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Environmental Impacts of COVID-19 Pharmaceuticals and Disinfectants.

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Abstract

With the outbreak of COVID-19 pandemic (SARS-COV-2), the use of several aging and irrelevant pharmaceuticals has increased strangely. Consequently, huge amounts of disinfectants and antibiotics were used prevent the spreading of COVID-19 and residual drugs are also constantly excreted in freshwater, raising concerns about potential ecotoxicological effects on aquatic organisms. The purpose of this study was to examine the prevalence of these disinfectants and pharmaceuticals in aquatic environment and their potential ecotoxicological effects and antimicrobial resistance (AMR)-promoting effects. The literature information was sourced from PubMed, Science Direct, Embase, MEDLINE, and China National Knowledge Infrastructure databases using Google Scholars, Academia, and Research gate as search engines. Results revealed that the long-term exposure to pharmaceuticals and disinfectants and its by-products may pose detrimental effects on public health, reproductive impairments, obstructive pulmonary diseases, cancers, skin damage, and damage of central nervous system. Some researchers found significant fluctuations in the community structure of planktonic species in exposed waters. Results also revealed that excess use or misuse antibiotic misuse can accelerated the development of AMR. The present assessment fills the knowledge gap on the prevalence and effects of COVID-19-related pharmaceuticals in on the aquatic environment and wildlife. The outcome our study recommends an urgent need for an ecotoxicological assessment and monitoring the flow of COVID-19-related pharmaceuticals in the aquatic environment. We also advocate for an effective waste water management and to improve the removal efficiencies of drug residues in wastewater.

Keywords: COVID-19, Disinfectants, Ecological risks, Pharmaceuticals, Surface water

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Introduction

Water quality has become a global concern and significant public health focus in the recent years. Several human used drugs have polluted rivers across the world and pose "a global threat to environment, human health, and wild life.[1,2] Polluted water is a major cause of disease transmission, causing an expected five million deaths worldwide every year.[3] Recently, in 2022, during COVID-19 pandemic, Wilkinson *et al*.[4] identified 61 active pharmaceutical contaminants at more than 1052 geographical locations along 258 rivers in 104 countries. The use of disinfectants, antibiotics, antiviral drugs, and other related therapeutic drugs amplified significantly during COVID-19 pandemic which pose negative effects on human and animal health.[5]

For example, in the United States alone, more than 250 million antibiotic prescriptions are written each year. In 2007, 96 million kg of antibiotics were used in China. These antibiotics are not partially metabolized or excreted in the body, and 30–90% is directly discharged in the waste system.[6] The conventional wastewater treatment plants (WWTP) can only remove 20–80% of drugs and their metabolites.[7] Consequently these disinfectants and drug residues are released directly or indirectly into the environment which are essential to be checked frequently in surface waters and sediments. Although effective treatment medications were not yet determined, the use sanitizers and several pharmaceuticals were significantly increased for the treatment of COVID-19 and to prevent the spread of the pandemic. The drug residues present in receiving waters are of great environmental concern as it may pose several ecotoxicological effects.[8] As of March 2020, China has distributed at least 2000 tons of disinfectant in Wuhan City alone.[9] The new coronavirus is a virus and antibiotics cannot be used directly to treat the pandemic; yet, many antibiotics are extensively used to defend against the inflammation and other illnesses caused by COVID-19. This increased use and abuse increased the quantity and dosage of sanitizers and antibiotics in the environment which consecutively increased the pollution load on aquatic ecosystem and human health. The release of these pharmaceuticals or their metabolites is ubiquitous and further promoted by excess use or misuse of these medicines. These chemicals are quickly absorbed through the mucosa of various organs and organ systems through the bloodstream and disrupt the physiology and metabolism of the animals.[10]

Few previous studies have briefly elucidated the effects and environmental releases of these drugs, but their evaluation and methodology were found to be unscientific.[11] Therefore, taking into universal concern, it is very much crucial to evaluate the ecological impact of these disinfectants and drugs used for the treatment of COVID-19 are really appropriate. Therefore, we have updated the available literature on the potential impacts of disinfectants and antibiotics on the aquatic ecosystems and on human health. For that reason, the effects of the abuse

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of disinfectants and COVID19-related drugs during COVID19 pandemic on the aquatic environment are of great concern and deserve further research.

MATERIALS AND METHODS

The literature information was sourced from PubMed, Science Direct, Academia, Embase, MEDLINE, Research Gate, and China National Knowledge Infrastructure databases using Google Scholar as search engines. Articles written in the English language were retrieved and included in the study. This article discussed the physical and chemical counter measures of microbial reduction agents and the prevention of CoVs, their potential toxicity, and safety to humans and the environment during the COVID-19 pandemic. As a final point, we highlighted certain means to reduce the development of drug resistance due to inappropriate production and practices among patients.

RESULTS AND DISCUSSION

Toxic Effects on Aquatic Ecosystem

Exposure to disinfectants and pharmaceuticals used during COVID-19 pandemic is believed affect non-target organisms and/or microorganisms.[12] A 10-year long-term study of O'Flynn *et al*.[13] evidently found that pharmaceuticals can pose a severe risk to surface water environments, with each stage of the lifecycle of the organisms. The active pharmaceutical ingredients (API) are released into the natural environment during manufacturing, use and dumping will have detrimental effect on ecosystems and human health (e.g., selecting antibiotic-resistant strains, feminizing fish, and increasing their vulnerability to predators).[14] A long-term study by Wilkinson *et al*.[4] detected APIs such as carbamazepine, metformin, and caffeine in surface water from 1052 sampling sites from 258 rivers in 104 countries.

The recent review literature of Shah and Rather[15] had shown the presence of various pharmaceutical residues in various water supplies of India. In a study, Broccoli *et al*.[16] found significant exotoxicological risks such as changes in cell size and decrease in chlorophyll content in two freshwater and three marine microalgae. Chia *et al*.[17] found that the presence of pharmaceutical chemicals in the aquatic environment can negatively affect phytoplankton life. Kumar *et al*.[18] found traces of SARS-CoV-2 gene imprints and antidrug resistance (ADR) *Escherichia coli* in the water bodies of Ahmedabad, India. Khan *et al*.[19] found high-priority pharmaceutical residues in five different sampling in the Yamuna River of Delhi. Singh and Suthar[20] detected 15 pharmaceuticals and personal care products (PPCPs) of higher ecological risk in River Ganges of India. Gopal *et al*.[21] detected active ibuprofen, diclofenac, and triclosan from Arkavathi River and its tributaries and lakes spread across the Bengaluru urban area in Southern India.

Ul'yanovskii *et al*.[22] found 29 umifenovir (antiviral drug) transformation products and its metabolites in the sediments of WWTP in the province of Arkhangelsk (North Russia). The study of Cappelli *et al*.[23] found eight pharmaceutical compounds of high ecological concern from a WWTP of Italy which received the sewages from a hospital dedicated for the treatment of COVID-19 patients. Quincey *et al*.[24] showed the presence of 28of –35 monitored human-use pharmaceuticals in 23 river sites which are at risk of proliferating antimicrobial resistance (AMR) and other toxicological endpoints within Kathmandu City and the Annapurna region of Nepal. The global scale study performed by Wilkinson *et al*.[4] shown carbamazepine, metformin, and caffeine as active pharmaceutical contaminants in surface waters of 1052 sampling sites along 258 rivers in 104 countries. For that reason, many ecotoxicological studies have focused on the formation of disinfection by-products (DBPs) and antibiotic residues in different environments and their toxic effects on different organisms.[25-27]

DBP and various drugs in surface water and wastewater from sewage treatment plants are typically measured at concentrations of 0.01–1.0 μg/L.[28] Their study also reported that environmental concentrations of several DBPs can hinder the growth of freshwater algae (*Spirodela polyrhiza*) by interfering with photosynthetic function through inhibition and disruption of chloroplast metabolism. At ecological concentrations, several new DBPs have been shown to provoke oxidative stress and DNA damage and trigger the DNA repair system.[28] Nabi *et al*.(2020)[29] found that massive use of disinfection practices could likely to cause a severe threat to the environment, wildlife, and biodiversity. The excess use of such disinfectants could also contaminate food and water resources or resting habitats of free-living animals. As there are no definite scientific guidelines for the large-scale use of disinfectants in open-air urban environments, it is decisive to develop strategies to reduce the environmental contamination caused by this practice.

The toxicological studies of Chaves *et al*.[30] have shown that human exposure to DBP can cause genotoxicity, cytotoxicity, asthma, skin rashes, bladder, and colon cancer. For that reason, the WHO has specified maximum values in its laid guidelines for various frequently detected DBPs. Certain drugs and pharmaceuticals can influence envelope synthesis, protein synthesis, and nucleic acid (DNA/RNA) synthesis in prokaryotic cells.[28] Perveen *et al*.[25] found a significant reduction in hematological parameters in fish common carp (*Cyprinus carpio*) exposed to DBPs. Their study also confirms that fish hepatocytes were sensitive toward chloroform and iodoform DBPs. The study of Liu *et al*.[31] found oxytetracycline, ciprofloxacin, norfloxacin, sulfadiazine, and chloramphenicol resistant Proteobacteria, Bacteroidetes, Verrucomicrobia, and Firmicutes and 17 species of human opportunistic pathogens in wastewaters collected from an ornamental fish market of North China. The study also found the prevalence of 21 antibiotic resistance genes (ARGs) and two integrase genes.

The recent study of Kumari and Kumar[32] identified ecological and human health risks exposure of COVID-19 drugs and their metabolites in Indian waters. Goswami *et al*.[33] investigated pharmaceutically active compounds and their possible environmental risks in wastewater receiving waters of Sri Lanka. Environmental exposure to certain antibiotics such as diclofenac, erythromycin, fluoxetine, and carbamazepine can cause alterations in the behavior, anatomy of gill, and kidney of rainbow trout. Such exposures also caused oxidative DNA damage and delayed hatching of zebra fish.[34] Ejtahed *et al*.[35] found that excess and regular use of household disinfectants is associated with dysbiosis of the intestinal flora of children, which can lead to flabby and obesity in infants.

Fluoroquinolone highly preferred drug for human against various bacterial infections. The experimental findings of Ramesh *et al*.[36] found histological anomalies in the gill, liver, and kidney tissues along with imbalanced oxidative defense system and alterations of plasma inorganic ions of *Cirrhinus mrigala* exposed to 1 μg/L ciprofloxacin. The recent findings of Duan *et al*.[37] shown that toxicity of sulfonamides (SA) antibiotics and its mixtures can pose a great risk to the growth and diversity of algae, crustaceans and fish, and other aquatic system. The studies of Wang *et al*. (2022)[38] found a significant change in the community structure of phytoplankton, zooplankton, benthic macro invertebrates, and bacteria in the water and sediment of Hanjiang River in China. Yoon *et al*.[39] found that H_2O_2 had adverse effect on locomotion and metabolism of zebrafish. Another recent study of Won *et al*.[40] found that exposure to disinfectants such as chloroxylenol (PCMX) and benzalkonium chloride changed the activities of antioxidant enzymes such as superoxide dismutase and catalase and increased reactive oxygen species even at low concentrations in a rotifer *Brachionus koreanus*. Ren *et al*.[41] found ecotoxic effects of sodium hypochlorite (NaOCl) on the swimming strength, avoidance behavior, and other anomalies in zebrafish exposed to NaOCl a common disinfectant.

The results of a study by Dhama *et al*.[42] confirmed that QAC based disinfectants and bleach allegedly enhance the risk of development of asthma, chronic obstructive pulmonary disease (COPD), sterility, and impairment of brain in children. The strong odors of certain disinfectants can cause asthma.[43] The results of a study of 2017 by European Lung Foundation evidently found that 663 health professionals, who used QAC and bleach routinely, have developed COPD.[42] Gül *et al*.(2009)[44] found dose dependent responses of NaOCl and increased mitotic activity, histopathological, and nuclear changes cellular changes including chromosomal aberrations and cell death (apoptotic and necrotic changes). Moreover, psychotic incidents due to SARS-CoV-2 infection have resulted in the intake of liquid disinfectants or breathing of chlorine based aerosol sprays in an attempt to purify their body. Such practices resulted in the development of acute respiratory distress syndrome and distress of lung that imitate the symptoms of COVID-19.[45]

SARS-CoV-2 is unlikely infects human through aquatic food sources. However, spike particles/peptide fragments of SARS-CoV-2 are known to provoke negative impacts on the health of wildlife. Sengar and Vijayanandan[46] evaluated the risk assessment of 98 pharmaceuticals and PPCPs which were detected in various water sources (treated wastewater, surface water, and groundwater) of India. The study revealed that 47% of the detected PPCPs in Indian waters were found to exert a possible risk (RQ >1) to both aquatic species and human health.

However, the study of Charlie-Silva and Malafaia[47] confirmed that exposure of neotropical Physalaemus cuvieri tadpoles to distinct protein fragments of the Spike protein of SARS-CoV-2 for 24 h can enhance the oxidative stress and the alteration in acetylcholinesterase (AChE) activity and it quite enough to affect the health of tadpoles. The recent multiple studies of Agathokleous *et al*.[48] evidently shown that chemicals used for several sanitizer products can induce drug resistance, hormesis in plants, animal cells, microorganisms, and other non-target organisms in dose-dependent manner. For that reason, it is essential to conduct the environmental risk assessment experiments if the predicted environmental concentration exceeds standard limits of the WHO.

AMR Evolution

Antibiotics save our lives, but their regular use can promote the spread of resistant strains. Antibiotics and antifungals kill some of the bacteria that cause infections, but they also kill beneficial bacteria that protect our body from infections. Consumption of excess antibiotics is the most key driver for the development of antibiotic resistance (ABR). A CDC report shows that about 30% of all antibiotics prescribed in the United States are avoidable or inappropriate.[49] Microorganisms can develop ABR through spontaneous mutations, horizontal gene transfer, and plasmids. The antibiotic-resistant microbes have resistance traits in their DNA that can multiply and pass to other microbial population through spontaneous mutations, horizontal gene transfer, and through plasmids.[50] According to a newly updated CDC report, more than 2.8 million infectious diseases are caused by antibiotic-resistant pathogens each year in the United States, killing at least 35,000 people. More precisely, this means that there is an infection every 11 s and death every 15 min.[51,52] AMR occurs when microorganisms develop the mechanism by which they protect themselves from the effects of antibiotics. AMR can affect public, agricultural, and veterinary facilities at every stage of life. This makes it one of the burning health problems in the world. Resistant pathogens can spread to humans, animals, and the environment through soil, water, and food supplies and cause fatal illness. Affected people should use second-line and third-line treatments. This causes economic burden and also serious side effects such as organ failure and prolonged treatment and recovery, which can be harmful to the patient.[53]

The study of Liu *et al*.[31] found oxytetracycline, ciprofloxacin, norfloxacin, sulfadiazine, and chloramphenicol resistant Proteobacteria, Bacteroidetes, Verrucomicrobia, and Firmicutes and 17 other opportunistic human pathogens in wastewaters of a fish market of North China. Their study also reported the prevalence of 21 ARGs and two integrase genes. The study of Jo *et al*.[54] found antibiotic resistant bacteria, virulent factors, and ARGs in fish farms located on Jeju Island of South Korea. Shah and Rather[15] reported the presence of active pharmaceutical residues in various water supplies in India. Singh and Suthar[20] discovered 15 harmful drugs and PPCP in the Ganges. Gopal *et al*.[21] found active ingredients of ibuprofen, diclofenac, and triclosan in the Arkavathi River and its tributaries of Bangalore in Southern India. Khan *et al*.[34] detected high-priority drug residues at five different sampling sites on the Yamuna River in Delhi. Kumar *et al*.[55] found traces of the SARSCoV2 gene and ADR *E. coli* in the waters of Ahmedabad, India.

The results of a study by Seethalakshmi *et al*.[56] revealed that production of antimicrobials and disinfectants during the COVID pandemic in response to bigger demand may be a major factor for the development of AMR among bacteria. The research work of Chia *et al*.[17] shown that the presence of pharmaceutical residues in the aquatic environment which adversely affected the lifespan of phytoplankton. The results of an experimental study of Broccoli *et al*.[16] have shown changes in cell size and reduced chlorophyll content in two freshwater and three marine microalgae exposed to EC_{50} concentrations of amoxicillin (antibiotic). Bardhan and Abraham[57] discovered cefalexin, amoxiclav, and nitrofurantoin resistant. Aeromonas caviae and A. hydrophila in Indian carps obtained from the local market in Kolkata, India. Quincey *et al*. (2022)[24] reported 28 high risks from human drugs at 23 river sites in the city of Kathmandu and the Annapurna region of Nepal.

In an experiment, Parthasarathy *et al*.[58] isolated multi-antibiotic resistant Vibrio parahaemolyticus from oysters of coastal parts of West Bengal, India. Lavanya *et al*.(2021)[59] detected drug-resistant Aeromonas species in Labeo rohita collected from the West Godavari and Nellore districts of Andhra Pradesh, India. The field investigation of Kumar *et al*.[18] compared the ADR in *E.* coli for 2 years (2018 pre-COVID era) and 2020 (COVID era) in the water bodies of Ahmedabad, India. Their study found significant increase in ADR of E. coli obtained from surface waters of year 2020 compared to ambient water bodies of 2018. The bacterium Edwardsiella tarda isolated from *Oreochromis niloticus* and *Clarias gariepinus* of rice field exhibited AMR against penicillin, aminoglycosides, fluoroquinolones, tetracyclines, SA, and lincosamides.[60] Senger and Vijayanandan[46] evaluated the risk assessment of 98 medicines and PPCPs detected in various water sources in India (treated wastewater, surface water, and groundwater). Their study also reported that 47% of PPCP detected in Indian waters could pose a risk to both aquatic environment and human health. Dewi *et al*.[61] found multiple drug resistant (erythromycin, ampicillin, tetracycline, and trimethoprim) E. coli, Salmonella, and Vibrio in fish farm on the west coast of Peninsular Malaysia. A cross-sectional study of Rizvi and Ahammad[62] detected that unnecessary use of antibiotics during COVID-19 increased AMR in some patients and microorganisms. A laboratory study by Chitungo *et al*.[63] discovered that antibiotic abuse may increase the incidence of ABR and multidrug resistant microbial strains in the environment. The results of a research by Segala *et al*.[64] found that misuse of COVID-19 drugs enhanced unexpected and high incidence of drug resistant Enterobacteriaceae and *Candida auris* among COVID-19 patients. Results of a single-centered study by Temperoni *et al*.[65] found ABR and a high incidence of opportunistic pathogens in isolated patients with COVID-19.

Manifestation of drug resistance among bacteria in the normal species and circulation of such resistant genes can contribute to an increased load of resistant, potentially pathogenic microorganisms lead to overgrowth of exogenic pathogens. The increased use of erroneous and poor quality of disinfectants and antimicrobials during COVID-19 pandemic have led to treatment stoppage, negative medical outcomes, and AMR development. Further, the delay and interruption of vaccination services might contribute to an increased risk of infections and overuse of antibiotics forced the vulnerable people to develop ABR.

Antimicrobial Stewardship Programs (ASPs)

Antimicrobial stewardship (ASP) is a collaborative agenda that supports the proper use of antibiotics such as drug selection, dose, duration, and routes of administration that improves patient conditions, alleviates microbial resistance, and diminishes the multiplication of infections by multidrug-resistant strains. Nevertheless, the current pandemic has caused interruption of routine health services. The mutual approaches of AMS and analytical stewardship guarantee to enhance the patient health by reducing the morbidity, mortality, and other adverse actions, and optimum use of existing resources. However, due to the lack of adequate data and training staff and resource deployment, AMS programs that rely entirely on interdisciplinary collaboration and practice are being ignored and reduced in priority. False propaganda, coupled with fear of COVID-19 within the medical community, has also led to higher cases of antimicrobial use and prescription against AMS principles.

The supervision of antibiotic use in the society is crucial to inform and assess strategies for the prevention and control of AMR. Governments (National and local) from all levels should frequently examine the trends of antibiotic use and suggest developing and executing standard operating procedures. Bases on the data and trends, we suggest to design awareness drives to improve and optimize antimicrobial use in communities.

CONCLUSIONS

Thus, as illustrated in this review, we believe that excess use of disinfectants and antibiotics can pose serious threats to the aquatic organisms and its environment and it will persist beyond the Covid-19 crisis. Several authors have reported prominent threats of infections, development of ABR and other serious outcomes in patients. People and aquatic organisms are at increased risk of bioaccumulation and biomagnification of AMR at the trophic stage of food chain. As human beings occupy the top position in the food chain, they are really exposed in a blend of elevated level of disinfectants, antibiotics, ARGs, and ARB.

Hence, the future environmental studies should focus not only the adverse effects of antibiotics and disinfectants but should also focus on combining effects of all these chemicals. Pharmaceutical residues remaining in surface water can have long-term public health implications, such as reproductive disorders, COPD, cancer, skin damage, and central nervous system disorders. Therefore, efficient technology and strategies are needed to develop new drugs that minimize these toxic effects and drug resistance. The problem of AMR can be addressed through the development and effective execution of appropriate policies. Various nations have ratified laws to fight from the prescription, use, and release of antibiotics in the environment. Strong regulatory framework and other actions are essential to reduce the production of fake and substandard products. The research should focus on the bioaccumulation and biomagnification of these emerging contaminants such as disinfectants, antibiotics, ARGs, and even ARB in human model. Fast and quick detection technology of COVID-19 will be useful to provide appropriate information and to guide the right use of disinfectants and antibiotics. Residues of disinfectants and antibiotics can be eliminated by photolysis, biodegradation, adsorption techniques, and development of artificial wetlands in the aquatic environment. Proper prescription and right use of antibiotics according to the antimicrobial stewardship (ASPs) plus quality diagnosis and proactive infection control measures can help to prevent/reduce the prevalence of disinfectants and pharmaceutical residues in the aquatic environment.

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