outfalls of selected rivers through polar charts in Dhaka Watershed. The OPI of outfalls from the Dhaleshwari River water as obtained in this research varied between 6.18 and 34.69, which corresponds to the heavily polluted category (OPI $\geq$ 4) among all other rivers evaluated in this study (**Figure 7A**). This indicates that all sampling sites along the selected stretches of the Dhaleshwari River have a significant degree of eutrophication (79). Outfall D-1 (Savar Tannery) had the highest OPI (34.69), and outfall D-3 (Sudkhira) had the lowest OPI (6.18) values throughout the sampling timeframe. All outfalls have been thus classified as heavily polluted (OPI $\geq$ 4). It is possible that the increased absorption of nutrients by phytoplankton and aquatic plants is to blame for the higher OPI values (80). Such facilities that release organic pollutants straight into marshes with no prior treatment may be held responsible for the devastating effects they have, as this information shows. In addition to the influence of Industries and Dying plants that immediately drain wastewater to the rivers without treatment, there is also a low flow of water coming from the Dhaleshwari River into the marshes. As a result of this action to dilute wastewater, the rivers have been labeled as organically contaminated wetlands, which is thought to be the reason for their poor quality (81).

Among the outfalls along Shitalakshya River, outfall S-6 was found to be slightly polluted (2 $\leq$ OPI $<$ 3), and outfall S-4 was observed as moderately polluted (3 $\leq$ OPI $<$ 4). **Figure 7** (polar charts) depicts that every selected outfall from Tongi Canal, Turag River and outfalls S-1, S-2, S-3, and S-5 of Shitalakshya could be classified as heavily polluted (OPI $\geq$ 4). Out of 24 outfalls in the Buriganga river, most of the outfalls are characterized by strong organic pollution (OPI $\leq$ 4) throughout the study period (**Figure 7B**). Outfall B-21 could be classified to be at the beginning of contamination (1 $\leq$ OPI $<$ 2). Furthermore, outfalls B-15, B-16, and B-19 observed as slightly polluted (2 $\leq$ OPI $<$ 3), outfalls B-1, B-13 to B-14, B-17, B-19, and B-22 to B-24 are found to be moderately polluted (3 $\leq$ OPI $<$ 4). Outfalls B-2 to B-12 and B-18 are classified as heavily polluted (OPI $\geq$ 4) (**Figure 7B**). The source

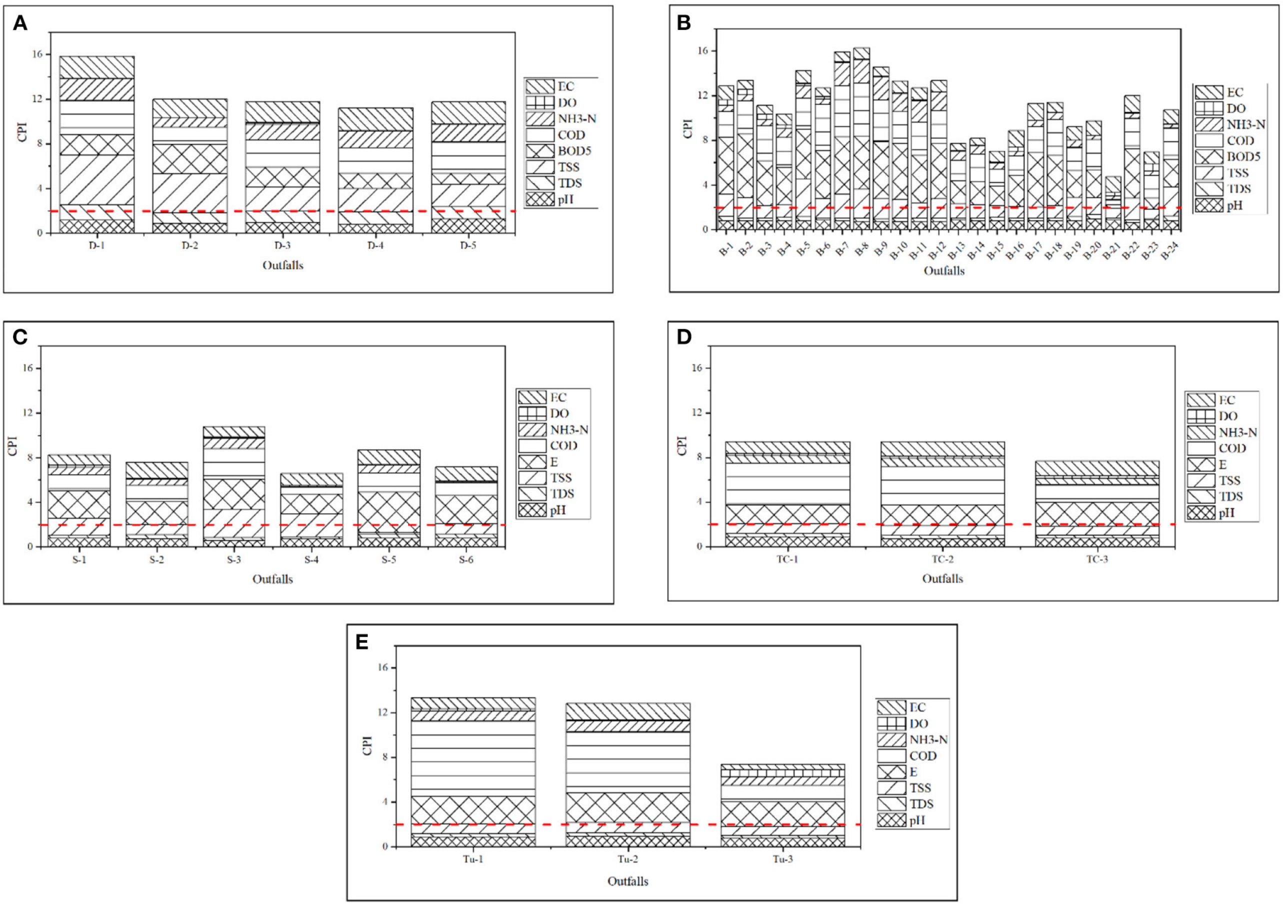

FIGURE 6 | (A–E) Assessment of CPI for the outfalls in **(A)** Dhaleshwari River, **(B)** Buriganga River, **(C)** Shitalakshya River, **(D)** Tongi Canal, and **(E)** Turag River (dotted lines indicate a severely polluted category of CPI).

of pollution for this water body includes a variety of pollutants (including household product residues and significant amounts of nitrogen and phosphorus) which are supposedly discharged on a regular basis directly into the river. Indiscriminate discharge from all sorts of sources causes the water quality of all of these rivers to be degrading. Assessment of organic pollution index (OPI) is mainly based on the concentrations of nitrate, nitrite, ammonium, and phosphate. Algae, bacteria, and protozoa require phosphorus for their metabolic development, making it a critical and limiting nutrient in ecosystems (82). Aquatic life is harmed by anthropogenic pollution that contains nitrites, phosphates, and ammonium containing product consumables.

Characterization Based on Ecological Risk Indices (E_{RI})

Hakanson developed a system for analyzing ecological risks related to toxic response indicators and pollution measurements (39). The Ecological risk indices for the outfall discharge from other peripheral rivers were also evaluated with the information gathered from different studies (83) and presented in **Table 4**. There is a downward trend in the ecological risk index (E_{RI}) for heavy metals assessed along with the Dhaleshwari river's locations, such as D-1 > D-5 > D-2 > D-4 > D-3. The calculated E_{RI} values ranged from 86.09 to 272.6 in the Dhaleshwari River. D-3, which represents the Dhalla (fish market) district, demonstrated the lowest value, while D-1, which represented the central Savar tannery area district, demonstrated the highest value. Due to the tannery's operations in leather and dying industries, there is a substantial danger of ecological destruction. According to **Table 4**, Outfalls D-1 (Savar tannery), D-5 (Nama Bazar) showed Very high risk ($200 \leq E_{RI} < 300$), and Outfalls D-3 (Dhalla, fish market), D-5 (AKS dying) showed Moderate risk ($100 \leq E_{RI} < 150$) all of which are indicating a disastrous degree of ecological risk (**Table 4**). Among the other rivers, Buriganga also observed very high risk ($200 \leq E_{RI} < 300$). The ecological risk index was very low ($E_{RI} < 100$), indicating low risk in the Shitalakshya River, Turag River, and Tongi Canal.

At each outfall, there may have been more significant concentrations of Cd, which might explain the higher E_{RI} measurements. The anthropogenic (human-induced) sources of Cd in the environment include phosphate fertilizers, non-ferrous metal mining or refining, and waste disposal (10). A large area of agricultural land surrounds Dhaka, and local people are using most of these lands to cultivate crops. Toxicity levels of Cd have

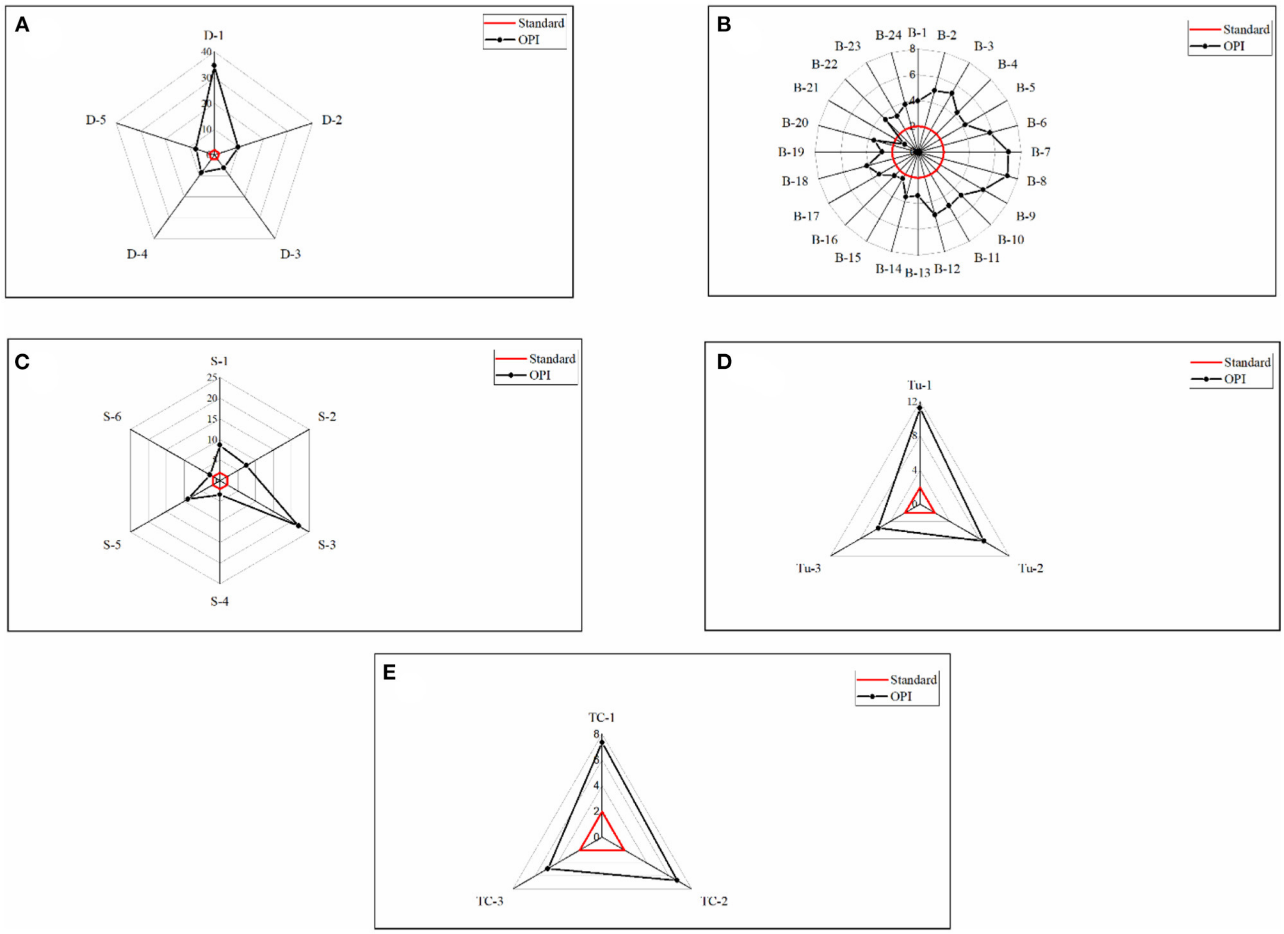

FIGURE 7 | (A–E) Assessment of OPI in the outfalls of **(A)** Dhaleshwari River, **(B)** Buriganga River, **(C)** Shitalakshya River, **(D)** Tongi Canal, and **(E)** Turag River (red lines indicate a heavily polluted level of OPI).

been found in crops and aquatic organisms. Untreated tannery waste, uncontrolled urbanization, raw effluent from various dying businesses, and leather waste along the chosen stretches are specific probable explanations for the ecological disaster.

Waste Loading Characteristics of Outfalls

The present study illustrates the waste loading estimations for the five rivers along with the outfalls locations in the waste loading map from **Figure 8** through **Figure 11**. **Figure 8** shows waste load contributions in the Dhaleshwari River. The pollution loadings were estimated based on the population density and areas of each drainage catchment from which discharges into the rivers occurred. Drainage network, population figures and unit loading figures were obtained from the Dhaka Water Supply and Sewerage Authority (DWASA) and Browder (84). Outfall D-1 contributes the most toward pollution in the present study from the Savar Tannery area with a BOD_5 loading rate of 22,043 kg/day, COD loading rate of 15,645 kg/day, NH_3-N loading rate of 6,416 kg/day, and TDS loading rate of 2,050 kg/day in Dhaleshwari River. Moreover, outfall D-3 could be characterized as the lowest polluted outfall with a BOD_5 loading rate of 2,043 kg/day, COD loading rate of 405 kg/day, NH_3-N loading rate of 166 kg/day, and TDS loading rate of 562 kg/day in Dhaleshwari River. Additionally, outfall D-4 also contribute to heavily polluted industrial discharge with a BOD_5 loading rate of 7,093 kg/day, COD loading rate of 31,190 kg/day, NH_3-N loading rate of 8,585 kg/day, and TDS loading rate of 2,450 kg/day in Dhaleshwari river.

Figures 9A,B represent the waste loading map for selected water quality parameters of the Buriganga River from 24 km of selected stretches, along with the outfall locations. **Figure 9A** depicts the waste loading from outfalls B-1 to B-12, which covered the areas of Aminbazar to Kamrangirchar Beribadh, whereas **Figure 9B** illustrate the waste loading from outfalls B-13 to B-24 which covered the areas of Ragunathpur to Fatullah (Narayanganj) along the Buriganga river. Outfall B-7 (Hazaribagh) with a BOD_5 loading rate of 5,143 kg/day, COD loading rate of 1,358 kg/day, NH_3-N loading rate of 1,001 kg/day, and TDS loading rate of 900 kg/day, contributed the highest loading among all the selected outfalls for Buriganga. Additionally, outfall B-10 (Kholamora) with BOD_5 loading

TABLE 4 | Ecological risk characterization of the peripheral rivers in Dhaka city.

Sampling outfall	E_r^i			E_{RI}	Risk grade
	Cd	Pb	Zn		
D-1	252	19.5	1.098	272.6	Very high risk
D-2	150	3.15	0.32	153.47	Considerable risk
D-3	78	7.65	0.442	86.09	Moderate risk
D-4	126	2.45	0.466	128.92	Moderate risk
D-5	228	9.85	0.858	238.71	Very high risk
Buriganga River	204	17.1	0.63	221.73	Very high risk
Shitalakshya River	15	5.55	0.624	21.174	Low risk
Turag River	48	6.7	0.93	55.63	Low risk
Tongi Canal	21.9	0.12	0.528	22.55	Low risk

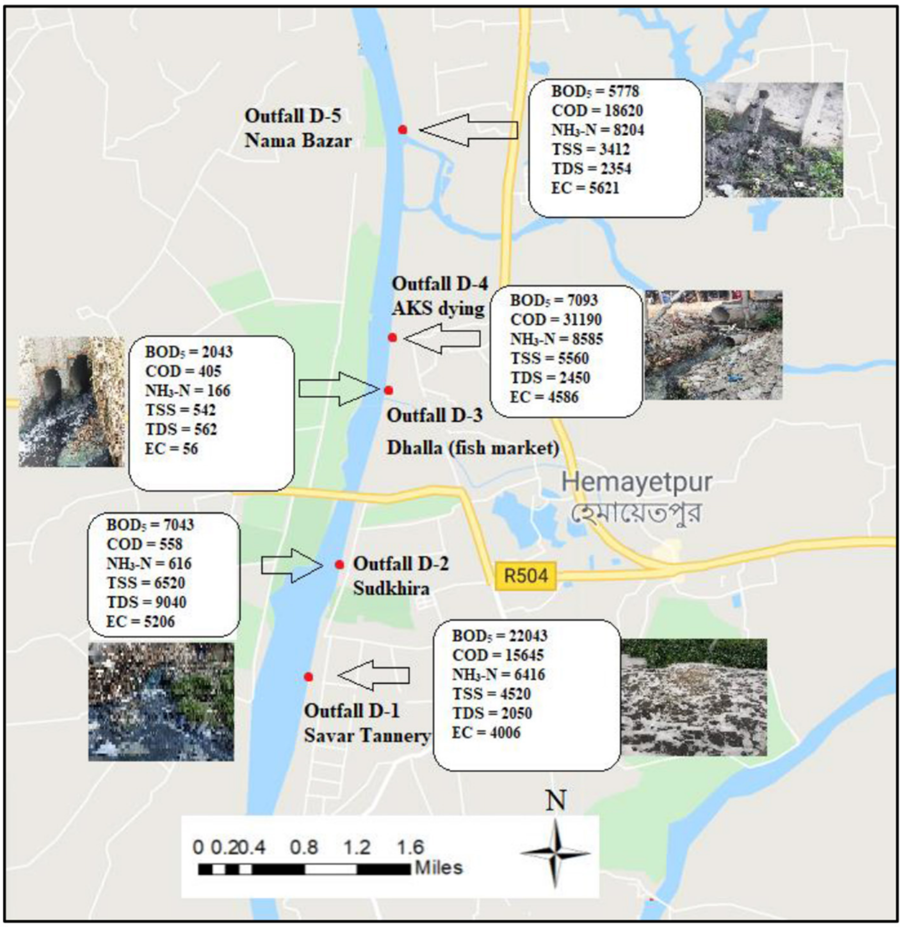

FIGURE 8 | Waste load contribution in Dhaleshwari River.

rate 4,778 kg/day, COD loading rate of 3,305 kg/day, NH_3-N loading rate of 906 kg/day, and TDS loading rate of 2,162 kg/day, contributed the second-highest loading among all the selected outfalls for Buriganga. Apart from BOD_5, COD, and TDS are also observed at significant levels between these two outfalls. Outfall B-10 discharged notable amounts of COD (1,820 kg/day), TSS (1,412 kg/day), and ammoniacal nitrogen (504 kg/day) during the study. Outfall B-8 (Hazaribagh) with a TDS loading rate of 2,162 kg/day contributed the highest load for TDS loading among all outfalls along Buriganga. In addition, among the industrial pollution sources, outfall B-24 at Fatullah, Narayanganj released the highest levels of NH_3-N (885 kg/day)

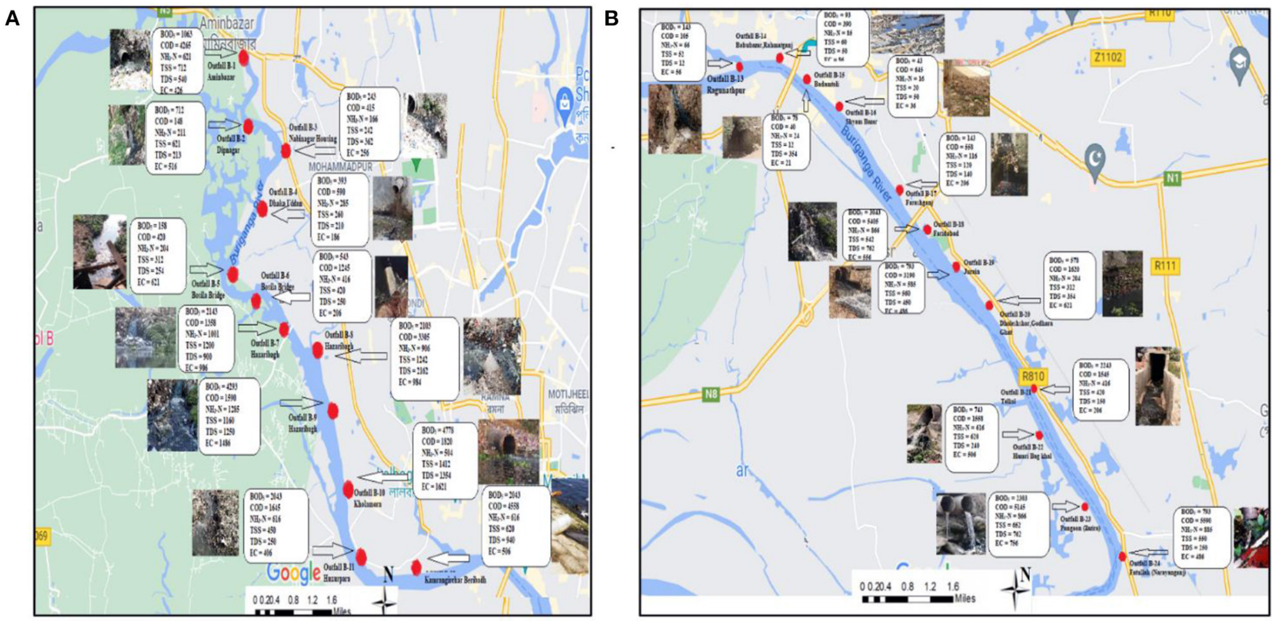

FIGURE 9 | (A,B) Waste load contribution in Buriganga River.

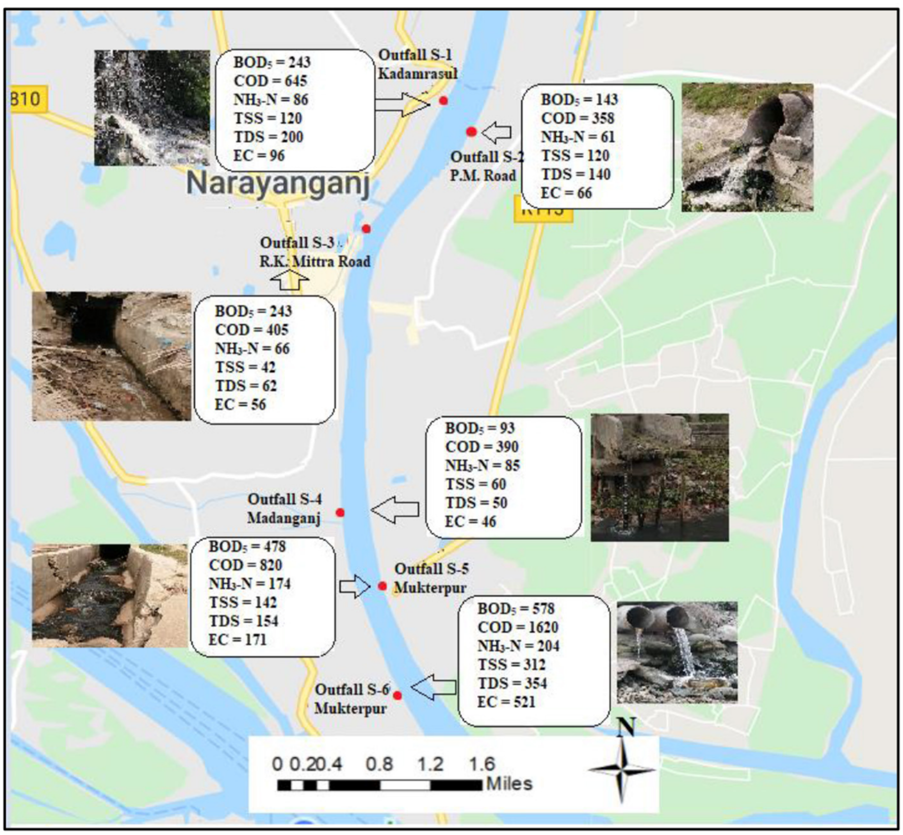

FIGURE 10 | Waste load contribution in Shitalakshya River.

and COD (5,590 kg/day) during the study as shown in **Figure 9B** along Buriganga. Similar to outfall B-4 (Dhaka Uddan), B-8 (Hazaribagh), B-9 (Hazaribagh) and B-12 (Kamrangirchar Beribadh) contributed significant amounts of NH_3-N, COD, BOD_5, and TDS in the Buriganga River. The chemical waste and dye injected from the local textile industries are likely responsible for high concentrations of COD and TSS. Overall, the waste loading data suggested that outfalls B-7 (Hazaribagh) to B-12 (Kamrangirchar Beribadh) constitute the significant pollution route along the Buriganga River.

Apart from that, Alam et al. (43) conducted an outfall study and reported only one outfall from the Hazaribagh area in Buriganga River, contributing as high as 12,245 kg/day of loading rate of BOD_5 from this individual outfall. From the present study, outfalls B-7, B-8, B-9, and B-10 fall in the same area known as the Hazaribagh area. In comparison, the current study identified four outfalls in total in the same area (B-7 through B-10) and measured BOD_5 loading rates of 5,143, 4,103, 4,293, and 4,778 kg/day for the outfalls B-7, B-8, B-9, and B-10 (respectively). Therefore, these outfalls should be considered contributing significantly in combination, especially when wastewater sources are discharged into the water next to the river bank directly from the industries. Although tanneries have shifted from Hazaribagh to Savar, there is a significant contribution from the existing and newly emerged outfalls if we consider the whole waste load in combination in the Hazaribagh area.

Figure 10 depicts waste load contributions in the Shitalakshya River. Outfall S-6, which is located at Mukterpur, observed the highest load contributed among all outfalls with a BOD_5 loading rate of 578 kg/day, COD loading rate of 1,620 kg/day, NH_3-N loading rate of 204 kg/day. In addition, Outfall S-5 which is also located at Mukterpur, observed the second highest load contributed among all outfalls with a BOD_5 loading rate of 478 kg/day, COD loading rate of 820 kg/day, NH_3-N loading rate of 174 kg/day. On the other hand, Outfall S-2, which is also located near P.M. Road, observed the lowest load contributed among all outfalls with a BOD_5 loading rate of 143 kg/day, COD loading rate of 358 kg/day, NH_3-N loading rate of 61 kg/day.

Waste loading maps of Turag River and Tongi Canal are illustrated in **Figures 11A,B** respectively, along with the outfall locations. High-intensity discharge was observed from outfall Tu-3 in Turag River with a BOD_5 loading rate of 843 kg/day and COD loading rate of 1,505 kg/day. Moreover, outfall Tu-2 also a contributed considerable amount of waste with a BOD_5 loading rate of 343 kg/day, COD loading rate of 858 kg/day and, TSS loading rate of 160 kg/day. In addition, in Tongi Canal, all the outfalls discharge an adequate amount of waste load from outfall TC-1 and TC-3. Considering above discussed facts, it is to be noted that there are many non-point (diffuse) sources entering the Buriganga-Dhaleswari- Shitalakshya-Tongi Canal-Turag River system, originating either from industries or from domestic wastes. Furthermore, these are causing the accumulation of contaminants into the aquatic ecosystem, which may create severe exposure and relatively high trophic level concentrations.

CONCLUSION

Rivers in Dhaka city, the capital of Bangladesh, undergo severe pollution threats due to ever-growing industrial establishments on the banks and indiscriminate discharge from industrial and municipal outfalls. This study performed and demonstrated comprehensive identification of outfalls along the outlying rivers of Dhaka city to highlight the pollution density along the rivers. The study also dealt with assessments of subsequent pollution status and aquatic ecological threats due to organic

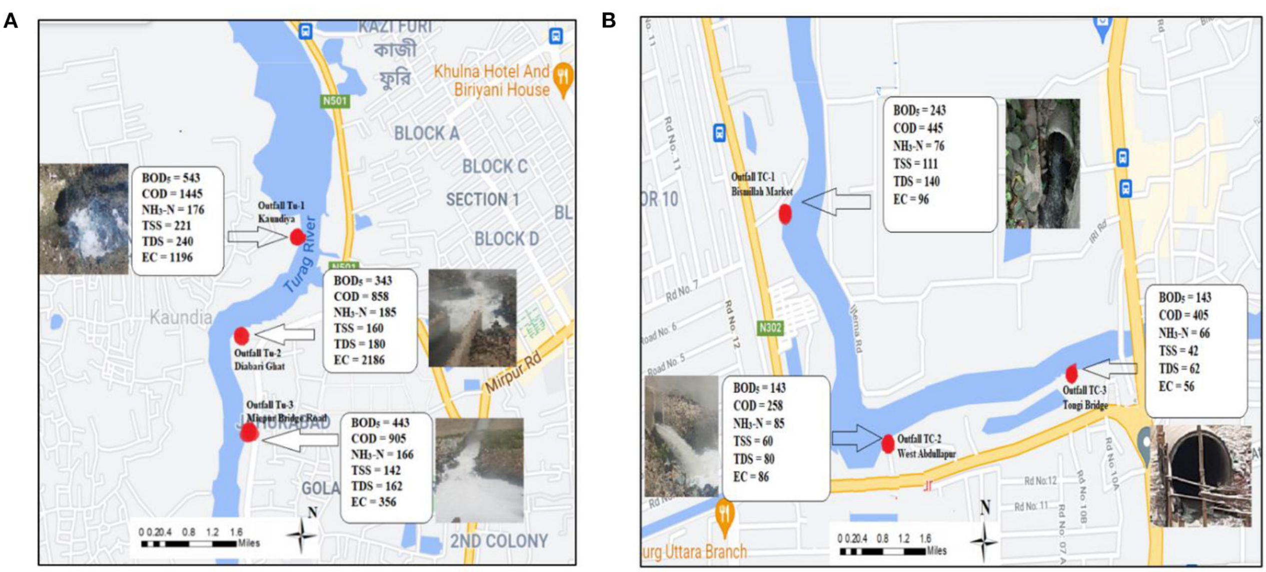

FIGURE 11 | (A,B) Waste load contribution in Turag River and Tongi Canal.

and inorganic water contaminants and heavy metals such as cadmium, lead and zinc that are discharged from the outfalls along the selected stretches of the peripheral rivers around the Dhaka watershed. Significant contamination with respect to dissolved solids and organic content was evident at each of the peripheral rivers. The concentration levels of the toxic metals in outfalls of the Savar tannery, Dhalla fish market AKS dying and Nama Bazar (D-5) areas of Dhaleshwari River, Turag River, and Buriganga river, in general, seemed to be of significant and of grave concern warranting regular and detailed investigation and monitoring. The Characterization based on Comprehensive and Organic Pollution Indices for each sampling outfalls of all the rivers in Dhaka Watershed confirmed severely polluted and heavily contaminated water. Ecological risk indices indicated comparatively Lower risk at Shitalakhshya and Tongi canal, Considerable risk at Turag, Very high risk at Dhaleshwari and Disastrous level of risk at Buriganga river. Furthermore, the waste loading estimation indicated that the outfalls located along the selected stretches of Dhaleshwari River, Amin Bazer, Hazaribagh and Faridabad area from Burganga River and Mukterpur area from Shitalakshya River contributed as the primary pollution sources. Substantial industrial waste was also released downstream near Tongi Canal and Turag River.

Surface discharge quality from outfalls, toxicity-based risk characterization and the observations for wastewater discharge revealed that nearby sources significantly impact the characteristics of surface water quality in Dhaka Watershed. If appropriate measures are not adopted soon enough, this will impact the river's ecological health with consequences toward public health. The ultimate solution to prevent the current pollution level along the river involves adequate coverage of sewer network, wastewater treatment and management. In the context of ever-increasing industrial expansion and urbanizations in Dhaka City, current research lays down the foundations for the regular monitoring of the river systems and effluents that it assimilates from the outfalls. Regular assessments of waste disposal amounts and pollutant loading contributions are required periodically in order to formulate strategies to mitigate the water pollution in Dhaka Watershed.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from [Department of Civil Engineering, University of Asia Pacific], but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. However, data are available from the authors upon reasonable request and with permission of [Department of Civil Engineering, University of Asia Pacific].

AUTHOR CONTRIBUTIONS

MI and NM: conceptualization, investigation, and writing—review and editing. MI: data collection, analysis, and writing—original draft preparation. NM: supervision. All authors have read and agreed to the published version of the manuscript.

FUNDING

This work was supported by the undergraduate thesis fund of the department of Civil Engineering, University of Asia Pacific, Dhaka, Bangladesh.

ACKNOWLEDGMENTS

The authors hereby declare that the work was part of undergraduate thesis work with support from Department of Civil Engineering at University of Asia Pacific and the Department of Soil, Water and Environment at Dhaka University in collaboration. No additional funding was received for performing any part of this study.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.880399/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers | Frontiers in Marine Science

TYPE Perspective
PUBLISHED 25 July 2022
DOI 10.3389/fmars.2022.936109

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OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Marine Biogeochemistry, a section of the journal Frontiers in Marine Science

RECEIVED 04 May 2022
ACCEPTED 27 June 2022
PUBLISHED 25 July 2022

CITATION
Hatje V, Sarin M, Sander SG, Omanović D, Ramachandran P, Völker C, Barra RO and Tagliabue A (2022) Emergent interactive effects of climate change and contaminants in coastal and ocean ecosystems. *Front. Mar. Sci.* 9:936109. doi: 10.3389/fmars.2022.936109

Emergent interactive effects of climate change and contaminants in coastal and ocean ecosystems

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The effects of climate change (CC) on contaminants and their potential consequences to marine ecosystem services and human wellbeing are of paramount importance, as they pose overlapping risks. Here, we discuss how the interaction between CC and contaminants leads to poorly constrained impacts that affects the sensitivity of organisms to contamination leading to impaired ecosystem function, services and risk assessment evaluations. Climate drivers, such as ocean warming, ocean deoxygenation, changes in circulation, ocean acidification, and extreme events interact with trace metals, organic pollutants, excess nutrients, and radionuclides in a complex manner. Overall, the holistic consideration of the pollutants-climate change nexus has significant knowledge gaps, but will be important in understanding the fate, transport, speciation, bioavailability, toxicity, and inventories of contaminants. Greater focus on these uncertainties would facilitate improved predictions of future changes in the global biogeochemical cycling of contaminants and both human health and marine ecosystems.

KEYWORDS

pollutants, impacts, knowledge gaps, ecosystem impacts, health impacts, climate change, ocean change, contaminants

Introduction

The multiple environmental stressors associated with human activities are dramatically impacting ocean systems, particularly the functions and ecological services that they provide (Doney et al., 2012). The magnitude of the cumulative impacts of multiple concurrent environmental stressors has been higher in coastal ecosystems than offshore areas, with contamination being one of the most prominent pressures (Halpern et al., 2008). The input of contaminants to the environment is of global concern when these contaminants exhibit persistence, widespread distribution and accumulation in organisms and the environment, and threatens the resilience of the Earth System processes (Steffen et al., 2015).

While successful efforts have been made to reduce specific pollutants (e.g., Stockhom Convention and Minamata Convention) in the marine environment, increased contamination continues to cause degradation with negative impacts on food security, food safety, and marine biodiversity (UN, 2021). Moreover, high technology industries are increasing the amount and variety of chemicals in use. Major technologies for decarbonization are expected to increase the inputs of new contaminants into marine waters, including the technology-critical elements (TCEs), such as rare earth elements (REE), platinum group elements (PGE), substitutes for regulated organic compounds, and nanoparticles, with undefined toxicity and fate in the environment (Lodeiro et al., 2017; Hatje et al., 2018; Dang et al., 2021; Pell et al., 2021).

The ubiquitous presence of contaminants, such as trace metals, persistent organic pollutants, plastics, and excess nutrients, in the marine ecosystems raises challenges for achieving the Sustainable Development Goal target 14.1 (to prevent and significantly reduce marine pollution of all kinds) by 2025. The relevance of ocean pollution, relative to contaminant type and impacts in ecosystems, is rapidly changing not only as a function of the magnitude, transport, exposure pathways, and proximity to sources but also because of parallel climate change (CC). Contaminants, in particular plastics, and CC are connected in different ways. Plastic production, for instance, relies on fossil fuels and contributes to the emissions of global greenhouse gases (GHG) at each stage of their life cycle (Zheng and Suh, 2019). It is estimated that over 56 billion Mt of CO_2e in GHG will be emitted between 2015 and 2050 due to plastic production (Hamilton et al., 2019).

Rising atmospheric CO_2 is one of the most critical problems of CC (Figure 1) because its effects are globally pervasive, leading to increasing ocean temperatures which in turn alter ocean circulation, drive a reduction of oxygen concentrations, retreating sea ice, rising sea-level, and altered precipitation and runoff. The increase in atmospheric CO_2, which results in a net transfer of CO_2 to the ocean, has also already caused the seawater $[H^+]$ to increase (known as 'ocean acidification'). Since the beginning of the industrial era, it is estimated that ocean acidification has caused a global mean reduction of ca. 0.1 pH units (i.e., an $[H^+]$ increase of ~1.6 nmol kg^{-1}) in the surface ocean (Fassbender et al., 2021), and a further decrease in pH of 0.3 - 0.5 units by the year 2100 in the surface ocean is possible (IPCC, 2021), posing far reaching effects on marine life (Gehlen et al., 2014; Boyd et al., 2016).

Climate change drivers and pressures, specifically warming, stratification, acidification, deoxygenation, sea-level rise, extreme events (Figure 1) display interlinkages that lead to cumulative, antagonistic and synergic interactions, which can then alter the environmental fate, transport, chemical and physical speciation, availability, toxicity of contaminant, and pathways in marine food webs (Borga et al., 2012; Avendaño et al., 2016; Kibria et al., 2021). The interaction types differ among organisms from different climatic regions, and their variability is also dependent on the type and concentration of the contaminant (Jin et al., 2021). The interactions between CC and contaminants can exacerbate global pollution and must be considered in an integrated manner to properly assess the risk and vulnerability of ecosystem structure and functions, and also human well-being. Therefore, investigating the responses of individual contaminants (e.g., change in speciation, bioavailability, and transport) to single CC forcing factors, although essential, provides an incomplete story and highlights the need for comprehensive, multi-stressors analyses to predict the impacts of these changes on coastal and ocean ecosystems, therefore, important science, policy, and societal goals. These current knowledge gaps hamper the reliable analysis and modeling of risks, vulnerabilities and impacts, and the sound management of contaminants.

Interactive effects of CC drivers and contaminants

Ocean warming that has grown substantially since the 1970s (IPCC, 2021) impacts the ocean circulation and water column stratification, affecting nutrient and contaminant supply as well as the distribution, growth, and a range of physiological rates of many species, including phytoplankton. Net primary production by phytoplankton primes the biological carbon pump and plays a key role in supporting climate regulation services, besides provision services, such as fisheries. Ocean warming is expected to decrease the primary production and the negative impacts on animal biomass can be amplified at higher trophic levels (Lotze et al., 2019). One of the main reasons is the potential shift in the essential trace metals (e.g., manganese, iron, zinc, copper, and cobalt) distribution and bioavailability that has a significant biological role in marine primary production. Iron, for instance, is a micronutrient that supports many metabolic reactions necessary for phytoplankton and bacteria. Its availability controls species composition, trophic structure, and the sensitivity of net primary production to CC (Morel and Price, 2003; Hutchins and Boyd,

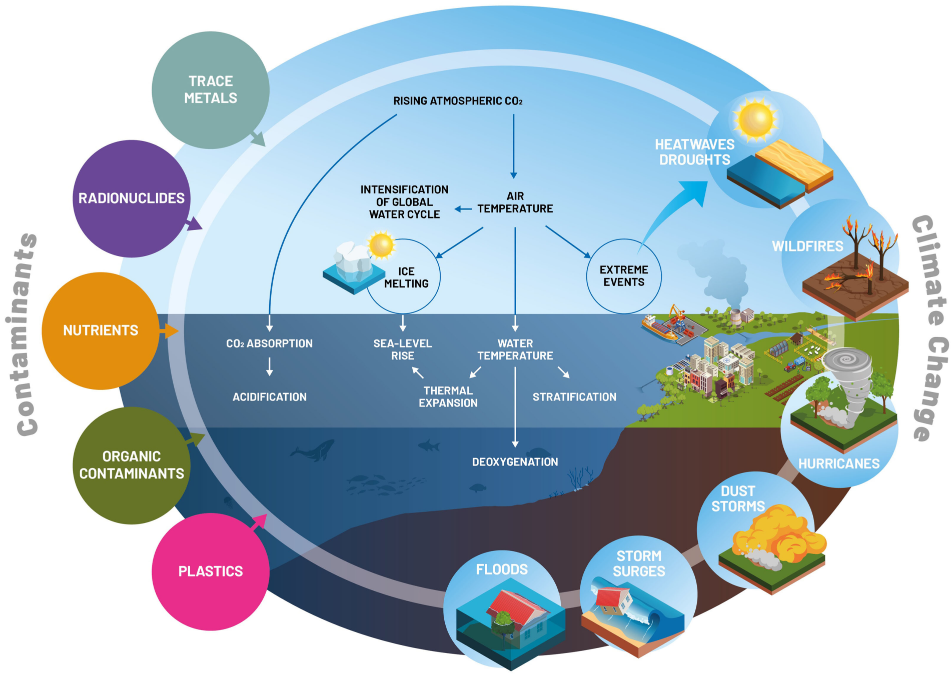

FIGURE 1
Conceptual model of the main climate change drivers and contaminants interacting and potentially exacerbating negative impacts on coastal and ocean ecosystems.

2016; Tagliabue et al., 2020). However, some essential trace metals such as Cu and Zn can also act as contaminants at high concentrations. Several studies have shown interactive effects of temperature increase and contaminants resulting, mostly, in enhanced bioaccumulation and toxicity of trace metals and organic contaminants (Baines et al., 2005; Mubiana and Blust, 2007; Delorenzo, 2015; Bates et al., 2021). The speciation of trace metals, which determines to a large extent the mobility, toxicity, and bioavailability (Tessier and Turner, 1996), is sensitive to CC drivers and responds to the environment physicochemical conditions and biotic interactions.

Additional CC drivers projected to worsen under ocean warming conditions and changes in upper-ocean stratification are associated with ocean oxygen loss and a subsequent expansion of the oxygen minimum zones (Stramma et al., 2008; Keeling et al., 2010). The increasing low oxygen conditions predicted by 2100 will drive substantial changes in water chemistry, as already can be seen in the Baltic Sea (Liblik and Lips, 2019; Limburg and Casini, 2019), Arabian Sea (Al Azhar et al., 2017), and other areas. In addition, changes are expected to ocean-climate feedbacks through the production of N_2O (Schmidtko et al., 2017) and in the biological pump strength that has a critical role in the fate and transport of carbon and persistent organic pollutants (POPs) (Galbán-Malagón et al., 2012).

Changes in the carbonate chemistry and ocean acidification (OA) resulting from the increase in CO_2 uptake by the ocean has a diverse effect on calcifying organisms, such as mollusks and pteropods, important prey groups for ecologically and economically important fish diets (Bednarsek et al., 2014). It also has negative impacts on foraminifera, corals, and phytoplankton (Doney et al., 2020), with the potential reduction in carbon export (Martin et al., 2020). Nitrogen fixation is expected to enhance by ~30%, whereas nitrification processes may be reduced by about the same factor (Wannicke et al., 2018) as a result of OA.

Thus, it affects nitrous oxide production, reducing the supply of oxidized nitrogen to the surface waters, creating an imbalance in the nitrogen cycle throughout the ocean (Beman et al., 2011). OA may also affect the production of other marine trace gases and result in further feedback to the atmosphere (Hopkins et al., 2020). Ocean acidification can have a significant impact on biogeochemical cycles and may alter the solubility, adsorption, bioavailability, toxicity, and rates of redox processes of metals in seawater (Millero et al., 2009; Gledhill et al., 2015; Stockdale et al., 2016). There is growing evidence that the combination of CC stressors and individual contaminants amplifies the negative effects produced in organisms (Nardi et al., 2017; Nardi et al., 2018; Freitas et al., 2019). On the other hand, an antagonistic effect of acidification, temperature increase, and Hg contamination has also been reported

(Sampaio et al., 2018). However, well-designed studies assessing the combined impacts of a suite of contaminants and multiple CC drivers are rare and the effects of changing pH in the interactions of metals complexed to organic ligands (Avendaño et al., 2016; Zhu et al., 2021) with marine organisms (Leal et al., 2018; Romero-Freire et al., 2020) are still lacking, although extremely important for the ocean productivity.

CC drivers operate alongside with contaminants synergistically and thus contribute to environmental change at a global scale. Moreover, some regions, such as the Arctic, are known to be more vulnerable and are therefore changing more rapidly due to the multiple co-occurring changes in temperature, freshwater content, sea ice cover, nutrient concentrations, and pH (Wassmann et al., 2011; Stjern et al., 2019; Arrigo et al., 2020; AMAP, 2021b). In addition, to these CC drivers, the Arctic ecosystems also present a high vulnerability to radionuclides contamination due to nuclear testing in the 1950s with additional inputs from accidents, weapons tests and substantial amounts of radioactivity dumped at sea with the potential for corrosion/leakage of the containers (UNSCEAR, 2000; AMAP, 2015). Further, permafrost, ice sheet, sediments, and soils can potentially become new sources of plutonium and cesium-137 to the marine environment through remobilization of radioactivity (Macdonald et al., 2003). Persistent organic pollutants (POPs) and metals (Hg, Pb, and Cd) and microorganisms released from thawing permafrost are also overlapping problems in the Arctic, whose risks are underestimated (Miner et al., 2021). There is evidence that Hg and POPs removed from the atmosphere and deposited on snow have been released to the environment at snowmelt, rapidly dispersing hazardous compounds through the atmosphere, continental and aquatic system and becoming bioavailable to be incorporated into food webs (Ma et al., 2016; AMAP, 2021a). As the Arctic warms, CC drivers may exacerbate this process beyond the biological threshold, which amplifies the significance for the understanding of the emission rate, cycling, and trends of contaminants under global changes.

Coastal vegetated ecosystems such as seagrasses, mangroves, and tidal marshes, are important sinks for contaminants, but are also environments that are particularly sensitive to CC (Bindoff et al., 2019). In particular, these environments are exposed to extreme events, like hurricanes and heat waves, which will likely increase thermal stress in these systems, and storm surges that may modify the water cycle intensity and promote contaminants remobilization from soils. It is predicted a mean global sea-level rise by 2100 of up to 1 m under a very high, but not unrealistic greenhouse emissions scenario (IPCC, 2021), resulting in higher susceptibility of small island states and coastal ecosystems to erosion and flooding. Global riverine contaminant inputs are likely to increase due to more intense and frequent precipitation and storm surges. For instance, Hg concentrations can increase up to six-fold in coastal areas following scenarios projecting up to 30 percent increased terrestrial runoff (Jonsson et al., 2017).

The understanding of the combined contaminants' response to CC drivers and how to forecast them will help policy makers to decide, for instance, whether the consumption of fish and shellfish is safe, or if areas where restoration and protection of coastal vegetated ecosystems must be prioritized to avoid the exposure of coastal communities to contaminants. For now, the scarcity of global pollution data, poor understanding of the effects and especially cumulative pressures of CC on multiple contaminants, as well as limited availability of global biogeochemical models are undermining projections and hampering sound pollution management. It will be necessary to increase our knowledge from laboratory, ecosystem-based field and process studies, as well as modelling, to have an overarching international action to facilitate and foster broad bidirectional science-policy interactions. The synergistic effects of various CC drivers are still mostly unexplored and demand urgent research studies (Cabral et al., 2019; Arrigo et al., 2020; Jin et al., 2021; Kibria et al., 2021).

We call on the international community to draw their immediate attention on these knowledge gaps and recommend to address appropriate research questions to ensure a systematic understanding of the effects of the complex interplay between contaminants and CC drivers on marine ecosystems. This knowledge will contribute to informed decision-making, following the Sustainable Development Goals (SGD) during the United Nations Decade of the Ocean Science.

Important knowledge gaps

There have been reviews of the impacts of CC on marine contaminants (Cabral et al., 2019; Kibria et al., 2021). Nevertheless, the available knowledge is limited to mostly laboratory studies that tested the effects of a single CC driver by one or more contaminants. The limited data on multiple concurrent CC drivers and their interaction with contaminants jeopardizes the construction of more generic patterns and models for predicting changes in biogeochemical cycles and their impacts on marine ecosystems. After reviewing the literature, we identified that the major knowledge gaps are:

1. The patchiness of the data on the spatial distribution of contaminants (nutrients, metals, radionuclides, and organic compounds), temporal trends, and associated uncertainties for the coastal and open ocean, especially in the southern hemisphere, has prevented investigators from reaching solid conclusions and assessments of exposure scenarios driving impacts to ecosystem integrity.
2. The complex mixture of contaminants in marine environments, coupled with the fact that even at low concentrations those contaminants can be toxic, poses

the need to develop analytical capabilities on a global level. This has also to consider the additional challenges associated with the increasing number of emerging contaminants (e.g., REE, PGE, pharmaceuticals, personal care products) entering the environment (Pedreira et al., 2018; Pichler and Koopmann, 2019; Pell et al., 2021; Borgå et al., 2022).

3. The need to develop well-designed laboratory and field experiments to test the interactions and synergies between multiple contaminants (e.g., changes in chemical speciation, abiotic and biotic removal processes, pathways in food web) and combined CC drivers on various organizational levels (individual to ecosystem). Climate change-contaminants sensitivity and vulnerability analyses are needed.
4. State-of-the-art models that integrate both CC and contaminants are needed to predict changes in the distribution, fate, and transport of contaminants in response to the CC scenario and forecast interactions between contaminants and humans.
5. Innovative, cross-border solutions to prevent the input of contaminants to marine ecosystems and mitigate their combined impacts associated with CC.

The way forward

To address the backdrop of the knowledge gaps, we call for a coordinated effort to assess the interaction between and impacts of CC on contaminants in marine environments. This endeavor should have an inclusive scope and promote field studies, including the definition of baseline levels in areas that haven't yet been explored, monitoring studies to evaluate long term trends (gaps 1 and 2), and process studies in specific regions to understand and predict the consequences of interactive effects between contaminants and CC in the chemistry and ecology of coastal and ocean systems (gap 3). CC-induced contaminant sensitivity/vulnerability in terms of persistence, bioaccumulation potential, and toxicity of organic and inorganic contaminants must be evaluated and modeled to predict and minimize future risks for humans and ecosystems. Such an effort will require support and building of capacity to deliver the necessary geographic scope (gap 1). Although our objective here is not to identify all possible research questions that need to be addressed, some points deserve attention. Land-based sources and hotspot reservoirs of contaminants (e.g., mangroves in the tropics, and Arctic ecosystems) in combination with regionally specific hydroclimate projections will determine plausible trajectories of marine pollution over the coming decades and need to be investigated. Expected increases in river flows will make rivers priority sources of contaminants (chemicals and plastics). Enhanced river fluxes (and flash-flood events) and sea-level rise will also promote the remobilization of litter and contaminants accumulated over time. Subsistence communities across low-lying coastal areas and specifically Small Island Developing States (SIDS) are particularly vulnerable. The impact of multiple CC stressors and contaminants will affect biodiversity, ecosystem resilience, and shellfish/fish industries due to changes in the speciation, toxicity, and bioavailability of contaminants. We still don't know which groups of contaminants are more likely to be most affected and become more toxic and deleterious for the marine food web and human health. Modeling exercises and combined model-data syntheses (gap 4) will help to address these critical issues providing a framework for quantifying the net CC and pollutant impacts on marine systems and to identify priority areas and strategies to minimize pollution impacts (gap 5) to maintain sustainable uses of the ocean. This approach could also help to prioritize contaminant classes that needs urgent attention, regional patterns, or effect trends (Persson et al., 2022).

Scientists are confident predicting that climate change is going to intensify and exacerbate extreme events (IPCC, 2021). Some of these changes are already happening, as seen in the unprecedented number and magnitude of extreme events of the last decade. Extreme events, such as floods, can promote the transport and translocation of chemical contaminants (Horowitz et al., 2014) and plastics (Ford et al., 2022) to large areas, exposing organisms to high concentrations of contaminants for an extended period (Barber et al., 2017; Izaditame et al., 2022), potentially causing more ecological adverse effects and health risks through various exposure routes, including bioaccumulation in the food web (Och et al., 2014; Crawford et al., 2022).

A general failure to achieve the integrated knowledge and management of human pressures on marine systems is increasing risks to the benefits that people draw from the ocean in terms of food security, material resources, human health and well-being, coastal safety, and the maintenance of key ecosystem functions. The scarce information on species and ecosystem-level threshold, tolerances, and tipping points for various CC drivers mean that predictions of risk, vulnerability, and responses are difficult to make, and confidence is low. This highlights the urgency for a better understanding of the synergies between contaminants and CC and the challenges to develop effective remediation and conservation of coastal and ocean ecosystems. This will only be achieved through fostering a different frame of interdisciplinary research including improved socio-ecological models and integrated ecosystem assessments, together with better integration of stakeholders (Holsman et al., 2017). A key next step will be to compile global databases of empirical measurements and modeling information on the effects of CC on contaminants for better informed predictions of future impacts, to support ecosystem-based planning decisions, to identify where pressing mitigation efforts are most needed, to plan proactive and more preventive management practices, and to monitor progress towards sustainable management actions.

Aware of this, the Join Group of Experts on the Scientific Aspects of Marine Environmental Protection (GESAMP) Working Group 45 (http://www.gesamp.org/work/groups/wg-44-ghg-impacts-on-contaminants-in-the-ocean) in a joint effort is systematically reviewing existing literature on the effects of changes in ocean physics and chemistry on the speciation, cycling, fate, transport, and bioavailability of trace metals, organic pollutants, radionuclides, and nutrients to identify knowledge gaps, make recommendations, and planning for future research directions. The understanding of CC drivers and contaminants interactions depends on the collaboration of the scientific community and other stakeholders to produce sound information to subsidize the protection of human health, marine ecosystems services, and functions.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Authors contributions

The production of the manuscript was coordinated by VH, who also prepared the first draft. All authors contributed to the content, structure and framing of the article. All authors contributed to the article and approved the submitted version.

Acknowledgments

All authors are part of the Working Group of Experts on the Scientific Aspects of Marine Environmental Protection (GESAMP WG45 - Climate Change and Greenhouse Gas Related Impacts on Contaminants in the Ocean), supported by the International Atomic Energy Agency (IAEA), the United Nations Environmental Program (UNEP), International Oceanographic Commission (IOC-UNESCO), the World Meteorological Organization (WMO), and the International Maritime Organization (IMO).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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frontiers | Frontiers in Public Health

TYPE Original Research
PUBLISHED 11 August 2022
DOI 10.3389/fpubh.2022.963257

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OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Environmental health and Exposome, a section of the journal Frontiers in Public Health

RECEIVED 07 June 2022
ACCEPTED 25 July 2022
PUBLISHED 11 August 2022

CITATION
Chen Y, Wang J, Xu P, Xiang J, Xu D, Cheng P, Wang X, Wu L, Zhang N and Chen Z (2022) Antidepressants as emerging contaminants: Occurrence in wastewater treatment plants and surface waters in Hangzhou, China. *Front. Public Health* 10:963257. doi: 10.3389/fpubh.2022.963257

Antidepressants as emerging contaminants: Occurrence in wastewater treatment plants and surface waters in Hangzhou, China

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Aims: Antidepressants have aroused wide public concern due to their widespread presence in water and their harm to human health and environment. This study was designed to evaluate the contribution of wastewater treatment plants (WWTPs) to the presence of antidepressants in the surface water.

Methods: Data was evaluated by analyzing water samples collected from the influent, effluent, upstream and downstream of the WWTPs on the rivers of interest in Hangzhou, Zhejiang Province, China. Besides, the study also assessed the impact of the release of antidepressants from WWTPs to the surface water on the drinking water. An automatic solid-phase extraction combined with ultra-high performance liquid chromatography-tandem triple quadrupole mass spectrometry (UPLC-MS/MS) was used to detect antidepressants.

Results: The most abundant compound was venlafaxine, followed by citalopram, sertraline, and fluvoxamine with concentrations between 0.6 and 87 ng/L. Antidepressants showed maximum concentrations at the effluent outlets of the WWTPs, and greater concentrations were found downstream than upstream of the WWTPs in Qiantang River. The results of source water and finished water showed that the detection concentration was lower than the detection limit of the method.

Conclusions: The less impact of the release of antidepressants from WWTPs to the surface water on the drinking water was identified. Nevertheless, these compounds were hardly removed by wastewater treatment processes. Thus, their risks deserve close attention.

KEYWORDS

antidepressants, occurrence, wastewater treatment plants, surface water, drinking water

Background

Antidepressants are a group of drugs used to treat psychiatric disorders (1), which can be classified as tricyclic antidepressants (TCA), serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and monoamine oxidase inhibitors (MAOIs) according to their mechanisms of action (2). The most frequently found psychiatric drugs were antidepressants such as fluoxetine, carbamazepine, citalopram, sertraline, and trazodone in concentrations of up to 2.0 ng/ L (3). In recent years, antidepressants have acquired much attention because of their occurrence in the environment water and aquatic organisms, as well as their potential harm to ecosystems and human wellbeing. Some research (4–7) suggests that the toxicological effects of antidepressants in different organisms, primarily fish, aquatic plants and mammals included changes in weight, pathological changes in brain, heart, and kidney, decrease in sperm dose (8). Antidepressants are introduced to the environment because of a variety of human activities. Much of the active ingredients in antidepressants which acted on humans are excreted to the environment, even some drugs are discarded without being used. (8) Most of them do not have 100% removal efficiency in WWTPs (9).

China has the largest population and the most pharmaceutical manufacturers in the world. The data from some major Chinese cities show that the total annual cost of antidepressants in 2014 was 2.679 billion RMB. The consumption sum of antidepressants was increased by years in 11 hospitals from Zhejiang during 2013–2017, and increased from 3,235,200 RMB in 2013 to 4,569,100 RMB in 2017; The top 3 drugs by consumption sum were fluoxetine,duloxetine,and venlafaxine; consumption sum of escitalopram accounted for a larger increase (proportion ration increased from 8th place in 2013 to first place in 2017). In China, antidepressants have been detected in Huangpu River, Dongting lakes, and Beiyun River (10, 11) with concentrations ranging from 3.2 to 22.9 ng/L. Occurrences of these antidepressants in the ambient river, water environment have been reported in the USA, France, Brazil, Canada, Australia, and the Czech Republic. Antidepressants were detected in rivers in concentrations ranging from 0.2 to 641 ng/L (12–16). As reported in the literature, antidepressant drugs have been found in several water bodies spanning different continents with a concentration ranging from Limit of Detections (LODs) to 326 ng/L in the influent and LODs to 374 ng/L in the effluent of 19 wastewater plants around metropolitan areas in Europe, Asia, America as well as Africa (17–20). Moreover, the concentrations of citalopram and fluoxetine detected in drinking water in the UK were ranging from 2.26 and 2.80 and 0.27 ng/L, respectively (21).

Zhejiang is one of the largest commercial and financial centers in China. Hangzhou, the capital of Zhejiang province, is a city with a population of more than 10 million. The dense population makes Hangzhou a large antidepressants consumption region in China as well as in the whole world. Qiantang River is the largest river in Zhejiang Province. It starts from Majinxi, the upstream of Qujiang River in the south. The river is 522.22 km long from its source, flowing through the southern part of Anhui province and Zhejiang Province, with a basin area of 55,058 square kilometers, and emptying into the East China Sea through Hangzhou Bay. Qiantang River system is a representative water body that has been impacted by urbanization in Hangzhou, Zhejiang province, which receives continuous effluents from industrial and/or sewage treatment plants. It has undergone serious deterioration in water quality in the recent years. Water and clean habitat are fundamental human needs. The Hangzhou section of Qiantang River is an important source of drinking water in Hangzhou. At the time of the study, the status of antidepressants in the water was unknown. In view of this, the aim of this study was to (i) examine the occurrence and distribution of antidepressants in the aquatic environment of Hangzhou and (ii) elucidate possible sources of those target antidepressants. The resulting data will be useful in enriching research on emerging pollutants in aquatic environments.

Methods

Study sites and sampling

We collected one samples of sewage from the inlet and outlet of the two main WWTPs in Hangzhou. The sewage was collected by a 2.5 L deep water sewage collector. Sample volumes of 1 L were added into pre-cleaned glass bottles. Since Qiantang River is the main receiving water body for treated and untreated wastewater in Hangzhou *via* tributaries and the sewerage systems, antidepressant pollution in the Qiantang River could potentially be widespread, especially near the WWTPs. The six grabbed samples (XA, XB, XC, SA, SB, SC) were taken from the main stream of the Qiantang River in late November 2020 (sampling points are georeferenced in Figure 1A). River waters were collected 0.5-m deep near the margin of each river (∼50 cm) using a mat high-density polyethylene bottle pre-washed with ultrapure water. Grab surface water samples were collected at a 0.5-m depth in Qiantang River, ∼0.5, 1, 2 km upstream and downstream of the WWTP1 effluent position of the river. The three samples (SD, SE, SF) were source waters from the three Drinking Water Treatment Plants (DWTPs) located in the Qiantang River. These samples were taken on a boat at 1.0-m depth in the Qiantang River using an amber glass bottle about 20 km upstream of WWTP1 (sampling points are georeferenced in Figure 1B). Three samples of source water and three samples of finished water from three water plants on Qiantang River as the source water were collected and tested for eight kinds of

10.3389/fpubh.2022.963257

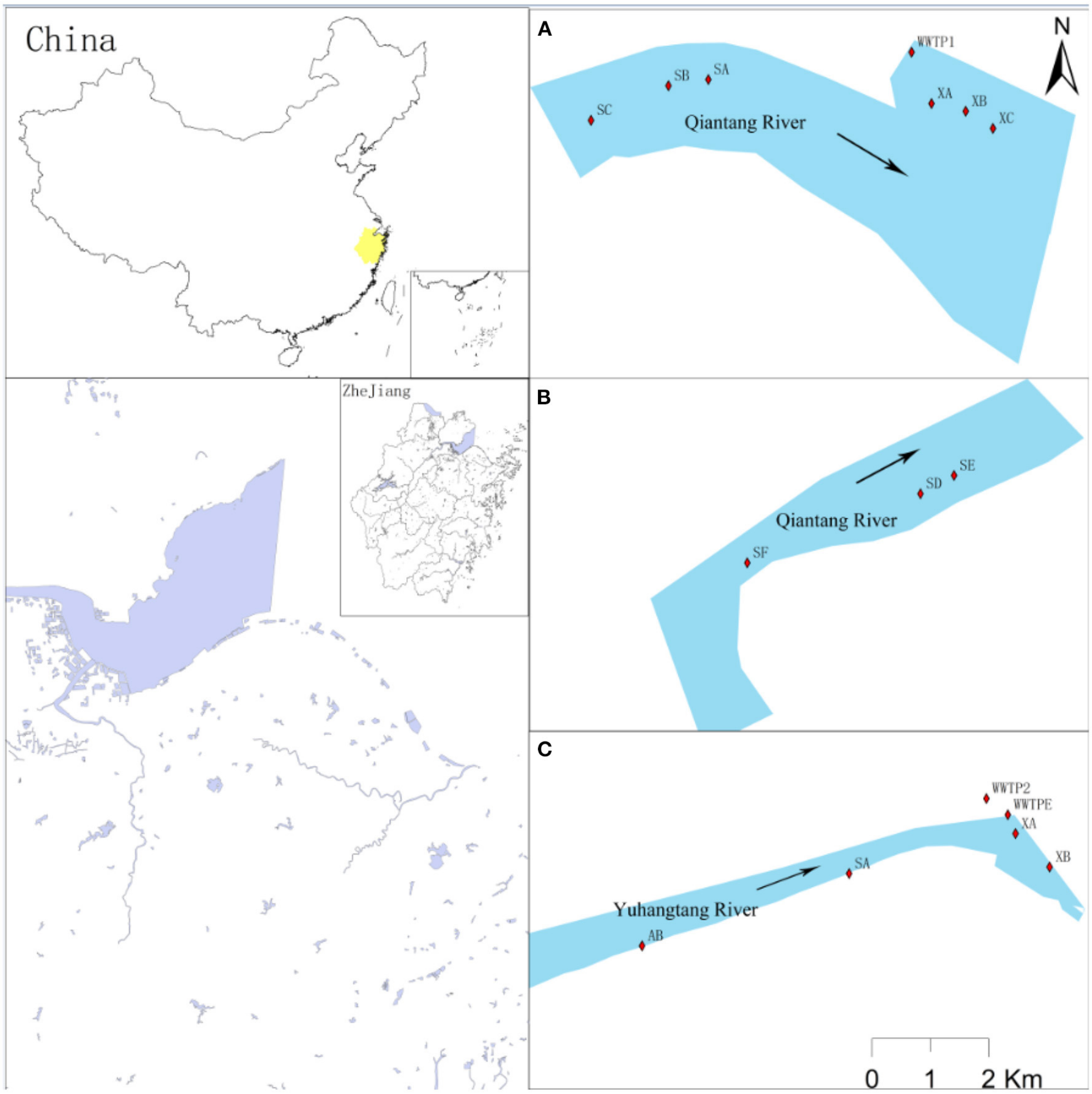

FIGURE 1
(A) Sampling locations in Qiantang River and WWTP 1. S(A,B,C) upstream of WWTP1, X(A,B,C) downstream of WWTP1. **(B)** Sampling locations in Qiantang River. S(D,E,F) locations of source water from the three DWTPs. **(C)** Sampling locations in Yuhangtang River and WWTP 2. S(A,B) upstream of WWTP2, X(A,B) downstream of WWTP2. WWTPE effluent of WWTP2

antidepressants. Sample volumes of 1 L were added into pre-cleaned glass bottles. Before collection, the bottles were pre-rinsed with sample water again. All glassware used in this study was thoroughly washed with detergent at the laboratory.

The other five samples (YSA, YSB, YK, YXA, YXB) were collected at the beginning of November 2020 (sampling points are georeferenced in Figure 1C). These samples were taken at 0.5-m depth in Yuhangtang River and 1, 2 km upstream and downstream of the ChengXi wastewater treatment plant effluent, respectively. One liter of the sample water was collected in a pre-cleaned amber glass bottle. All these samples were stored in dark at 4°C for <24 h and were extracted as soon as possible in order to minimize the degradation. Once in the laboratory, all the samples analyzed in this study were adjusted to pH value 2.5 with hydrochloric acid and then filtered with GF/C (Whatman) glass fiber filter. During sample collection, a global positioning system (MG 758; Un Strong) was used to locate the sampling sites.

Chemicals and reagents

Standards of eight antidepressants, paroxetine (Par), citalopram (Cit), and clomipramine (Clo) were purchased from Chiron (Norway). Amitriptyline (Ami), fluoxetine (Flu), venlafaxine (Ven), Sertraline (Ser) and trimipramine (Tri) were produced by the Shanghai Anpel Scientific Instrument Corporation. The physicochemical properties of the investigated compounds are shown in Table 1. The internal standards (IS) were obtained from Toronto Research Chemicals Dr. E. HPLC-grade methanol and acetonitrile were purchased from Merk (Darmstadt, Germany), and HPLC-grade formic acid was purchased from ACS Corporation (US). The ultra-pure water was produced by Milli-Qunit (Millipore, USA). Other chemicals and solvents were of analytical grade provided by Shanghai Anpel Scientific Instrument Corporation, Shanghai Lingfeng Reagent Corporation, Guoyao Corporation, and Guangdong Guanghua Reagent Corporation.

Solid phase extraction procedure

The solid phase extraction (SPE) procedure referred to EPA 1694 extracted under acidic (pH 2.0 ± 0.5) conditions for determination of compounds upper than 200 kinds by auto-solid phase extraction. Samples were first filtered by GF/C glass filter, and then 125 mg EDTA-Na4 was dissolved to 250 ml filtered liquid and adjusted to pH 2.5. Next 10 ng IS was added. An Oasis HLB (500 mg, 6 ml) was used for concentration and purification. First, 6 ml methanol were used for activation SPE column and 6 ml ultra-pure water for equilibrium. Then, samples were loaded at 5 ml/min and washed using 5% methanol aqueous, and the SPE column was dried with nitrogen. Then, 10 ml methanol was used for elution, and the elution solvent was evaporated to 1.0 ml under a gentle nitrogen stream at 40°C and filtered using a glass filter to a 2 ml sample bottle for detection. The accuracy of the method was performed by sample spike at three concentration (10, 20, and 100 ng/L) in source water, the Methodological Validation data were listed in Table 2. Ultra-pure water with spike of eight antidepressants was detected for quality control. In addition, every kind of samples (source water, influent water, finished water) also detect with parallel samples and spike samples in every 10 samples.

Liquid chromatography–mass spectrometry

A 1-µl aliquot of each sample extract was separated using a Waters I-Class ultra-performance liquid chromatograph coupled to a Xevo TQ-S triple quadrupole mass spectrometer. A Waters UPLC Cortecs C18 reversed-phase column (150 mm × 3.0 mm, 1.6 µm) was used for the separation of compounds. The column was maintained at 30°C at a flow rate of 0.3 ml/min. Mobile phase A was 0.1% formic acid aqueous, and mobile phase B was 0.1% formic acid acetonitrile. The gradient (%B) is as follows: 0∼0.5 min, 5%; 10 min, 35%; 16 min, 60%; 18 min, 75%; 19∼20 min, 100%; and 20.1∼23.5 min, 5%. To get the best detection signal for all basic analytes, the mass spectrometer was operated in electro-spray ionization (ESI) positive ion mode and multiple reaction monitoring (MRM) transition mode. Following the selection of the parent ions, daughter ions were obtained at a series of collision energies and selected according to the fragmentation that produced a useful abundance of fragment ions. The most abundant daughter ion was used for quantification and the second most abundant daughter ion for reliable identification. The following optimized parameters were used for the quantification of all compounds: drying gas temperature, 500°C; drying gas flow, 800 L/h; cone gas flow, 150 L/h; capillary voltage (+), 0.5 kV. The optimal LC-MS/MS parameters chosen for the identification and quantification of the eight antidepressants and five internal standards are listed in Table 1.

Statistical analyses

The sampling distributions were labeled with ArcGIS10.2. Two parallel samples were taken from each sampling point, and the mean values were taken for analysis. Microsoft Excel 2013 was used to make tables and figures.

Results and discussions

Occurrence of antidepressants in influent and effluent of WWTPs

Six sampling sites were selected covering the Qige and Chengxi WWTPs. These include the import and export sewage from the first and third phase of Qige and west of the city sewage treatment plants as shown in Figure 2. Four kinds of antidepressants were detected. Venlafaxine was detected in the highest concentrations (50.25 ± 1.05 ng/L) in all wastewater samples [median ± interquartile range (IQR)]. It was found in much higher concentrations than other antidepressants. Citalopram, sertraline, and fluvoxamine came next. The highest concentration of citalopram and sertraline was 5.75 and 4.25 ng/L, respectively, detected in the Import and export of WWTP1. SSRIs have been found in several water bodies spanning different continents,the average influent concentration of SSRIs in 11 WWTPs around metropolitan areas in the Pacific Coast and the Caribbean Lowlands was 600 ng/L and the average effluent concentration was 100 ng/L (8). In Canada, citalopram has been detected in five WWTPs, with concentrations in the influent and effluent ranging from 136 to 326 and 86 to 223 ng/L, respectively (14). Venlafaxine has been found in the United States at concentrations ranging from 210 to 220 ng/L

TABLE 1 List of the optimized MRM parameters and the selection of IS.

Compounds	Retention time (min)	Precursor ion (m/z)	Cone voltage (V)	Quantification trace	Collision energy (eV)	Identification trace	Collision energy (eV)	Selection of IS
Amitriptyline	10.61	278	45	190.9	25	232.9	20	Amitriptyline-D3
Venlafaxine	7.88	278.2	20	120.8	35	260	10	Venlafaxine-D6
Duloxetine	10.38	298	30	153.8	5	183	20	Duloxetine-D7
Sertraline	11.16	305.9	35	158.7	30	274.7	10	Sertraline-D3
Fluoxetine	10.96	310.3	30	148.5	5	43.8	5	Sertraline-D3
Fluvoxamine	10.19	319.2	15	145	40	199.9	25	Sertraline-D3
Citalopram	9.21	325.2	10	233.9	25	262	20	Citalopram-D6
Paroxetine	9.88	329.9	10	150.9	25	192	35	Citalopram-D6
Amitriptyline-D3	10.59	281	45	191	25			
Venlafaxine-D6	7.85	284.1	20	121	35			
Duloxetine-D7	10.38	305.1	30	154	5			
Sertraline-D3	11.15	308.9	35	158.8	30			
Citalopram-D6	9.18	331	10	233.9	25			

TABLE 2 Regression equation, coefficient, limit of detect (LOD), limit of quantification (LOQ), recovery and relative standard deviation (RSD) of eight antidepressant drugs ($n = 3$).

Compounds	Equation	r	LOD (ng/L)	LOQ (ng/L)	Spike at 10 ng/L		Spike at 20 ng/L		Spike at 100 ng/L	
					Recovery (%)	RSD (%)	Recovery (%)	RSD (%)	Recovery (%)	RSD (%)
Fluoxetine	$Y = 1.11288X + 0.469408$	0.99215	1.2	4	113.4	5.18	103.2	4.17	97.5	2.52
Paroxetine	$Y = 0.113207X + 0.02586$	0.99655	1.2	4	80.1	6.83	84.3	3.46	89.7	3.15
Citalopram	$Y = 0.357815X\text{-}0.028035$	0.99844	0.3	1	104.5	3.17	99.5	2.45	98.8	1.63
Sertraline	$Y = 7.84844X + 0.362173$	0.99882	1.2	4	95.1	3.09	97.8	2.88	101.1	1.27
Venlafaxine	$Y = 0.495962X + 0.015519$	0.99802	0.6	2	107.5	4.03	104.8	3.65	99.7	2.10
Amitriptyline	$Y = 2.03739X + 0.051898$	0.99898	1.2	4	94.1	3.12	96.7	2.16	99.4	1.08
Duloxetine	$Y = 0.39801X + 0.091894$	0.99723	3	10	104.3	3.89	102.5	3.22	98.6	2.02
Fluvoxamine	$Y = 2.52171X + 0.26504$	0.99668	1.2	4	86.8	5.62	89.3	4.66	92.1	3.17

in two WWTPs (22). In Beijing, China, venlafaxine was detected in three different WWTPs at concentrations of 31.8, 63.7, and 30.3 ng/L, respectively (23). The main types of antidepressants detected in this study were consistent with those reported in the literature above, and the concentrations were lower than those reported in other countries while consistent with domestic reports. The concentrations of antidepressants in the effluent were close to or even higher than those in the influent. The summary of concentrations of antidepressant drugs in the Import and export of WWTPs was listed in Table 4, the results in this study were consistent with those reported domestic and international, demonstrating that these compounds were hardly removed by wastewater treatment processes? Thus, their risks deserve close attention.

At present, there is little research on antidepressants in WWTPs in China. Only one report cited above was found. This study expanded data on antidepressant levels in WWTPs.

Occurrence of antidepressants in Qiantang River and Yuhangtang River

Surface water was collected ~1.0, 1. 5, 2.0 km upstream and downstream of the two WWTPs' sewage draining exits. The sample point locations are shown in Figure 1. The results are shown in Figure 3. Three kinds of antidepressants were detected, and the levels were generally in the range of a few tenths to tens of ng/L. Venlafaxine was detected in all samples with the highest levels in the sewage draining exit of WWTP2, where the concentration was 54.2 ng/L. The venlafaxine level is higher than Huangpu River, Dongting River, and Beiyun River in China, which range from 1 to 22.9 ng/L (10, 11, 30), but lower then Leca River in Portugal (3) and Guayllabamba River in Ecuador, where venlafaxine was reported in concentrations of up to 55,000 ng /L (31). The summary of concentrations of antidepressant drugs in WWTPs in other countries was listed in Table 3. Citalopram was also detected in the two rivers, with concentrations ranging from <LODs to 4.8 ng/L, with the highest levels in the sewage draining exit of WWTP2. Sertraline was detected only in Yuhangtang River, with concentrations ranging from <LODs to 1.9 ng/L. The trend of antidepressants concentration at different sampling points in the same river is shown in Figure 3. The concentration of antidepressants was maximum at the sewage disposal outlet of the WWTPs and then decreased progressively along the upper and lower reaches of the river. To better understand the effect of WWTPs on the environment, we compared the concentrations of antidepressants upstream and downstream of rivers. The concentrations of citalopram and venlafaxine were higher downstream of Qiantang River than upstream, the sampling locations in the abscissa follow the river flow from upstream to downstream of Qiantang River was shown in Figure 3A. Significantly, an increase tread was observed in the level of antidepressants from upstream to downstream of the WWTPs along the river of SE-SD-SC-SB-SA-XA-XB-XC, indicating WWTPs are sources of antidepressants into the environment. The WWTPs might be source of river basin pollution. While the concentration of venlafaxine was higher upstream of Yuhangtang River than downstream. The other two antidepressants concentrations were similar upstream and downstream in Yuhangtang River which was shown in Figure 3B. There are two sewage outlets in Yuhangtang River, one of which has been identified by us, and the other is upstream of the sewage outlet, but the location is not clear. This may be

TABLE 3 Summary of concentration of antidepressant drugs in WWTPs.

Anti depressants	Location	Source	Concentration (ng/L) Influent	Concentration (ng/L) Effluent	Reference
Fluoxetine	Costa Rica	WWTP	~60	~100	(24)
	Canada	WWTP(5)	9~26	7.6~20	(14)
	China	WWTP(3)	0.6~4.25	0.3~1.05	This study
Sertraline	USA	WWTP		3	(25)
	Canada	WWTP(3)	12~26	8.1~16	(14)
	China	WWTP(3)	0.6~1.5		This study
Citalopram	Canada	WWTP(5)	136~326	131~223	(14)
	China	WWTP(3)	0.6~3.2	0.3~7.6	This study
Imipramine	Spain	WWTP		3	(26)
	China	WWTP		10.9	(23)
Venlafaxine	Portugal	WWTP	39.4~66.7	327~374	(27)
	USA	WWTP		210~220	(22)
	China	WWTP(3)	40.25~80.4	21~87	This study

TABLE 4 Summary of concentration of antidepressant drugs in surface waters.

Anti depressants	Location	Source	Concentration (ng/L)	Reference
Fluoxetine	Brazil	Santos Bay	0.58	(27)
Citalopram	Czech Republic	Blanice River	24	(16)
	China	Qiantang River	~4.8	This study
Venlafaxine	China	Beiyun River	22.9	(28)
	Portugal	Leça River	641	(3)
	South Africa	Jukskei River	0.2~4.0	(29)
	Portugal	Lis River	159	(27)
	China	Qiantang River	~54.2	This study
Sertraline	China	Huangpu River	3.2	(30)
	China	Yuhangtang River	~1.9	This study

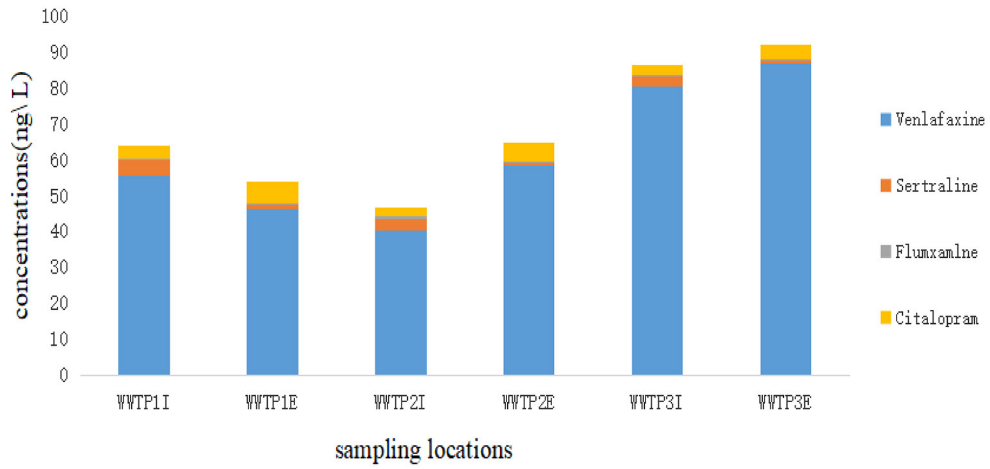

FIGURE 2
Concentration of antidepressant drugs in WWTPs.

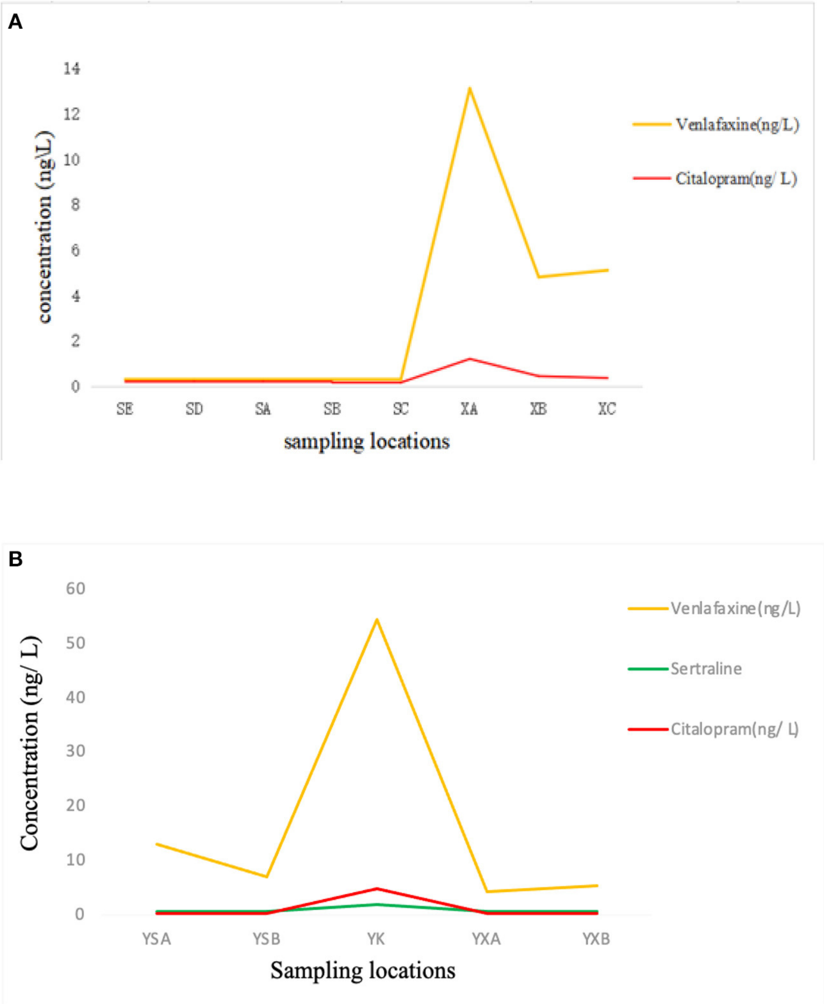

FIGURE 3
(A) Concentration of antidepressant drugs in Qiantang River. **(B)** Concentration of antidepressant drugs in Yuhangtang River.

the reason for higher concentrations of venlafaxine upstream of Yuhangtang River than downstream. The other reason could be the mixing effect of passing freight vessels on Yuhangtang River. The summary of concentrations of antidepressant drugs in surface waters in other countries was listed in Table 4. Antidepressants discharged from WWTPs into the surface water, then through the mixed dilution of waterbody and human activities. The decay process of the target substance in river is complicated.

Occurrence of antidepressants in source water and finished water

We collected three samples of source water and three samples of finished water from three water plants on Qiantang River as the source water and tested them for eight kinds of antidepressants. The results showed that the detection concentration was all lower than the detection limit of the method. The levels were significantly lower than those reported in drinking waters in other countries. In the UK, citalopram and fluoxetine have been detected in drinking water at concentrations of 2.26–2.80 and 0.27 ng/L, respectively (21). The maximum concentration of citalopram in Danube-derived tap water from the Budapest metropolitan region (Hungary) was 0.590 ng/L (1). Only trace amounts of antidepressants including citalopram (up to 1.5 ng/L), sertraline (up to 3.1 ng/L), and venlafaxine (up to 1.9 ng/L) were detected in tap water in Warsaw (Poland) (32). Antidepressants discharged from WWTPs into the river, through the mixed dilution of waterbody, the concentration in the downstream gradually decreased. The concentration of antidepressants in the upper reaches of Qiantang River which as the source of drinking water was low, thus indicating that the health risk of these substances in Qiantang River as a source of drinking water might be low.

Strengths and limitations

At present, there is only one report on antidepressants in WWTPs in China. Expanded data on antidepressant levels in WWTPs is needed. The resulting data will be useful in enriching research on emerging pollutants in WWTPs and aquatic environments. However, our study also has some minor shortcomings. For example, the number of samples collected from WWTPs did not consider sampling at different time intervals, resulting in a small number of overall samples. However, this study has a certain indicative value as a suggestive study. Further consideration will be given to improving the design in subsequent studies.

Conclusions

In the present study, we investigated the occurrence of eight antidepressants in the inlet and outlet of two WWTPs and the upstream and downstream of their sewage river. Three samples of source water and finished water were collected from three water plants on Qiantang River as the source water and tested for eight kinds of antidepressants. It is worth mentioning the less impact of the release of antidepressants from WWTPs to the surface water on the drinking water. Nevertheless, the concentrations of antidepressants in the effluent were even higher than those in the influent, demonstrating that these compounds were hardly removed by wastewater treatment processes. Thus, their risks deserve close attention.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

YC, PX, ZC, and XW made contributions to the conception and design of the study. YC, JX, DX, and PC collected the samples and cleaned the data. JW, LW, and NZ tested the samples. YC did the statistical analysis and drafted the article. All authors contributed interpreting the results and revised the draft critically.

Funding

This study was supported by the Foundation of the Medical Scientific Research of Zhejiang Province (2020KY514, 2021KY621, 2022RC121, and 2022RC122).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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frontiers | Frontiers in Public Health

TYPE Review
PUBLISHED 17 November 2022
DOI 10.3389/fpubh.2022.1002015

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OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to
Environmental health and Exposome,
a section of the journal
Frontiers in Public Health

RECEIVED 24 July 2022
ACCEPTED 20 October 2022
PUBLISHED 17 November 2022

CITATION
Sun G, Zhang Q, Dong Z, Dong D,
Fang H, Wang C, Dong Y, Wu J, Tan X,
Zhu P and Wan Y (2022) Antibiotic
resistant bacteria: A bibliometric
review of literature.
Front. Public Health 10:1002015.
doi: 10.3389/fpubh.2022.1002015

Antibiotic resistant bacteria: A bibliometric review of literature

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Antibiotic-resistant bacteria (ARB) are a serious threat to the health of people and the ecological environment. With this problem becoming more and more serious, more countries made research on the ARB, and the research number has been sharply increased particularly over the past decade. Therefore, it is quite necessary to globally retrace relevant researches on the ARB published from 2010 to 2020. This will help researchers to understand the current research situation, research trends and research hotspots in this field. This paper uses bibliometrics to examine publications in the field of ARB from 2010 to 2020 that were retrieved from the Web of Science (WOS). Our study performed a statistical analysis of the countries, institutions, journals, authors, research areas, author keywords, Essential Science Indicators (ESI) highly cited papers, and ESI hotspots papers to provide an overview of the ARB field as well as research trends, research hotspots, and future research directions in the field. The results showed that the number of related studies is increasing year by year; the USA is most published in the field of ARB; China is the most active in this field in the recent years; the Chinese Acad Sci published the most articles; Sci. Total Environ. published the greatest number of articles; CM Manaia has the most contributions; Environmental Sciences and Ecology is the most popular research area; and "antibiotic resistance," "antibiotics," and "antibiotic resistance genes" were the most frequently occurring author keywords. A citation analysis showed that aquatic environment-related antibiotic resistance is a key research area in this field, while antimicrobial nanomaterial-related research is a recent popular topic.

KEYWORDS

antibiotic resistant bacteria, antibiotic resistance, antibiotics, bibliometrics, keyword analysis

Introduction

Antibiotic-resistant bacteria are resistant to both natural and synthetic antibiotics (1) and thus have become a health concern worldwide. Multi-drug resistant bacteria (MDRB) with stronger resistance can be resistant to 3 or more antibiotics in clinic (2–5). Bacteria can develop intrinsic resistance to certain antibiotics, but can also acquire resistance to antibiotics (6). Among them, the path for bacteria to acquire or development antibiotic resistance which roots in the irrational usage of antibiotics is to prevent antibiotics from entering target, change the antibiotic targets and inactivate antibiotics (6–9). The irrational usage of antibiotics can lead to the prolonged exposure of bacteria to sublethal concentrations of antibiotics which is a key to the resistance selection (10, 11). Because antibiotics with sublethal concentrations cannot kill bacteria, but can affect the frequency of mutations, horizontal gene transfer (HGT) and gene recombination of bacteria, and have a chance to enrich existing low-level resistant mutations or improve the level of drug resistance mutation. The spread of antibiotic resistance among different bacterial populations is achieved through HGT (12). HGT refers to the transfer of antibiotic resistance genes (ARGs) between bacteria by transformation, transduction, and conjugation with the help of plasmids, integrons, transposons and so on (13). A large number of bacterial species are resistant to macrolides, sulfonamides, tetracyclines, and other antibiotics in the biological systems (14). Antibiotic has become synonymous with "antibacterial drug" in some degree, therefore, in this review antibiotic has been used.

Antibiotics are not completely metabolized in the human body, and some are excreted into the sewage with urine and feces in prototype (10). As the sewage treatment process has created a potential environment suitable for the development and spread of antibiotic resistance, such as high bacterial density, pressure caused by pollutants such as heavy metals and antibiotics, etc. Therefore, the discharge of treated sewage gives rise to a large number of ARB and ARGs in the surrounding ecological environment (e.g., aquatic system and soil) (12, 15–21). Moreover, the proportion of antibiotic resistance in chickens, pigs, and wild animals has also increased greatly (22), thus causing a serious burden of infection to human beings (23–25), and greatly affecting the ecological environment (26). Humans can be infected with ARB in different ways. For example, ARB in communities and medical settings can be transmitted through person-to-person contact (27). Healthcare associated infections (HAIs) are infections caused to patients by invasive devices or surgical procedures, such as catheter-associated urinary tract infections, surgical site infections, and ventilator-associated pneumonia (28), which are also common infections with ARB. Antibiotic-resistant bacteria can also be transmitted to people through the environment. For example, driven by hydrological processes such as runoff and infiltration, the treated sewage enters the sources of drinking water, such as surface water and groundwater, after being discharged into the environment, resulting in ARB and ARGs in the drinking water sources (29). However, conventional drinking water treatment is mainly designed to remove contaminants such as heavy metals, solid particles and pathogenic microorganisms, rather than to remove ARB, which may even promote the transmission of ARB from the environment to humans (29, 30). Soil may lead to the transfer of resistance determinants from the environment or zoonotic bacteria to humans (31). When the ARB infect the human body, it can transfer to the human pathogenic bacteria. Once the pathogenic bacteria develop resistance, it is harder to control and treat bacterial infections (29). For example, antibiotic resistance may lead to increased virulence and pathogenicity, increased morbidity and mortality, longer hospital stays, and reduced availability of antibiotics (32, 33). According to the WHO, 10 million people may die from ARB infections every year by 2050. In 2010, the Infectious Diseases Society of America started the "10 × '20 Initiative", with the goal of developing 10 effective antibacterial medications by 2020 (34). The WHO published a priority list in 2018 to guide the creation of new antibiotics (35). However, the rate of new antibiotic research and development is surprisingly slow (36). Very few new structural classes of antibiotics have been introduced since 2000 (37, 38), e.g., cyclic lipopeptide (daptomycin) (39, 40), oxazolidinone (linezolid) (41), etc. Yet more and more bacteria are resistant to many antibiotics used clinically (42, 43). We are no longer confident in the face of more and more bacterial infections (6). Therefore, new antimicrobial strategies are particularly important (44). In the early stage, it was mainly treated in combination with other antibiotics, such as streptomycin and penicillin. The combination of antibiotics has a synergistic effect, which not only has better efficacy than a single drug, but also can inhibit the drug resistance selection of a single drug (45, 46). With the development of multi-drug resistant bacteria, antibiotic substitutes (47) such as phage therapy (48–50), nanomaterials (51–54), bacteriocins (55), antibodies, and probiotics (56) have been attracted more attention.

The earliest monographic study in the field of ARB was published in 1990, and it provided an initial description of the antibiotic resistance mechanism (57). Findings over the subsequent decade included the identification of ARB in aquaculture for the first time (58–60), which was based on irrational antibiotic use in aquaculture (61). In addition, preliminary studies on the spread of ARB (62, 63), doctors' prescriptions (64) as well as phage therapy (65) were performed. During the period from 2000 to 2009, the findings focused on the fact that ARB and ARGs were discovered in wastewater and drinking water (66, 67). Antibiotic resistance (68–70), nanorods (71), phage therapy (72), and rational antibiotic use interventions (73) were further studied. In the last decade, with the development and application of polymerase chain reaction (PCR) assays (74, 75) and metagenomic analysis (76–79), the abundance of multiple ARGs could be identified. Consequently, ARB and ARGs were detected in aquatic systems, such as wastewater (80, 81), rivers (82–85), lakes (86), seawater (87), drinking water (88), reclaimed wastewater (89), and aquaculture (90), as well as animal husbandry (91, 92), compost (93), soil (94, 95), and vegetables (96, 97). For the sake of preventing the spread of ARB and ARGs in the environment and mitigating the damage to humans, animals and the ecological environment, an increasing number of researchers have devoted themselves to finding solutions to this difficult problem. Hence, a large number of processes for removing antibiotics, ARB and ARGs from wastewater have emerged, including chlorination (98, 99), ultraviolet (UV) (100, 101), advanced oxidation processes (AOPs) (102, 103), ozonation (104), solar photo-Fenton (105–107), photocatalytic oxidation (108, 109), constructed wetlands (CWs) (110), and membrane bioreactors (MBRs) (111). Even though studies on ARB and ARGs in wastewater and drinking water were carried out from 2000 to 2009 and from 2010 to 2020, the research content from 2010 to 2020 was more focused. Since the comparison and analysis of ARB and ARGs were generally conducted from 2000 to 2009, most of the samples collected in this stage were from source water, effluent from sewage treatment plants or rivers, while the research from 2010 to 2020 targeted more on the sewage treatment process. The samples collected in this stage may come from different treatment steps in the sewage process. For example, it may come from sand filtration and peracetic acid treatment (112) or various sewage treatment methods, e.g., chlorination (99), ozone (104), etc. Moreover, the detection technologies employed during 2010–2020 are more efficient, such as high-throughput sequencing technology (14).

ARB is highly interrelated to human and ecological health, and there has been more extensive previous studies in this field, the priority list of ARB (35), ARB persistence (113), the challenge of ARB in the food industry (114), the antibiotic resistance profiles (19, 22) antimicrobial strategies (115–117) and antibiotics discovery (36). ARB are a serious threat to the health of people and the ecological environment. With this problem becoming more and more serious, more countries made research on the ARB, and the research number has been sharply increased particularly over the past decade. Therefore, it is quite necessary to globally retrace relevant researches on the ARB in recent 10 years. This will help researchers to understand the current research situation, research trends and research hotspots in this field.

Bibliometric analysis is an effective method for quantitatively assessing academic papers and can be used to investigate the evolution of certain fields, and the results can provide an overview of a certain field as well as research trends, hot topics, distribution of research power and future research directions (118–122). The advantage of bibliometric is that it is not limited by geography, allowing data to be collected by country in a particular area to analyze research globally (123). In addition, specific data analysis software can process the results of bibliometric analyses and present them in a more three-dimensional form (124–127). Therefore, bibliometric analyses have been applied to many fields, such as medicine (128–130), chemistry (131), psychology (132), computer science (133, 134), and robotics (120). In addition, bibliometrics is also widely applied to the aspect of research method, for example, the publications related to such research methods as TOPSIS (135), Analytic Hierarchy Process (136), and ordered weighted averaging operator (137) can also make knowledge recreation by bibliometrics.

To our knowledge bibliometric analysis of publications in the field of ARB has been conducted, but related studies only focused on antibiotics in soil (138) and ARGs (139). Since the study of ARB is multifaceted, such as generation (6), impact (23), control (140), and treatment (55) of ARB, and so on, a comprehensive analysis of ARB research from a bibliometric perspective remains necessary. The goal of this paper is to apply a bibliometric approach to review the leading countries, institutions, authors, and journals, research areas, national and institutional collaborations, author keywords, and ESI highly cited and hot papers to provide research situation, research trends and research hotspots in the field of ARB between 2010 and 2020 globally and then propose future research directions.

Materials and methods

A bibliometric analysis of publications in the field of ARB published between 2010 and 2020 is presented in this paper. Data were obtained from the Science Citation Index Expanded database (SCI-E) and Social Sciences Citation Index database (SSCI). Scopus, Pubmed and Google Academic indeed cover more publications than Web of Science. However, the publications included into the core complications of WOS generally receive higher recognition and it is the most widely accepted database for analysis of science publications (141). Therefore, WOS was chosen as the data source for this study. First, the subject field was set to "antibiotic resistant bacteria", the date range was set to 2010-01-01 to 2020-12-31, and the document type was set to "article" and "review" for the search. The corresponding country, institution, journal, author, author

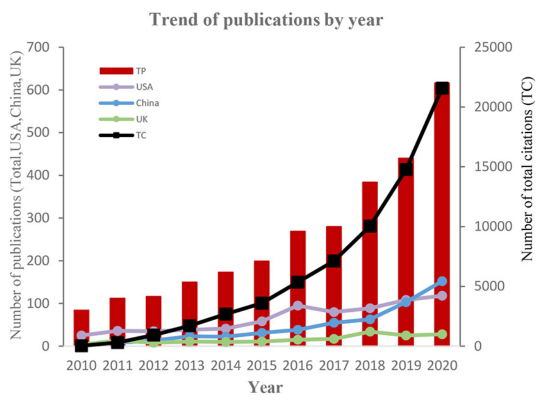

FIGURE 1
Trends in the number of published articles related to ARB by year. TP, total papers; TC, total citations.

TABLE 1 The top 20 most productive countries/regions in the ARB field.

Rank	Country	TP	TC	h-index	ACPP	nCC	SP (%)
1	USA	723	27,927	78	38.63	67	40.11
2	China	513	16,157	64	31.5	43	32.75
3	UK	176	10,977	43	62.37	64	69.32
4	Germany	168	10,219	43	60.83	57	61.90
5	Italy	140	8,384	36	59.89	48	52.14
6	Spain	139	6,584	38	47.37	52	64.75
7	India	134	2,941	30	21.95	43	34.33
8	South Korea	121	3,168	32	26.18	35	37.19
9	Sweden	104	7,246	33	69.67	48	59.62
10	Canada	101	6,148	34	60.87	46	64.36
11	France	99	7,044	32	71.15	55	64.65
12	Japan	99	2,317	24	23.4	32	39.39
13	Australia	98	6,120	36	62.45	47	75.51
14	Portugal	96	6,808	34	70.92	47	44.79
15	Netherlands	79	5,778	32	73.14	45	62.03
16	Poland	79	3,298	27	41.75	39	34.18
17	Brazil	77	1,509	22	19.6	19	41.56
18	Switzerland	67	4,386	28	65.46	39	59.70
19	Iran	55	969	18	17.62	11	18.18
20	Turkey	49	876	15	17.88	17	28.57

TP, total papers; TC, total citations; ACPP, average citations per publication; nCC, number of cooperative countries; SP, Share of publications.

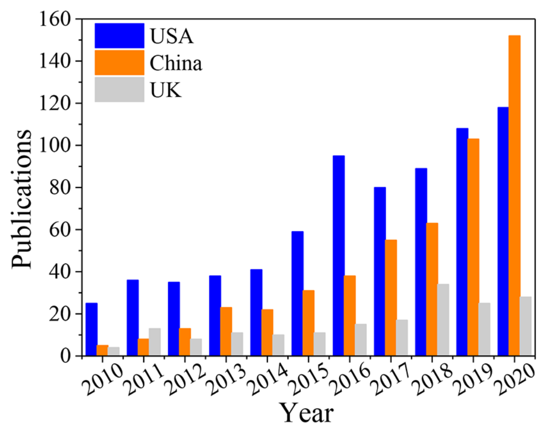

FIGURE 2
Number of ARB-related publications per year from 2010 to 2020 in the USA, China and the UK.

keywords, and research area of publications meeting the search criteria are listed. The same data were extracted from ESI highly cited and hot papers. Then, the Derwent Data Analyzer (DDA10.0 build 27,330, Search Technology Inc., Norcross, GA, USA), which is a tool for data cleaning, mining and visual processing, was used to clean the derived data.

Although ARB is an acronym for antibiotic resistant bacteria, it was not included in the search formula because the acronym is used in other fields. Antimicrobial include antibiotics, however it was not included in the search formula, because antimicrobial is not only effective against ARB, it is also effective against mycoplasma, chlamydia, viruses, etc. Articles from Scotland, Wales, England, and Northern Ireland are included as papers from the UK. Each journal's impact factor is derived from the 2020 JCR. Not all relevant articles were included in this analysis, and those that did not match the search rules were excluded. In this review DDA has been used to make matrix map, cluster map, bubble chart and cross-correlation plot. Since publications are time-sensitive, this paper only analyzed the literature published from 2010 to 2020.

Results

From 2010 to 2020, 2,823 papers in the ARB field were published by authors in 116 countries, including 99 ESI highly cited papers and 3 ESI hot papers. These publications can be divided into 11 languages, including 2,793 in English (98.94%), 10 in German (0.35%), 6 in Spanish (0.213%), 3 in French and Polish (0.106%), 2 in Hungarian and Portuguese (0.071%), and 1 in Chinese, Dutch, Italian and Turkish (0.035%). The growth trend of articles related to the ARB field from 2010 to 2020 was described (Figure 1). During this period, the number of articles published in this field increased by more than seven-fold, with the number of articles published from 2018 to 2020

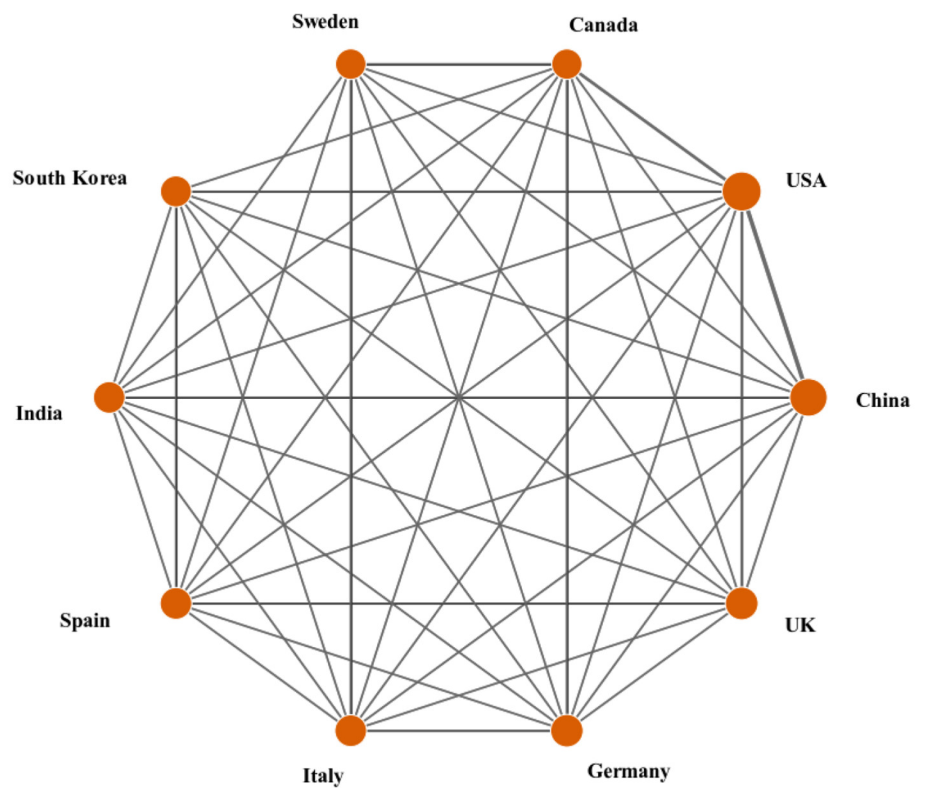

FIGURE 3
Collaboration matrix map among the top 10 productive countries/regions.

increasing significantly. This finding indicates that ARB has attracted increasing concern year by year, and it also shows that the impact of ARB on human beings is increasing.

Contribution of leading countries/regions

The top 20 countries in terms of total quantity of publications in the ARB field between 2010 and 2020 were identified (Table 1). The USA is the country with the most publications in this field, followed by China and the UK, whose publications account for 25.61, 18.17, and 6.23% of the total publications, respectively. The same result can be seen in the ranking of total citations; that is, the USA is first, followed by China and the UK. Figure 2 shows the number of ARB-related publications per year from 2010 to 2020 in the USA, China and the UK. It can be seen that China issued very few publications from 2010 to 2013, less than the UK and the USA, while in 2019 the number of publications in China rose significantly. In 2020 China has already surpassed the USA in the number of relevant publications. This indicates that China is considerably more active in this research field during recent years. It is likely related to the large population in China, the high prevalence of antibiotic abuse (142), the relevant policies (143, 144) and higher scientific research fund support (145). Among the top 20 countries, 11 countries were in Europe, 5 countries were in Asia, and 4 countries were in the Americas, which shows that ARB have attracted global attention.

Cooperation of leading countries/regions

The most impactful science comes from international collaboration (146), which is based on the flow and integration of knowledge. Different countries/regions may have different emphases when studying ARB, although resource complementarity and continuous innovation impulses can be achieved by collaboration. International collaborative publications are joint papers written by scholars from multiple countries. The number of cooperative countries (nCC) refers to how many countries a country has cooperated with in a certain field. It can be concluded from Table 1 that among all countries, the USA, the UK, Germany, Spain and France have more cooperation with other countries. To better understand the current state of international collaboration in the ARB

TABLE 2 The top 20 most productive institutions in the ARB field during 2010–2020.

Rank	Institutions	TP	TC	ACPP	h-index	TPR (%)	Country/Region
1	Chinese Acad Sci	77	3,443	44.71	31	2.728	China
2	Univ Porto	37	2,046	55.30	21	1.311	Portuguese
3	USDA ARS	36	986	27.39	17	1.276	USA
4	Univ Catolica Portuguesa	34	4,239	124.68	24	1.204	Portuguese
5	Univ Chinese Acad Sci	32	1,455	45.47	18	1.134	China
6	Univ Salerno	28	2,732	97.57	19	0.991	Italy
7	Tsinghua Univ	27	1,355	50.19	18	0.956	China
8	Zhejiang Univ	26	450	17.31	11	0.921	China
9	Karolinska Inst	25	704	28.16	13	0.886	Sweden
10	Univ Gothenburg	24	2,070	86.25	17	0.850	Sweden
11	Univ Queensland	24	1,091	45.46	15	0.850	Australia
12	Univ Copenhagen	23	1,299	56.48	13	0.815	Denmark
13	Uppsala Univ	23	1,590	69.13	15	0.815	Sweden
14	Natl Univ Singapore	22	1,047	47.59	16	0.779	Singapore
15	Tongji Univ	22	905	41.14	15	0.779	China
16	Univ Cyprus	22	3,609	167.73	17	0.779	Cyprus
17	Univ Maryland	22	796	35.91	14	0.779	USA
18	Sun Yat Sen Univ	21	576	27.43	11	0.743	China
19	Univ Minnesota	21	1,275	60.71	12	0.743	USA
20	Nankai Univ	20	1,154	57.70	13	0.708	China

TP, total papers; TC, total citations; ACPP, average citations per publication; TPR, the percentage of articles of institutions in total publications.

field, a network graph between the top 10 countries/regions was created using the DDA software (Figure 3). The circle size symbolizes the countries' contributions, the lines connecting the circles indicate cooperation between countries, and the thickness of the lines indicates the number of collaborative publications. It can be seen from Figure 3 that almost all of the top 10 countries in publications have ever cooperated with each other. The line between the USA and China is the thickest, which indicates that the number of cooperative publications between the USA and China is the largest in this field, followed by the number of cooperative publications between the USA and Canada.

Contribution of leading institutions

Statistics on the contributions of leading institutions can help us identify the most authoritative professional institutions in the ARB field. There are 3,430 institutions involved in ARB research, and the top 20 are summarized (Table 2). Among these 20 institutions, there are 40% institutions in Europe and Asia, respectively, while the majority of those in Asia are from China. Although the Chinese Acad Sci has published a large amount of articles, the total citations and average citations per paper are not the highest. Although several European institutes do not have a large number of publications, such as Univ Catolica Portuguesa and Univ Cyprus, the quality of articles is relatively high, which can be seen from their high total citations and average citations per paper.

The output and quality of scientific research were positively correlated with the degree of international collaboration (147). A cluster map of the collaboration among the top 15 institutions was created with DDA software (Figure 4). Obviously, Gothenburg University, the Chinese Acad Sci and Tsinghua University showed the most extensive collaborations with other institutions in the ARB field. In addition, the USDA ARS, Karolinska Inst and Univ Queensland have a greater number of collaborations with institutions in different countries; thus, their degree of internationalization was high. The collaborations between the Chinese Acad Sci and Univ Chinese Acad Sci and between Univ Porto and Univ Catolica Portuguesa were the most frequent. Institutions in European countries were more closely connected with those in neighboring countries/regions, which was similar to that in Asia, possibly because of factors such as institutional relationships and geographical proximity.

Contribution of leading journals

The collation of published journals revealed that a total of 983 journals published ARB-related research from 2010

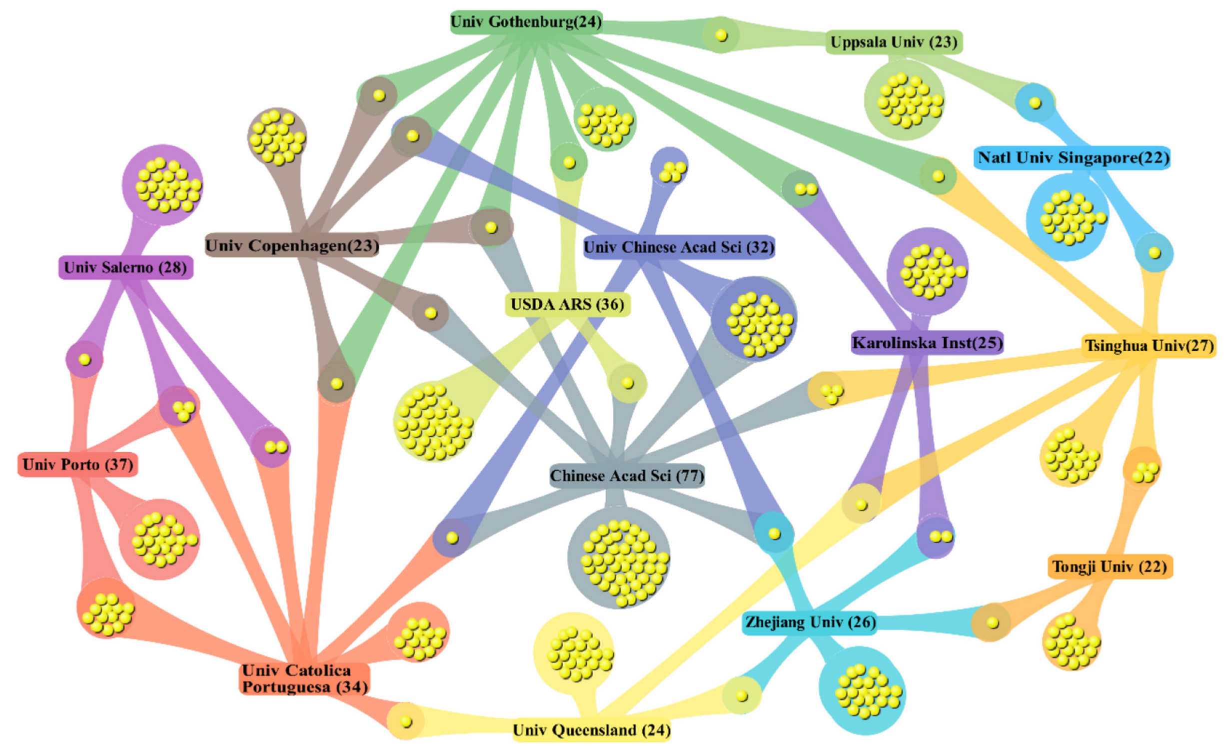

FIGURE 4
DDA cluster map on cooperation of the top 15 institutions.

to 2020. The top 30 journals by the number of articles are displayed (Table 3). These 30 journals have published a total of 911 articles on ARB, accounting for 45.86% of the total literature. Forty-three percent of these journals were related to the environment, 20% were related to microbiology, 13% were related to medicine, 10% were related to engineering technology, and 3% was related to materials and chemistry each. The breadth of disciplines involved reflects that ARB represent an interdisciplinary research field.

Contribution of leading authors

Statistics on leading authors can help us understand the top experts in the ARB field. A total of 13,966 authors were counted among 2,823 articles, of which 12,086 authors only published one article, 337 authors published three articles, and 15 authors published 10 or more articles. The top 20 authors in the number of articles and their institutions are summarized (Table 4). These authors published 245 articles, accounting for 8.67% of all articles. CM Manaia has published the most articles in this field and made important contributions to the presence and removal process of antibiotics, ARB and ARG in wastewater and antibiotic resistance in the environment. L Rizzo mainly studied sewage treatment processes, such as photocatalysis and UV. In addition to the study of sewage treatment processes, D Fatta-Kassinos also contributed to the reuse of wastewater.

Contribution of leading research areas

Statistics on the research areas can help us grasp the shift of research emphasis in a specific field. There are 90 study areas associated with ARB, and the top 20 based on the number of articles are concluded (Table 5). The research areas of ARB are not only related to microorganisms, diseases, drugs, and chemistry but also related to the environment, engineering, agriculture, materials and oceanography, with the greatest number of publications related to the ecological environment. The top 5 areas accounted for 76.83% of all articles published, indicating that the environment, microbiology, engineering, drug and chemistry are the top research areas in the ARB field.

The bubble chart can show the research trends and emphasis in a specific field more stereoscopically (205). A bubble chart is depicted to showing the top 20 ARB research areas

TABLE 3 Top 30 journals publishing papers in ARB research.

Rank	Journal title	TP	TC	ACPP	IF	TPR (%)
1	Sci. Total Environ.	110	5,546	50.42	7.963	3.897
2	Front. Microbiol.	79	2,656	33.62	5.64	2.798
3	PLoS One	69	1,780	25.8	3.24	2.444
4	Water Res.	65	4,684	72.06	11.236	2.303
5	Chemosphere	40	1,799	44.98	7.086	1.417
6	Sci Rep	40	591	14.78	4.38	1.417
7	Antibiotics-Basel	36	391	10.86	4.639	1.275
8	Environ. Sci. Pollut. Res.	35	936	26.74	4.223	1.24
9	J. Hazard. Mater.	30	992	33.07	10.588	1.063
10	Antimicrob. Agents Chemother.	29	984	33.93	5.191	1.027
11	Environ. Sci. Technol.	28	2,215	79.11	9.028	0.992
12	Int. J. Environ. Res. Public Health	28	772	27.57	3.39	0.992
13	Environ. Pollut.	27	956	35.41	8.071	0.956
14	mBio	26	1,154	44.38	7.867	0.921
15	Environ. Int.	25	1,177	47.08	9.621	0.886
16	Appl. Environ. Microbiol.	22	997	45.32	4.813	0.779
17	ACS Appl. Mater. Interfaces	19	636	33.47	9.229	0.673
18	Appl. Microbiol. Biotechnol.	19	545	28.68	4.813	0.673
19	Microb. Drug Resist.	18	228	12.67	3.431	0.638
20	Clin. Infect. Dis.	17	1,844	108.47	9.079	0.602
21	Environ. Monit. Assess.	17	409	24.06	2.513	0.602
22	J. Antimicrob. Chemother.	17	476	28	5.79	0.602
23	Microorganisms	16	118	7.38	4.128	0.567
24	Water Sci. Technol.	16	168	10.5	1.915	0.567
25	Chem. Eng. J.	15	500	33.33	13.273	0.531
26	J. Environ. Qual.	14	395	28.21	2.751	0.496
27	J. Food Prot.	14	196	14	2.077	0.496
28	Molecules	14	408	29.14	4.412	0.496
29	Ecotox. Environ. Safe.	13	670	51.54	6.291	0.461
30	Int. J. Nanomed.	13	370	28.46	6.4	0.461

TP, total papers; TC, total citations; ACPP, average citations per publication; IF, Impact Factor 2020; TPR, the percentage of articles of journals in total publications.

(Figure 5). The numbers on the bubbles reflect the number of publications. "Environmental Sciences and Ecology" is the dominant research direction in the ARB field. From 2010 to 2020, the number of publications in this field increased and was the greatest overall, and it showed significant annual growth since 2017. "Microbiology" is also a research direction of increasing concern. The number of publications related to "Microbiology" every year is also on the rise, although a certain gap is observed. Compared with "Environmental Sciences and Ecology," "Microbiology" received greater attention in the initial stage. Previously, the number of publications in the "Engineering" direction increased slowly but substantially between 2018 and 2020. The number of publications related to "Materials Science" was low in the initial phase but increased significantly after 2015, reaching a peak in the last 2 years.

Analysis of author keywords

A keyword collection based on abundant academic findings in a research field over a long period of time can reveal the overall characteristics, developmental trends, and internal connections of such research. The top 30 author keywords from 2,823 publications were sorted and displayed in a bubble chart (206–209) in this study (Figure 6). The number on the bubble represents the times that the author keywords appeared in the corresponding year. In this paper, we combined author keywords with the same meaning through the DDA. Eventually, a total of 5,506 author keywords were obtained. Among them, 4,276 author keywords appeared only once, which accounted for 77.67%; 573 author keywords appeared twice, which accounted for 10.41%; and 6 author keywords appeared more than 100 times, which accounted for ~0.11%. Among them, "Antibiotic

TABLE 4 Contribution of the top 20 authors in ARB research.

Rank	Author	TP	TAR	TC	ACPP	h-index	Institution (current), country/region
1	Manaia, CM (148–150)	33	20	3,296	99.88	24	Univ Catolica Portuguesa, Portugal
2	Rizzo, L (151–153)	26	22	2,704	104	19	Univ Salerno, Italy
3	Fatta-Kassinos, D (154–156)	21	9	3,754	178.76	16	Univ Cyprus, Cyprus
4	Larsson, DGJ (157–159)	17	9	2,036	119.76	15	Univ Gothenburg, Sweden
5	Nunes, OC (160–162)	16	8	1,358	84.44	13	Univ Porto, Portugal
6	Pruden, A (140, 163, 164)	14	6	1,335	95.36	11	Virginia Tech, USA
7	Topp, E (165–167)	14	6	1,866	133.29	13	Agr and Agri Food Canada, Canada
8	Webster, TJ (168–170)	13	12	673	51.77	11	Northeastern Univ, USA
9	Schwartz, T (67, 171, 172)	12	2	2,687	223.92	11	Karlsruhe Inst Technol, Germany
10	Boopathy, R (173–175)	11	11	320	29.09	9	Nicholls State Univ, USA
11	Harnisz, M (176–178)	10	2	569	56.9	9	Univ Warmia and Mazury, Poland
12	Hong, PY (179–181)	10	9	347	34.7	9	King Abdullah Univ Sci and Technol, Arabia
13	Korzeniewska, E (182, 183)	10	6	569	56.9	9	Univ Warmia and Mazury, Poland
14	Pamer, EG (184–186)	10	6	1,481	148.1	8	Mem Sloan Kettering Canc Ctr,USA
15	Suzuki, S (187–189)	10	7	983	98.3	10	Ehime Univ, Japan
16	Ahn, J (190–192)	9	9	58	6.44	4	Kangwon Natl Univ, South Korea
17	Call, DR (193–195)	9	3	153	17	5	Washington State Univ, USA
18	Guo, MT (196–198)	9	9	312	34.67	9	Tongii Univ, China
19	Lundborg, CS (199–201)	9	1	402	44.67	8	Karolinska Inst, Sweden
20	Zhang, T (202–204)	9	3	1,223	135.89	8	Univ Hong Kong, China

TP, total papers; TAR, total number of articles for which they are responsible; TC, total citations; ACPP, average citations per publication.

resistance," "Antibiotic-resistant bacteria," "Antibiotics," and "Antibiotic resistance genes" had the highest appearance frequency. Much of the research on "Antibiotic resistance" has focused on the existence of "Antibiotics," "Antibiotic-resistant bacteria," and "Antibiotic resistance genes" in "Wastewater" and the environment and associated removal techniques. There are also many related studies on "Antibiotics," "Antimicrobials," "Antimicrobial peptides," "MRSA," "Nanoparticles," and "Muti-drug resistant bacteria".

The cross-correlation plot shows that two keywords occurred in one paper at the same time. Through the co-occurrence analysis of author keywords, the cross-connection between each author keywords can be better revealed. We designed a cross-correlation plot of the leading 30 author keywords by DDA (Figure 7). The size of the circle reflects how frequently the author keywords appear in total articles; the line connecting the two circles indicates that the two author keywords appear in the same article. The dashed line indicates a correlation between the two author keywords ranging from 0.25 to 0.5, and the solid line means 0.5–0.75. Undoubtedly, the author keywords with the highest frequency also correspond to the largest circles. We can also clearly discover that the author keywords appearing at the same time as "Antibiotic resistance" are the most, indicating that their research scope is wider. Among them, "Antibiotic-resistant bacteria" and "Antibiotic resistance genes," "Resistance" and "Antibiotics," "Phage therapy" and "Bacteriophage," "Enterobacteriaceae" and "ESBL", and "Antibiotic resistance genes" and "Tetracycline" are five pairs of closely related keywords, indicating that those two keywords had a high frequency of appearing simultaneously in an article.

Analysis of ESI highly cited papers

The frequency of citations is a valuable metric for evaluating the impact of scientific papers (210, 211). The ESI highly cited papers refer to papers published in the last decade that presented a citation frequency ranked within the top 1% worldwide within the previous 2 months. Therefore, this paper adopts ESI highly cited papers to explore the hot topics of recent studies. The top 20 most cited papers in the ARB field from 2010 to 2020 are revealed (Table 6). Among these papers, the USA contributed 4 papers and the UK, Sweden and China each contributed 3 papers. Investigations to determine how antibiotic resistance develops in bacteria is the most frequently subject. Studies have focused on the main mechanisms of antibiotic resistance. The impact of ARB infection on humans is also of particular concern. In 2015, ARB infections were estimated to cause numerous deaths in Europe, with a high burden in infants and elderly individuals. Antibiotic resistance in wastewater has been a hot research topic in the last decade, with many

TABLE 5 Contribution of the top 20 research areas in ARB field.

Rank	WOS research area	TP	TPR (%)	TC	ACPP	h-index
1	Environmental sciences and ecology	697	24.69	28,631	41.08	83
2	Microbiology	545	19.306	23,188	42.55	71
3	Engineering	317	11.229	13,193	41.62	62
4	Pharmacology and pharmacy	314	11.123	8,238	26.24	46
5	Chemistry	296	10.45	9,583	32.38	51
6	Science and technology—other topics	279	9.883	8,932	32.01	55
7	Infectious diseases	261	9.246	11,324	43.39	42
8	Biotechnology and applied microbiology	210	7.439	5,330	25.38	41
9	Biochemistry and molecular biology	195	6.908	5,829	29.89	41
10	Water resources	159	5.632	6,370	40.06	39
11	Materials science	155	5.491	4,824	31.12	40
12	Public, environmental and occupational health	151	5.349	4,160	27.55	31
13	Immunology	109	3.861	4,722	43.32	33
14	Food science and technology	98	3.472	2,023	20.64	24
15	Veterinary sciences	82	2.905	995	12.13	18
16	Agriculture	76	2.692	1,978	26.03	24
17	General and internal medicine	71	2.515	3,320	46.76	25
18	Physics	51	1.807	1,490	29.22	21
19	Marine and freshwater biology	49	1.736	725	14.8	17
20	Biophysics	43	1.523	1,213	28.21	21

TP, total papers; TRP, percent of total articles in the field; TC, total citations; ACPP, average citations per publication.

studies related to Enterococcus and Escherichia coli. In addition, Acinetobacter baumannii, Pseudomonas aeruginosa (218), vancomycin-resistant Enterococcus (VRE) and methicillin-resistant Staphylococcus aureus (MRSA) (219) have a relatively large impact on humans and have recently received more attention. Guidelines for biological risk assessments of ARB production and transmission in the environment have also been controversial subjects in recent years because of their important roles in controlling antibiotic resistance in the environment.

Analysis of ESI hot papers

ESI hot papers are papers published in the last 2 years that have a citation frequency ranked within the top 0.1% worldwide in the previous 2 months. Three ESI hot papers published in 2020 were identified (Table 7). The hottest papers in the last 2 years describe the generation and fate of antibiotics, ARB and ARGs in sewage treatment plants around the world. The second paper reviews the research progress of antimicrobial nanofiber wound dressings since 2015, especially recent advances in biohybrid dressings made from cross species. The last hot paper summarizes the physicochemical properties of 5 photothermal agents and their application in antimicrobial photothermal therapy.

Latest developments

From January 2021 to 2022, 19 highly cited papers in total met the search conditions, among which 2 were hot papers. The research contents of these highly cited papers mainly focus on the three aspects as follows. Initially, there are many researches on substances and preparations that can play an antibacterial role. For example, the antibacterial mechanism of nanomaterials (222), and molecularly imprinted polymers (223), the research review of antibacterial peptides in the source, structure, clinical trials (224), etc., the mechanism of prebiotics to remove intestinal pathogens (225), as well as the activity and antibacterial mechanism of antimicrobial agents from plants (226). Secondly, there are also many studies on the existence of micro pollutants, including the distribution and concentration of antibiotic resistance genes in the environment (227), the pollution status, sources and potential risks of antibiotics in surface water (228), and the production and removal of resistant microorganisms in hospital wastewater (229). What's more, these studies also touched upon aspects of water treatment technology, such as the mechanism of action of photocatalytic removal of antibiotics and inactivated bacteria (230), the effect of ozone removal of ARB and ARGs (231), and the overview of microalgae for environmental remediation (232).

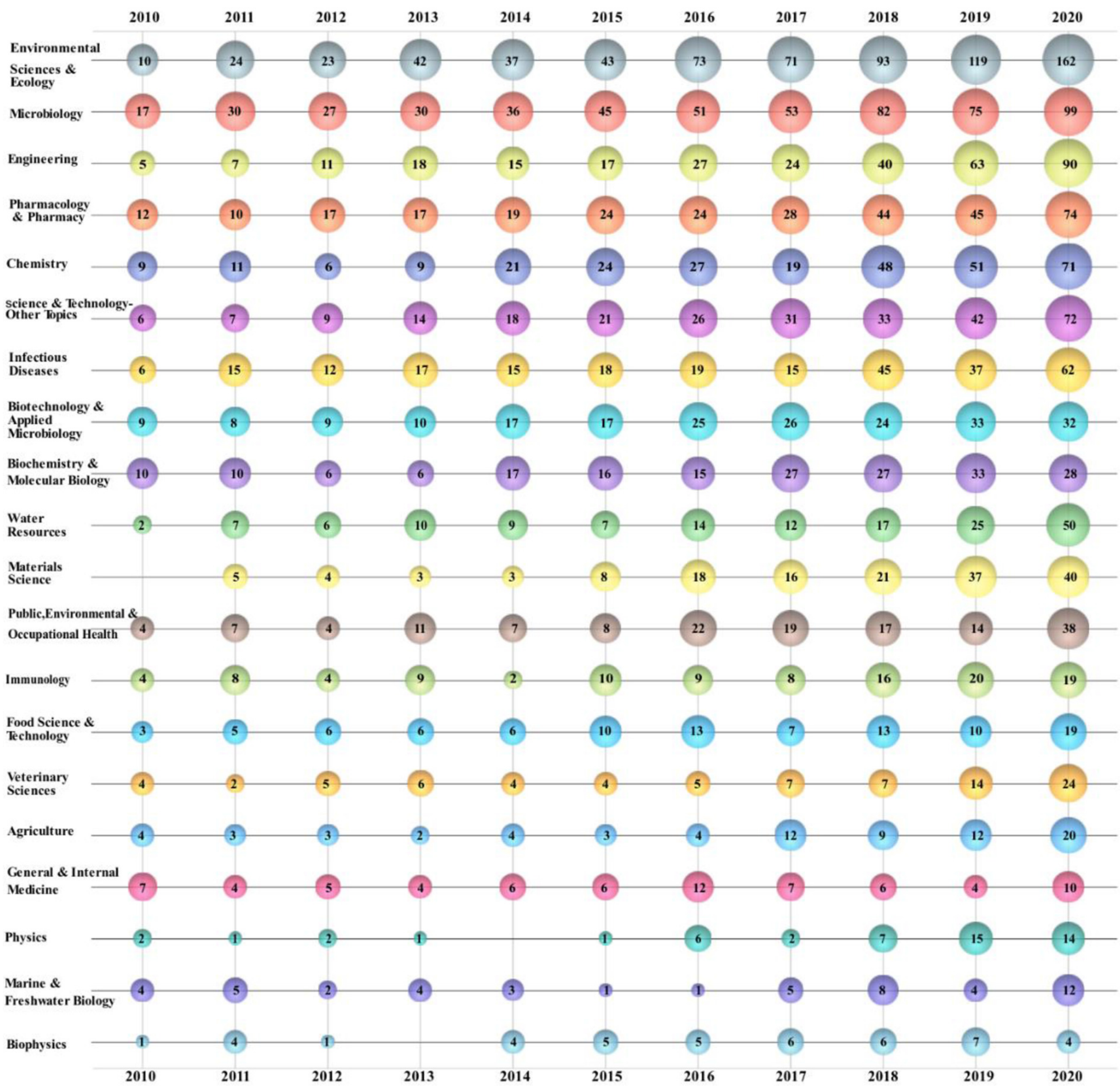

FIGURE 5
Bubble chart of top 20 ARB research areas.

Discussion

Emerging research elements

According to the statistical analysis of author keywords from 2010 to 2020, new author keywords have emerged in this field. Since the new author keywords appear less frequently, which has not shown in the chart. Here only introduce the new author keywords that appear comparatively more frequently. The 2019 COVID-19 pandemic, triggered by SARS-CoV-2 (233–236), has placed a tremendous burden on both the health care system and human society (237–239). It was found that the incidence of carbapenem-resistant Enterobacteriaceae infections have rapidly increased in critically ill patients with COVID-19 (240). Surprisingly, maintaining social distance has been shown to help reduce the transmission of SARS-CoV-2 and ARB (241). In addition, polypeptides are not only potential substitutes for the treatment of ARB infection but are also effective in the treatment of COVID-19 (242). Nanoparticles are not only effective antibacterial agents but also antibacterial drug delivery carriers. Electrospinning represents a new technology for preparing nanofibers in the last 2 years, and it is very suitable for generating antibacterial nanomaterials because nanomaterials produced using this technology have a large

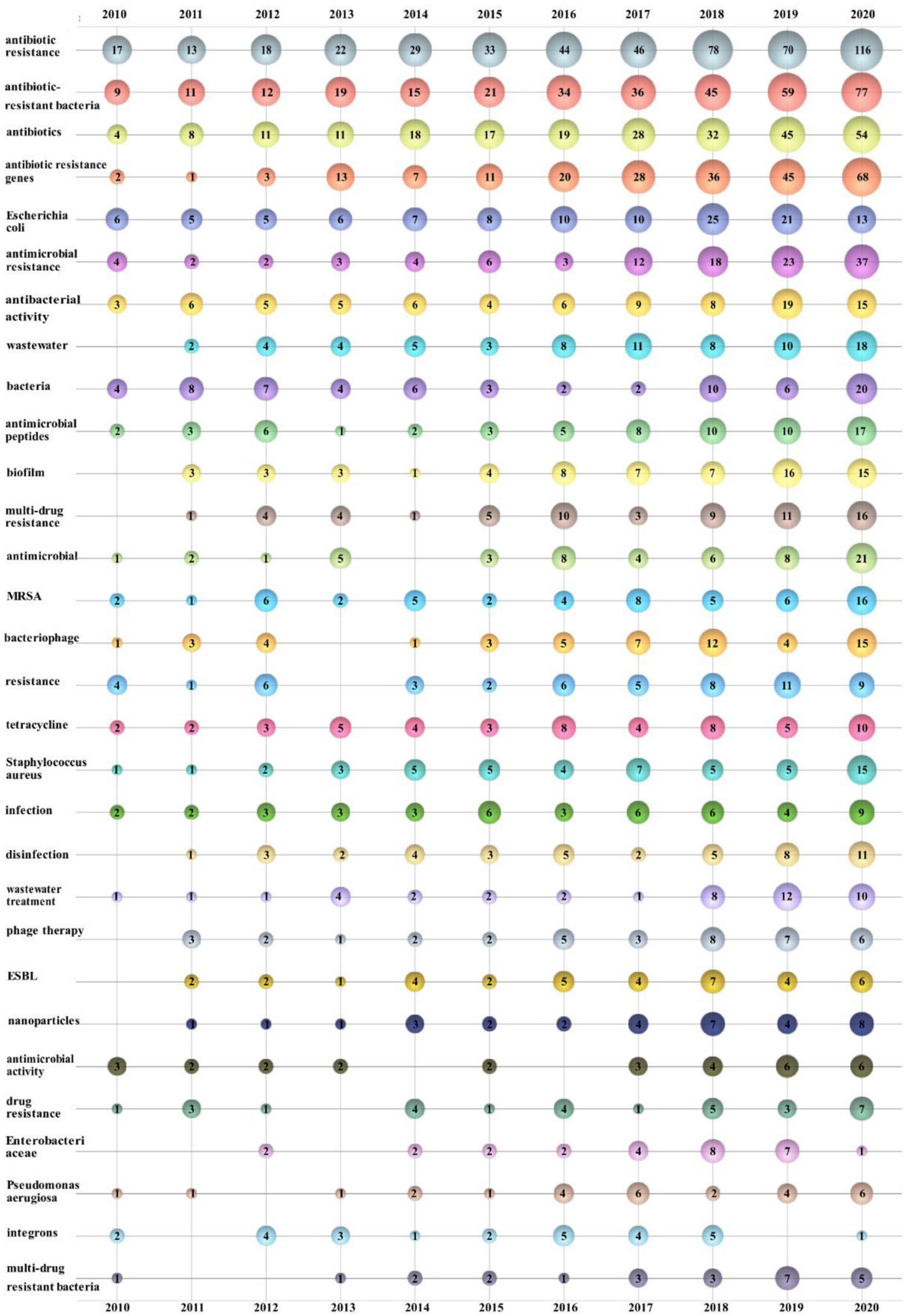

FIGURE 6
Bubble chart of the top 30 author keywords by year.

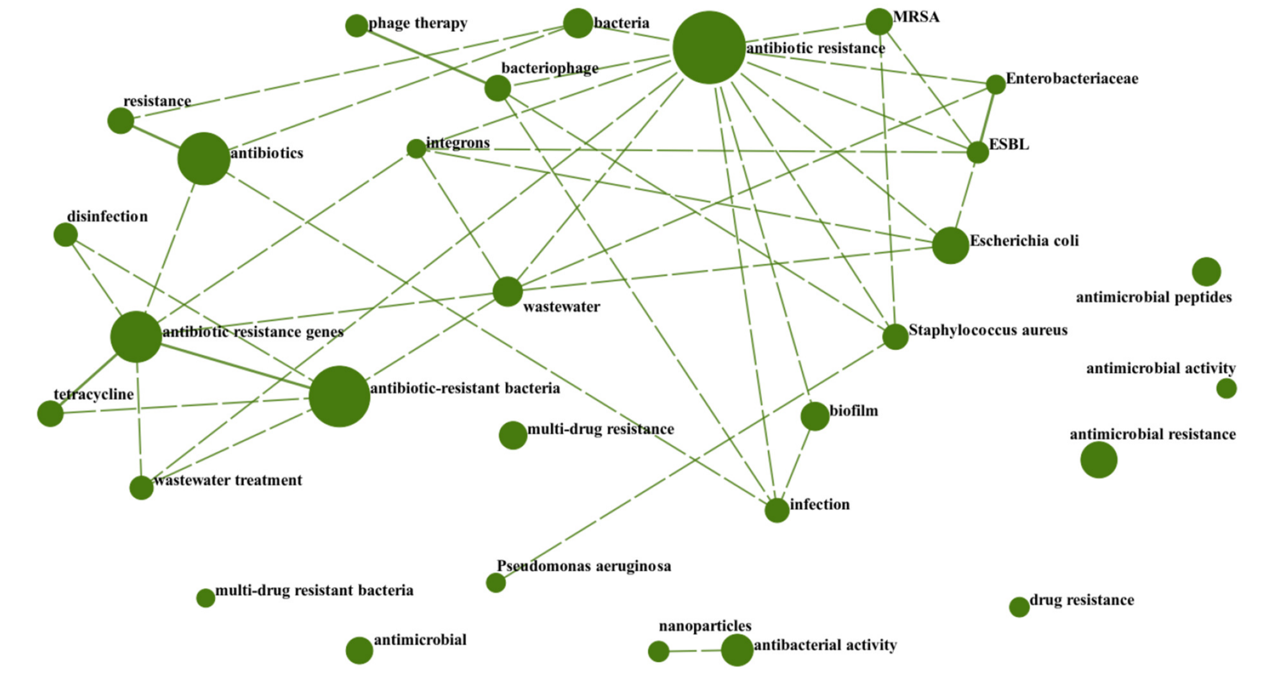

FIGURE 7
Cross-correlation graph of the top 30 author keywords.

specific surface area and controllable structure (221, 243). In the past 2 years, studies have linked machine learning with ARB identification. Compared with traditional DNA sequencing, spectral diagnostic data are analyzed by machine learning algorithms to accurately identify ARB and ARGs (244, 245). In addition, studies have applied machine learning models for the early prediction of subclinical mastitis to reduce the risk of ARB (246).

Future research directions

It is well known that the goal of studying antibiotic resistant bacteria is to resist ARB by understanding the mechanisms of the generation, evolution as well as transmission of the antibiotic resistance, such as the implement of sewage treatment processes; to find effective methods to reduce the harm caused by antibiotic resistant bacteria to global humankind and ecosystem, such as the research and development of new antibiotics, antibiotic substitutes, adjuvants.

According to the author keywords bubble chart (Figure 6), cross-correlation graph (Figure 7) and ESI highly cited papers (Table 6), it can be found that the research on antibiotic resistance has been the first place and plays a leading role in this field for the last decade. The scope of research mainly includes the existence of antibiotic resistance in the aquatic systems (247), sewage treatment processes, and negative effects (248, 249). This may be related to the early abuse of antibiotics (250) in many countries, such as China (142, 251–254), USA (255, 256), India (257), Italy (258), and so on. It is undeniable that those studies play a significant role in the understanding of antibiotic resistance. However, some studies have pointed out that MRSA existed long before the antibiotics was used (259). Mutations in microbial metabolism can also lead to antibiotic resistance (260). This just goes to show that our understanding of antibiotic resistance is not thorough enough. Further research on the induction factors and relevant mechanisms that lead to antibiotic resistance is required in the future.

According to the ESI hot papers (Table 7), nanomaterials have been the hottest topic in this field in the last 2 years, which is closely related to their superior antibacterial properties. However, according to the author keywords bubble chart (Figure 6) and cross-correlation graph (Figure 7), it can be found that the research on antimicrobial peptides and bacteriophages has gradually increased in the last decade but has not received enough attention. Peptide-based antibiotics have been found to be effective against MDRB because bacterial resistance responds slowly to the action mode of peptide natural products (261). Encrypted peptide kills bacteria by targeting the cell membranes of pathogenic bacteria and is not susceptible to selective resistance (262). At present, research has found candidate peptide antibiotics in human intestinal flora using machine learning (263), which breaks through the path dependence on the traditional antibiotic discovery. Bacteriophages have been

TABLE 6 The top 20 most cited publications of ESI in ARB research field during 2010–2020.

Rank	Corresponding authors	Title	TC	TCY	Publication year	Journal	Country/Region
1	Piddock, LJV	Molecular mechanisms of antibiotic resistance (6)	1,578	263	2015	Nat. Rev. Microbiol.	UK
2	Tacconelli, E	Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis (35)	1,350	450	2018	Lancet Infect. Dis.	Germany
3	Rizzo, L	Urban wastewater treatment plants as hotspots for antibiotic resistant bacteria and genes spread into the environment: a review (18)	1,184	148	2013	Sci. Total Environ.	Italy
4	Manaia, CM	Tackling antibiotic resistance: the environmental framework (212)	896	149.33	2015	Nat. Rev. Microbiol.	Portugal
5	Cassini, A	Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modeling analysis (23)	814	407	2019	Lancet Infect. Dis.	Sweden
6	Cotter, PD	Bacteriocins—a viable alternative to antibiotics? (55)	804	100.5	2013	Nat. Rev. Microbiol.	Ireland
7	Fleming-Dutra, KE	Prevalence of inappropriate antibiotic prescriptions among US ambulatory care visits, 2010–2011 (9)	736	147.2	2016	JAMA-J. Am. Med. Assoc.	USA
8	Andersson, DI	Microbiological effects of sublethal levels of antibiotics (10)	744	106.29	2014	Nat. Rev. Microbiol.	Sweden
9	Gilmore, BF	Clinical relevance of the ESKAPE pathogens (31)	634	79.25	2013	Expert Rev. Anti-Infect. Ther.	UK
10	Guidos, RJ	10 × '20 Progress-development of new drugs active against gram-negative bacilli: an update from the Infectious Diseases Society of America (34)	539	67.38	2013	Clin. Infect. Dis.	USA
11	Xagoraraki, I	Release of antibiotic resistant bacteria and genes in the effluent and biosolids of five wastewater utilities in Michigan (213)	551	55.1	2011	Water Res.	USA
12	Zhu, YG	Antibiotic Resistome and its association with bacterial communities during sewage sludge composting (214)	484	80.67	2015	Environ. Sci. Technol.	China
13	Larsson, DGJ	Management options for reducing the release of antibiotics and antibiotic resistance genes to the environment (140)	434	54.25	2013	Environ. Health Perspect.	Sweden
14	Czaplewski, L	Alternatives to antibiotics-a pipeline portfolio review (47)	413	82.6	2016	Lancet Infect. Dis.	UK
15	Xagoraraki, I	Correlation of tetracycline and sulfonamide antibiotics with corresponding resistance genes and resistant bacteria in a conventional municipal wastewater treatment plant (215)	437	48.56	2012	Sci. Total Environ.	USA

(Continued)

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TABLE 6 (Continued)

Rank	Corresponding authors	Title	TC	TCY	Publication year	Journal	Country/Region
16	Mao, DQ	Occurrence of sulfonamide and tetracycline-resistant bacteria and resistance genes in aquaculture environment (90)	442	49.11	2012	Water Res.	China
17	Grenni, P	Ecological effects of antibiotics on natural ecosystems: a review (26)	390	130	2018	Microchem J.	Italy
18	de Kraker, MEA	Mortality and Hospital Stay Associated with resistant *Staphylococcus aureus* and *Escherichia coli* bacteremia: estimating the burden of antibiotic resistance in Europe (24)	360	36	2011	PLos Med.	Netherlands
19	Meng, XZ	Usage, residue, and human health risk of antibiotics in Chinese aquaculture: a review (216)	365	91.25	2017	Environ. Pollut.	China
20	Diamadopoulos, E	Detection and fate of antibiotic resistant bacteria in wastewater treatment plants: a review (217)	351	43.88	2013	Ecotox. Environ. Safe.	Greece

TC, total citations; TCY, total citations per year.

found in human intestines either, which are in a harmonious symbiotic relationship with intestinal flora, rather than an antagonistic mode (264). Bacteriophage related therapies are in the concern once more (265). In addition, there has been also some progress in the relationship between intestinal flora and antibiotic resistance (266), the effect of antibiotics on intestinal flora (267), the effect of vaccines on antibiotic resistance (268), and antibiotic-resistant bacterial inhibitors (269). However, these studies are not thorough enough (270, 271). Therefore, it is necessary to pay attention to the diversification of research and strengthen the research on antibiotic substitutes, human intestinal flora and adjuvants in the future.

Antibiotic resistance imposes a heavy burden on human beings. A study on the worldwide burden of antibiotic resistance (272) found that the mortality in the whole age interval caused by antibiotic resistance is the highest in the Africa. Pseudomonas aeruginosa, MRSA and other MDRB have caused a large number of deaths. This suggests that low-resource settings bear the heaviest burden, which is consistent with the statistical analysis of this study in the leading countries or regions (Table 1), leading institutions (Table 2) and leading authors (Table 4). Although countries in Africa have made some contributions in this field (273–278), the relevant research is not sufficient and is not in the leading position, the understanding of antibiotic resistant bacteria is not enough. According to the author keywords bubble chart (Figure 6), it can be found that MRSA, Pseudomonas aeruginosa and other MDRB have received more attention in recent 2 years (279). The extremely strong resistance not only causes great losses to humans, but also threatens the existing antibiotics. Studies have shown that the COVID-19 pandemic has led to overuse of antibiotics in many areas, which will aggravate the antibiotic resistance (280, 281). Therefore, every country needs to establish strict antibiotic prescription guidelines to regulate antibiotic use. However, one study has shown that reducing antibiotic prescriptions cannot stop the spread of antibiotic resistant (282). There is a gap between antibiotic stewardship in the paper and in practice (283). Even treatments that match susceptibility of pathogens may result in resistance, because the development of antibiotic resistance is essentially driven by rapid re-infection of different strains of the patient with prescription resistance (284), and they suggest that the personalized antibiotic treatment suggestions can be given by predicting the patient's past infection or history using the machine learning, thus reducing the emergence of ARB. However, ARB can circulate and transfer between humans and animals. Therefore, it is not enough to reduce the propagation of antibiotic resistance by simply managing the use of antibiotic in human beings. There is no boundary among environment, animal and human beings. The control of antibiotic resistance requires simultaneous communication and cooperation of these three fields, rather than the separation of them (285).

In conclusion, this research proposed the possible future research direction in the field of ARB by starting from the

TABLE 7 The hot papers of ESI in ARB research field.

Rank	Corresponding authors	Title	TC	Publication year	Journal	Country/Region
1	Wang, JL	Occurrence and fate of antibiotics, antibiotic resistant genes (ARGs) and antibiotic resistant bacteria (ARB) in municipal wastewater treatment plant: an overview (220)	155	2020	Sci. Total Environ.	China
2	Boccaccini, AR	Antibacterial biohybrid nanofibers for wound dressings (221)	146	2020	Acta Biomater.	Germany
3	Peng, Q	Nanomaterials-based photothermal therapy and its potentials in antibacterial treatment (44)	67	2020	J. Control. Release	China

TC, total citations.

aspects of controlling the transmission of ARB and developing new antibiotics. Aspect of relevant research on new antibacterial agents: As peptide-based antibiotics have potential to defend against the ARB, many scholars are paying attention to its design and development (286–288). However, studies show that some problems occur after this kind of antibiotics are used, for example, it causes short half lives *in vivo*, protease degradation and others (289). Therefore, the research on the interaction between peptide-based antibiotics and human bodies (290, 291) and the decoration of its chemical structure (261) shall be further conducted in the future. In addition, it is inevitable for peptide-based antibiotics to become drug-resistant, despite its relatively low possibility of becoming antibiotic resistant. So, it is required to concern how to limit the drug resistance rate of new peptide-based antibiotics in the future. In the future, it is possible to research how to use bacteriophages to recover the complexity of damaged microbiota and how to use bacteriophages to operate HGT microbial genomes in microbial flora from the mutual beneficial aspect between intestinal bacteria and bacteriophages (264). Aspect of controlling the transmission of ARB: In conclusion, corresponding measures shall be taken on three aspects including humans, animals and environment to control the transmission of ARB in the future. On the aspect of humans, concerning the gap between antibiotics management and research and the actual situation (283), it is required to research the actual using condition antibiotics in humans across the world. In addition, it is equally important to reduce the use of antibiotics so as to control the generation and transmission of antibiotic resistance, especially in countries short of resources (292). Therefore, it is demanded to research the measures on how to reduce the use of antibiotics in the future, for instance, to develop relevant vaccines or hygiene system (293, 294), etc. On the aspect of environment, wastewater can transmit ARB and ARGs not only to humans, but also to the ecological environment (19). Despite the growing number of studies on sewage treatment, there is still a lack of a unified standard and program for sewage treatment. In terms of animal husbandry and aquaculture, a global policy is required to control the use of antibiotics on animals and prevent the ARB and ARGs from spreading to humans through food chains (295). What's more, we should also research how to use and manage antibiotics jointly from the three aspects of humans, animals and environment. It is possible to develop toward the direction of constructing the biological risk assessment platform (296) and electronic monitoring system (293, 297).

Conclusions

In this study, we provided a research overview of the field of ARB. Over time, ARB have become a global threat, and an increasing amount of related research has been carried out. Both developed countries, represented by the USA, and developing countries, represented by China, have made significant contributions to this field. There are relatively few relevant studies from Africa, but antibiotic-resistant bacterial infections in Africa are of great concern (298). ARB represent an interdisciplinary research field, with most studies focused on environmental and microbial aspects. Particularly, antibiotic resistance is not only a research focus in this field but also a research hotspot. Although some progress has been made with novel antibiotics, further research is still needed (299–301). In the future, we can strengthen the financial support (302) and technical and knowledge cooperation (303) for the research and development of new antibacterial drugs (304–306), etc. In this case, bacteriocins, phage therapy, nanomaterials, human intestinal flora and machine learning have inspired hope for the treatment of ARB infection. However, further relevant studies are still needed in the future. Since 2021–2022 related publications are not included, this study provides an overview of the latest research progress in this field based on the 2021–2022 ESI highly cited papers in the field of ARB.

Certain limitations were observed in this study. For example, articles without authors keywords were not included in the analysis. In summary, this study will hopefully inspire researchers in the field of ARB and assist them in further understanding the research trends, research hotspots, and future research directions in this field. Although WOS has covered many publications, however, some publications from database such as Scopus, PubMed, may not be included in this study.

Author contributions

YW and QZ contributed to the conception and design of the study and wrote the first draft of the manuscript. QZ organized the database and performed the statistical analysis. GS and DD reviewed and edited the manuscript. GS and ZD provided financial support. All authors contributed to manuscript revision, read, and approved the submitted version.

Funding

This research was funded by Science Technology Department of Zhejiang Province (No. 2022C25007).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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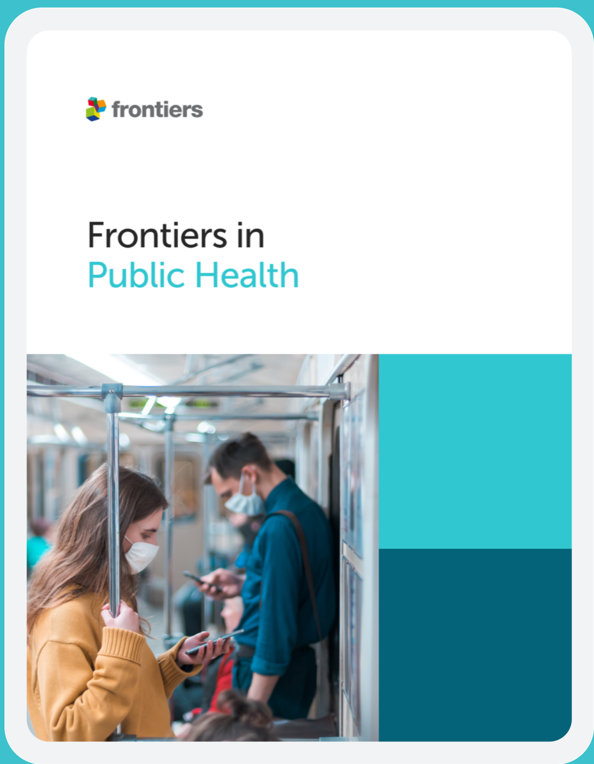

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